Phase II trial to evaluate the combination of capmatinib + spartalizumab in advanced oesogastric adenocarcinoma

METIMGAST

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS CONCERNING A MEDICINAL PRODUCT FOR HUMAN USE

Version N°4.2 dated 08/06/2022
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The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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Titre complet	Phase II évaluant l'association capmatinib + spartalizumab dans les adénocarcinomes oesogastriques avancés
Acronyme/référence	METIMGAST
Investigateur coordonnateur	Pr Thomas APARICIO, Hôpital Saint Louis, Paris
Promoteur	Assistance Publique – Hôpitaux de Paris
Justification scientifique	Les adénocarcinomes gastriques métastatiques ont un mauvais pronostic qui a peu évolué au cours des dernières décennies. Récemment l'immunothérapie avec des anticorps anti-PD1 a montré des résultats encourageant chez une partie des patients. Le capmatinib, un inhibiteur sélectif de MET a montré des capacités immunomodulatrices et une synergie avec un inhibiteur de PD-1 le spartalizumab. Cette association est testée dans le traitement du carcinome hépatocellulaire indépendamment de l'amplification MET.
Objectif et critère d'évaluation principal	L'objectif de l'étude est d'évaluer le taux de réponse à 6 mois de l'association capmatinib + spartalizumab chez des patients pré-traités pour un adénocarcinome oesogastrique. Le taux de réponse global (ORR) sera évalué par imagerie toutes les 9 semaines et il sera défini comme la proportion de patients ayant au moins une réponse tumorale objective (complète ou partielle) selon les critères RECIST v1.1, dans les 6 mois.
Objectifs et critères d'évaluation secondaires	- Evaluer la tolérance de l'association pendant le 1er et le 2ème cycle (cf chap 4.1.2.) - Evaluer la tolérance de l'association pendant toute la durée du traitement et les toxicités retardés de l'immunothérapie pendant 2 ans (cf chap 10.3.2.) - Evaluer le meilleur taux de réponse et la durée de la réponse tumorale - Evaluer la survie sans progression jusqu'à 2 ans après l'inclusion - Evaluer la survie globale jusqu'à 2 ans après l'inclusion - Selon les résultats de l'analyse intermédiaires : évaluer la tolérance et l'efficacité du spartalizumab en monothérapie chez les patients avec tumeur sans amplification MET Objectifs exploratoires : - Evaluer la pharmacocinétique du capmatinib en fonction de la présence d'une gastrectomie ou d'un traitement par inhibiteur de la pompe à proton - Evaluer la réponse tumorale en fonction de : a) Taux résiduel de capmatinib au J1 du cycle 2 et du cycle 3 b) En fonction de l'amplification de MET en FISH sur le prélèvement réalisé en local c) En fonction du taux de polynucléaires neutrophiles et du taux d'HGF circulant à l'inclusion et au J1 du cycle 2.
Schéma expérimental	Phase II avec 2 cohortes selon l'amplification MET. Cohorte 1 : tumeur sans amplification MET (<6 copies); Cohorte 2: tumeur avec amplification de MET (≥ 6 copies). Traitement : Capmatinib 400 mg matin et soir + Spartalizumab 300 mg toutes les 3 semaines pour un maximum de 12 mois ou jusqu'à toxicité inacceptable, progression ou refus du patient. Pour la cohorte 1 : Une analyse intermédiaire du critère principal d'efficacité sera effectué chez les 30 premiers patients inclus évaluables traités par la combinaison Capmatinib +

	Spartalizumab. Les règles d'arrêt ou de poursuite sont précisées dans la table 1 du paragraphe 12.1. Le schéma comporte un monitoring séquentiel de la toxicité, réalisé sur l'ensemble des 2 cohortes.
Population	Patients atteints d'un adénocarcinome oesogastrique métastatique ou localement avancé ayant reçu au moins une ligne de chimiothérapie à base de sel de platine et de fluoropyrimidine avec une progression documentée pendant ou après chimiothérapie
Critères d'inclusion	- Adenocarcinome oesogastrique localement avancé ou métastatique confirmé histologiquement et cytologiquement. - Tumeur non résécable. - Progression documentée pendant ou après au moins une ligne de chimiothérapie à base de sels de platine et de fluoropyrimidine. - Les patients ayant une tumeur HER2 (HER2 +++ ou HER2++ et FISH ou SISH+) doivent avoir reçu un traitement par trastuzumab - Evaluation de l'amplification MET tumorale par FISH - Statut de performance ECOG ≤ 1. - Tumeur mesurable selon les critères RECIST1.1. - Possibilité d'avaler et de retenir un traitement oral. - Age ≥18 ans. - Les femmes en âge de procréer et les hommes sexuellement actifs doivent accepter de suivre les instructions relatives aux méthodes de contraception pendant toute la durée des traitements à l'étude par le capmatinib et le spartalizumab, jusqu'à 7 jours après la dernière dose de capmatinib et 150 jours après la dernière dose de spartalizumab. - Consentement à participer à l'essai après information éclairée - Affiliation à un régime de sécurité sociale
Critères de non inclusion	- Impossibilité de déglutition - Traitement préalable par immunothérapie ou inhibiteur de MET - Toxicité d'un grade supérieure à 1 persistantes reliée à un traitement précédent, à l'exception de l'alopécie de tout grade et de la neuropathie de grade 2 liée à un traitement antérieur au sel de platine. - Autre tumeur maligne évolutive ou traitée depuis moins de 3 ans à l'exception du carcinome épidermoïde ou basocellulaire cutané complètement réséqué ou d'un carcinome in situ complètement réséqué. - Vaccination avec vaccin vivant dans les 4 semaines avant l'initiation du traitement à l'étude. - ATCD de réaction d'hypersensibilité à d'autres anticorps monoclonaux. - Pneumopathie interstitielle ou non infectieuse - Maladie autoimmune active ou antécédent de maladie autoimmune (les patients atteints de vitiligo, de diabète sucré contrôlé de type I avec une dose d'insuline stable, d'hypothyroïdie auto-immune résiduelle nécessitant uniquement un remplacement hormonal ou de psoriasis ne nécessitant pas de traitement systémique peuvent être inclus). - Transplantation d'organe - Infection active non contrôlée - Infection VIH - Infection virale B active non traitée (les patients atteints d'hépatite B active (AgHBs positif) peuvent être inclus à condition que la charge virale (ADN du VHB) à la sélection soit

	<100 UI/mL. Les patients peuvent recevoir un traitement antiviral avec de la lamivudine, du ténofovir, de l'entécavir ou d'autres agents antiviraux avant le début du traitement de l'étude pour supprimer la réplication virale). - Infection virale C (ARN du VHC positif) (les patients qui ont obtenu une réponse virologique soutenue après un traitement antiviral et qui présentent une absence d'ARN du VHC détectable ≥ 6 mois après la fin du traitement antiviral sont éligibles). - Lésion du système nerveux central non traitée ou symptomatique Toutefois, les patients sont éligibles si : a) toutes les lésions connues du SNC ont été traitées par radiothérapie ou chirurgie et b) le patient est resté sans preuve de progression de la maladie du SNC ≥4 semaines après le traitement et c) les patients doivent avoir cessé leur traitement aux corticostéroïdes depuis plus de 2 semaines - Cardiopathie cliniquement significative non contrôlée - Syndrome coronarien aigu récent ou cardiopathie ischémique instable. - Insuffisance cardiaque congestive ≥ classe III ou IV selon la définition de la New York Heart Association. - Syndrome du QT long (supérieur à 480 ms chez la femme et 470 ms chez l'homme), histoire familiale de mort subite ou de syndrome congénital du QT long. - Hypertension artérielle non contrôlée définie par une tension artérielle systolique ≥ 150 mm Hg et/ou une tension artérielle diastolique ≥ 100 mm Hg, avec ou sans médicament antihypertenseur. L'initiation ou l'ajustement des médicaments antihypertenseurs est autorisé avant le début du traitement - Chirurgie datant de moins de 4 semaines - Radiothérapie datant de moins de 2 semaines - Grossesse ou allaitement ou absence de contraception efficace chez une femme fertile. - Homme sexuellement actif sauf si utilisation de préservatif pendant les rapports pendant la prise de capmatinib et pendant 7 jours après l'arrêt du traitement, et ne doivent pas concevoir d'enfant pendant cette période. - Traitement concomitant par inducteur puissant du CYP3A et ne pouvant pas être interrompus ≥1 semaine avant le début du traitement. - Traitement chronique par corticostéroide (>10 mg/jour prednisone ou équivalent) ou toute thérapie immunosuppressive 7 jours avant la date prévue de la première dose du traitement à l'étude. - Résultats biologiques anormaux : - Bilirubine totale ≥ 1.5 x ULN - Phosphatase alcaline ≥ 5 x ULN - Alanine aminotransferase (ALAT) > 3 x N - Aspartate aminotransferase (ASAT) > 3 x N - Coagulation : Temps de prothrombine >4 seconds de plus que la normale ou International Normalized Ratio (INR) > 1.7 - Polynucléaires neutrophiles <1.5 x 10^9/L - Plaquette <75 x 10^9/L - Hémoglobine <9 g/dL - Clairance de la créatinine (calculée selon la formule de Cockcroft-Gault, ou mesuré) <45 mL/min - Lipase >2 N - Troponine >2 N

	- Potassium, Magnésium, Phosphore, Calcium total (corrigée sur l'albumine) hors des valeurs normales (les patients peuvent être inclus en cas de correction par supplémentation pendant la phase de sélection) - Patient sous protection juridique - Participation à une autre étude interventionnelle avec traitement
Traitement faisant l'objet de la recherche	Spartalizumab et capmatinib (Novartis)
Groupe comparateur	Non applicable
Autres actes ajoutés par la recherche	Un prélèvement de 5 ml à l'inclusion et au J1 du cycle 2 pour analyse du taux circulant d'HGF et des prélèvements de 5 ml pour pharmacocinétique au J1 du cycle 2 (5 prélèvements pour 20 patients, 2 prélèvements pour 70 patients) et du cycle 3 (2 prélèvements)
Bénéfices attendus pour les participants et pour la société	Amélioration de la survie
Risques et contraintes ajoutés par la recherche	Risques de toxicités des traitements à l'étude Risques liées aux prélèvements sanguins pour la pharmacocinétique.
Déroulement pratique	1/ Sélection • Vérification des critères d'éligibilité • Information et signature du formulaire de consentement • Enregistrement de la sélection du patient en se connectant au site web eCRF (CleanWeb). Le numéro d'identification du patient dans la recherche sera attribué. • Recueil des données patient : démographiques, patient, antécédents et caractéristiques tumorales • Evaluation clinique : statut de performance OMS, poids et taille, tension artérielle • Détermination de l'amplification de *MET* par FISH sur matériel d'archive. Si la détermination de l'amplification de MET a déjà été réalisée dans le cadre du soin elle n'est pas à refaire lors du screening pour l'inclusion du patient. • Examens biologiques, évaluation radiologique et électrocardiogramme. 2/ Inclusion • Revue des critères d'éligibilités • Revue des résultats des examens et des évaluations réalisés lors de la Sélection : - Evaluation radiologique : scanner thoraco-abdomino-pelvien CT-scan (ou IRM abdominale et scanner thoracique en cas de contre-indication), avec mesure des lésions cibles selon les critères RECIST v1.1. - Evaluation clinique : Statut de performance, poids et taille, pression artérielle - Examen biologiques, électrocardiogramme - Détermination de l'amplification de *MET* • Réalisation d'un test de grossesse (urinaire ou sanguin) si applicable • Prélèvements sanguins pour étude ancillaire • Prescription et attribution des traitements 3/ Pendant le traitement

	Cycle 1: Examen clinique et biologique avec recueil des toxicités, pendant le 1er cycle à J8, 15 et 22 (=J1 du cycle 2). Au J1 du cycle 2: prélèvement sanguin pour étude ancillaire. Avant chaque cycle, toutes les 3 semaines : • Examen clinique : Statut de performance ECOG, poids, presion artérielle • Prélèvements sanguins J1 du cycle 3 pour étude ancillaire • Evaluation des toxicités selon la classification NCI-CTC V5 Evaluation de l'efficacité toutes les 9 semaines : • Evaluation radiologique : o Scanner thoraco-abdomino-pelvien (ou IRM abdominale et scanner thoracique non injecté si contre-indication)
Nombre de sujets sélectionnés	90
Nombre de centres prévisionnel	10 centres recruteurs situés dans 7 hôpitaux ou instituts - Hôpital Saint Louis, Paris : département de gastroentérologie et cancérologie digestive, CIC - Centre Léon Bérard, Lyon : service d'oncologie médicale - Centre Georges François Leclerc, Dijon : service d'oncologie médicale et Unité de phase précoce - Institut Gustave Roussy, Villejuif : service d'oncologie digestive - Institut Universitaire du Cancer, Toulouse : service d'oncologie médicale digestive - Hôpital Haut Levêque,, Bordeaux : service Hépato-gastroentérologie et Unité de recherche clinique - Centre Hospitalier Régional Universitaire Jean Minjoz de Besançon : service d'oncologie médicale
Durée de la recherche	- Durée d'inclusion : 18 mois - Durée de participation (Sélection + traitement + suivi) : 25 mois - Durée totale : 43 mois
Nombre d'inclusions prévues par centre et par mois	1 inclusion par centre et par mois
Analyse statistique	Deux cohortes seront constituées selon le schéma de l'essai : - Cohorte 1 incluant les patients sans amplification MET(<6 copies). Un total de 81 patients permettra avec une puissance de 90% et un risque alpha de 5% de détecter un taux de réponse de 30% comparé à la référence de 15%, incluant une analyse intermédiaire après l'inclusion de 30 patients avec une règle d'arrêt du traitement en association pour futilité, selon un schéma bayésien de phase 2 [Lin R et al, JNCI 2020]. En cas d'arrêt précoce pour futilité, les inclusions seront poursuivies (51 patients supplémentaires, total 81). Dans ce cas, l'échantillon des 51 patients traités en monothérapie de spartalizumab permettra avec une puissance de 80% de détecter un taux de réponse de 20% sous spartalizumab en monothérapie (≤8% de réponse étant inacceptable), suivant une comparaison exacte binomiale. - Cohorte 2 incluant les patients avec amplification de MET (≥6 copie) a visée exploratoire. Les inclusions dans la cohorte 2 continueront jusqu'à la fin des inclusions dans la cohorte 1 et pour un maximum de 9 patients. Un monitoring séquentiel de la toxicité sera réalisé sur l'ensemble des 2 cohortes [Ivanova et al.-Clin Invest-2015].

	Les analyses seront réalisées avec le logiciel R. Data management et analyses seront réalisées dans le Service de Biostatistique et Information Médicale, Hôpital Saint Louis, Paris (Pr S Chevret), qui un centre de traitement des données labellisé INCa.
Source de financement	INCA et NOVARTIS
Comité de Surveillance Indépendant prévu	Un comité de de surveillance indépendant se réunira tous les 6 mois pendant la durée de l'étude et pourra être saisi à tout moment par le secteur vigilance ou le comité scientifique à travers le secteur promotion de la DRCI.

SUMMARY

Full title	Phase II trial to evaluate the combination of capmatinib + spartalizumab in advanced oesogastric adenocarcinoma
Acronym/reference	METIMGAST
Coordinating investigator	Pr Thomas APARICIO, Hôpital Saint Louis, Paris
Scientific Director (if applicable)	NA
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Oesoastric advanced adenocarcinoma have a poor prognosis without improvement in the last decades. Recently immunotherapy with anti-PD1 antibodies provides encouraging results on a subset of patients. capmatinib, a MET inhibitor shown imunomodulatory effect and a synergy with spartalizumab a PD-1 inhibitor. This combination is currently evaluated in the treatment of hepatocellular carcinoma whatever MET expression.
Main objective and primary endpoint	To evaluate the tumor response to the regimen at 6 months after inclusion. The overall response rate (ORR) will be assessed by imaging every 9 weeks and will be defined as the proportion of patients with at least one objective tumour response (complete or partial) according to RECIST v1.1 criteria within 6 months.
Secondary objectives and endpoints	- To evaluate the safety of the regimen during the first and second cycles of administration (up to day 42 (D42)) (cf chap 4.1.2.) - To evaluate the safety and tolerability of the regimen during the whole course of treatment for all kind of toxicities and up to 2 years for immunotherapy-related toxicity (cf chap 10.3.2.) - To characterize the tumor response to the regimen (duration, time to response) - To estimate the progression free survival, up to 2 years after inclusion - To estimate the overall survival, up to 2 years after inclusion - According to the results of interim analysis: to evaluate tolerance and efficacy of spartalizumab monotherapy in patient with non-amplified MET tumor **Ancillary studies**

	- To evaluate pharmacokinetics of capmatinib according to the presence of a gastrectomy and of a concurrent treatment with a proton pump inhibitor - To evaluate the tumor response in specific subgroups: a) According to the residual level of capmatinib at Cycle 2 Day1 (C2D1) b) According to *MET* amplification level in FISH on the archival tumor sample c) According to the baseline and C2D1 neutrophil count and circulating HGF level
Design of the study	Multicenter single-arm phase II trial with 2 cohorts according MET amplification level. Cohort 1: tumor without MET amplification (< 6 copies); cohort 2: tumor with MET amplification (≥6 copies). Treatment : Capmatinib 400 mg mg-BID + Spartalizumab-300 mg-Q3W for a maximum of 12 months or until progression, patient's refusal or unacceptable toxicity. For the cohort 1 interim analysis for the primary endpoint on the first 30 evaluable enrolled patients. The rules for stopping or continuing the trial are specified in Table 1 of paragraph 12.1.
Population of study participants	Patients with advanced oesogastric adenocarcinoma that have received at least one previous chemotherapy line with platinium salt and fluoropyrimidin and with a documented progression during or after chemotherapy .
Inclusion criteria	- Histologically or cytologically documented locally advanced or metastatic oesogastric adenocarcinoma. - Unresectable tumor. - Patients must have received at least one prior systemic chemotherapy based on platinium salt and fluoropyrimidine with documented progression during or after chemotherapy. - Patients must have received trastuzumab in case of HER2 positive tumor (HER2 +++ or HER2++ and FISH or SISH+) - Determination of tumor MET amplification by FISH available - ECOG Performance Status ≤ 1. - Measurable tumoral disease according to RECIST 1.1 criteria. - Patients must be willing and able to swallow and retain oral medication. - Age ≥18 years. - Women of childbearing potential and males who are sexually active must agree to follow instructions for method(s) of contraception for the duration of study treatments with Capmatinib and Spartalizumab until 7 days after the last dose of Capmatinib and 150 days after the last dose of Spartalizumab - Consent to participate in the trial after information - Affiliated to a social security system

Exclusion criteria	- Previous treatment with immunotherapy or MET inhibitor - Impossibility to take oral medication - Persistent toxicities related to prior treatment of grade greater than 1, except for alopecia any grade and grade 2 neuropathy related to previous treatment with platinium salt. - Presence or history of another malignant disease that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type. - Use of any live vaccines within 4 weeks of initiation of study treatment. - History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs). - History or current interstitial lung disease or non-infectious pneumonitis - Active autoimmune disease or a documented history of autoimmune disease (Patients with vitiligo, controlled type I diabetes mellitus on stable insulin dose, residual autoimmune-related hypothyroidism only requiring hormone replacement or psoriasis not requiring systemic treatment are permitted). - Allogenic bone marrow or solid organ transplant - uncontrolled active infection - Human Immunodeficiency Virus (HIV) infection - Untreated active Hepatitis B infection (HBsAg positive) (Patients with active hepatitis B (HBsAg positive) may be enrolled provided viral load (HBV DNA) at screening is <100 UI/mL. Patients may receive antiviral treatment with lamivudine, tenofovir, entecavir, or other antiviral agents before the initiation of study treatment to suppress viral replication). - Untreated active hepatitis C (HCV RNA positive) (patients that achieved a sustained virological response after antiviral treatment and show absence of detectable HCV RNA ≥6 months after cessation of antiviral treatment are eligible) - Untreated or symptomatic central nervous system (CNS) lesion. However, patients are eligible if: a) all known CNS lesions have been treated with radiotherapy or surgery and b) patient remained without evidence of CNS disease progression ≥4 weeks after treatment and c) patients must be off corticosteroid therapy for ≥2 weeks - Clinically significant, uncontrolled heart diseases. - Recent acute coronary syndrome or unstable ischemic heart disease - Congestive heart failure ≥ Class III or IV as defined by New York Heart Association - Long QT syndrome (> 480 ms in women and 470 ms in men), family history of idiopathic sudden death or congenital long QT syndrome.

	- Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥150 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening. - Surgery less than 4 weeks - Radiotherapy less than 2 weeks - Pregnancy or breastfeeding or women of child-bearing potential, unless they are using highly effective methods of contraception. - Sexually active males unless they use a condom during intercourse while taking capmatinib and for 7 days after stopping treatment and should not father a child in this period. - Participants receiving treatment with strong inducers of CYP3A and could not be discontinued ≥ 1 week prior to the start of treatment. - Systemic chronic steroid therapy (>10 mg/day prednisone or equivalent) or any immunosuppressive therapy 7 days prior to planned date of first dose of study treatment. - Patient having out of range laboratory values defined as: - Total bilirubin ≥ 1.5 x Upper Limit of Normal (ULN) - Alkaline phosphatase (ALP) ≥ 5 x ULN - Alanine aminotransferase (ALT) > 3 x ULN - Aspartate aminotransferase (AST) > 3 x ULN - Coagulation: Prothrombin Time (PT) >4 seconds more than the ULN or International Normalized Ratio (INR) >1.7 - Absolute neutrophil count (ANC) <1.5 x 109/L - Platelet count <75 x 109/L - Hemoglobin <9 g/dL - Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) <45 mL/min - Serum lipase >2 ULN - Cardiac troponin I (cTnI) elevation >2 x ULN - Potassium, Magnesium, Phosphorus, total Calcium (corrected for serum albumin) outside of normal limits (patients may be enrolled if corrected to within normal limits with supplements during screening) - Patients under legal protection -Participation to another interventional study whith treatment
Investigational medicinal product(s)	Capmatinib 400 mg BID + Spartalizumab 300 mg Q3W for a maximum of 12 months or until progression, patient's refusal or unacceptable toxicity.
Comparator treatment	Not applicable
Interventions added for the study	Blood sample for pharmacokinetics
Expected benefits for the participants and for society	Survival improvement

Risks and burdens added by the study	Risks associated with the toxicities of the investigational drugs Risks associated with the blood sampling of the pharmacokinetics
Practical implementation	**Screening visit** - Verification of eligibility criteria - Information and signature of the consent form - Registration of the patient selection by connecting into the eCRF website (CleanWeb). The patient's research identification number will be assigned. - Collection of patient data: demographic, patient, history and tumour characteristics - Clinical assessment: ECOG performance status, weight and height, blood pressure - MET amplification determination by FISH on archival material. If MET amplification determination has already been performed as part of the care, it does not need to be repeated during the screening for patient inclusion. - Biological examinations, radiological assessment and electrocardiogram. **Inclusion visit** - Review of eligibility criteria - Review of the results of the examinations and assessments carried out during the Selection: • Collection of patient data: demographic, patient, history and tumour characteristics • Radiological assessment: thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT scan in case of contraindication), with measurement of target lesions according to RECIST v1.1 criteria. • Clinical assessment: performance status, weight and height, blood pressure • Biological examination, electrocardiogram • Determination of MET amplification - Pregnancy test (urine or blood) if applicable - Blood samples for ancillary study - Prescription and allocation of treatments **During the treatment** Cycle 1: Toxicities will be assessed by clinical evaluation and blood tests during the first cycle at days 8, 15 and 22 (=D1 of cycle 2). At D1 of cycle 2: blood samples for ancillary studies Before each cycle, every 3 weeks: • Complete clinical evaluation: ECOG Performance status, weight, blood pressure • Clinical laboratory assessments • Toxicities: evaluated by NCI-CTC 5.0 classification, adverse events Efficacy assessments every 9 weeks:

	• Radiological evaluation: thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT-scan not injected if contraindication)
Number of participants included	90
Number of centres	10 clinical centers of 7 public hospitals or institute located in France - Hôpital Saint Louis, Paris : Gastroenterology and Digestive Oncology department, CLIPP and CIC - Centre Léon Bérard, Lyon : Medical Oncology, CLIPP - Centre Georges François Leclerc, Dijon : Medical Oncology, CLIPP and Unité de phase précoce - Institut Gustave Roussy, Villejuif : Digestive Oncology, CLIPP - Institut Universitaire du Cancer, Toulouse : Medical Oncology, CLIPP - Hôpital Haut Levêque , Bordeaux : Hepato-Gastroenterology and Unité de recherche clinique - Centre Hospitalier Régional Universitaire Jean Minjoz de Besançon: Medical Oncology
Duration of the study	- inclusion period:18 months - participation period (treatment + follow-up): 25 months - total duration: 43 months
Number of enrolments expected per site and per month	1 inclusion per site and per months
Statistical analysis	Two cohorts will be constituted: - Cohort 1 to enrol patients with no MET amplification (<6 copies). Specifically, a total of 81 patients will ensure 90% power with a 5% type I error rate to detect a 30% response rate compared to reference 15%, including an interim analysis after 30 patients have been included with a futility stopping rule, using a Bayesian optimal time-to-event Phase II design [Lin R et al, JNCI, 2020]. In case the trial is terminated early for futility, inclusions will continue but spartalizumab monotherapy, for 51 additional patients in cohort 1 (total 81). In that case, this sample of 50 patients with spartalizumab monotherapy will allow to detect 20% response rate in patients under monotherapy (against 8% as unacceptable) with >80% power and a 5% type I error rate, using a binomial exact comparison. - Cohort 2 to enrol patient with MET amplification (≥6 copie) for exploratory purpose only. The enrolment in cohort 2 will be ongoing until cohort 1 is completed and for a maximum of 9 patients. A sequential continuous toxicity montoring will be conducted across both cohorts [Ivanova et al.-Clin Invest-2015]. Endpoints will be described with count and percentage for categorical endpoints (toxicity, AEs), and with mean, median, 95% confidence interval (or 95% credibility

	interval if appropriate), interquartile range for continuous endpoints. Time-to event endpoints (PFS and OS) will be estimated using the non-parametric Kaplan Meier estimator, to obtain the survival estimates up to 24 months after inclusion. Analyses will be performed using R statistical platform. Along with data-management, analyses will be conducted in the Department of Biostatistics and Medical Information of Hôpital Saint Louis, Paris (Pr Sylvie Chevret), which is a labelled Centre de Traitement des Données INCa.
Funding sources	INCa and NOVARTIS
Study will have a Data Safety Monitoring Board	A data safety monitoring board will meet every 6 months for the duration of the study and may be consulted at any time by the vigilance sector or the scientific committee through DRCI's promotion sector.

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

An immunomodulatory role of capmatinib was recently suggested. Concomitant MET inhibition promoted adoptive T cell transfer and checkpoint immunotherapies in murine cancer models by increasing effector T cell infiltration in tumors. This therapeutic effect was independent of tumor cell-intrinsic MET dependence. In the absence of MET inhibition, neutrophils recruited to T cell-inflamed microenvironments rapidly acquired immunosuppressive properties, restraining T cell expansion and effector functions. In cancer patients, high serum levels of the MET ligand HGF correlated with increasing neutrophil counts and poor responses to checkpoint blockade therapies (1). Another pre-clinical study reported that the combination of capmatinib + PD-1 antibody was more efficient than capmatinib alone or PD-1 antibody alone in a model of hepatocellular carcinoma. Moreover, the combination of MET-inhibitor and PD-1 antibody increased the activated tumor-infiltrating CD8+ T-cell (2).
A Phase Ib/II study of capmatinib in combination with spartalizumab in advanced hepatocellular carcinoma is currently recruiting (NCT02795429). No other trial with this combination is ongoing in oesogastric cancer.
The purpose of the proposal is to evaluate the efficacy and safety of the combination of capmatinib and spartalizumab in pre-treated oesogastric adenocarcinoma. Moreover, efficacy will be assessed according to MET expression or amplification level and PD-L1 expression in order to obtain data to identify potential sub-group(s) of patients that will benefit the most from the combination treatment.

2.2 Description of knowledge relating to the condition in question

Oesogastric adenocarcinoma is the second more frequent digestive cancer in the world and remains associated with poor prognosis. Even after curative intent surgery, local and distant recurrences or death are still over 50% even in a recent large trial (6). In metastatic or unresectable disease, median overall survival remains poor. Polychemotherapy combining fluoropyrimidine, platinium salts, taxane or irinotecan provides median overall survival below 12 months (7-10). In the sub-group of patients with a HER2 overexpression, trastuzumab in addition to chemotherapy improves overall survival in first line (11).

Second line chemotherapy with taxane or irinotecan results in a small survival improvement, around 2 months, but poor objective tumor response (0% with irinotecan (12), 7% with docetaxel (13)). Addition of anti-VEGFR monoclonal antibody ramucirumab to paclitaxel improves survival and response rate compared to paclitaxel alone (28% vs 16%) (14).

2.3 Summary of relevant pre-clinical experiments and clinical trials

Immunotherapy with anti-PD-1 antibody, pembrolizumab, gives comparable results to paclitaxel with a tumor response rate of 16% vs 14% and a better safety profile in second line (4). In the sub-group of patients that have a high expression of PD-L1 (Combined Positive Score (CPS) ≥10) or tumor microsatellite instability, the effect of pembrolizumab is enhanced. FDA gave approval for pembrolizumab monotherapy for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS≥1) with disease progression on or after prior chemotherapy including fluoropyrimidine and platinum and if appropriate, HER2-targeted therapy. Nevertheless, other anti-PD-L1 as nivolumab showed activity on advanced gastric adenocarcinoma irrespective of the PD-L1 status (15). Mismatch Repair (MMR) deficiency (or microsatellite instability) and Epstein-Barr virus (EBV) tumor positivity have been also shown as mutually exclusive strong predictors of pembrolizumab activity (16). Mutation load analysis adds little predictive value to MMR and EBV determination.

MET amplification is present in around 5%-6% of oesogastric adenocarcinoma and represents an oncogenic driver and therapeutic target (17). If targeting c-MET receptor with monoclonal antibody was disappointing, the use of small-molecule multitarget inhibitor crizotinib revealed a response rate in 3/9 patients with MET-amplified oesogastric (Gene Copie Number >6 evaluate by FISH on 100 nuclei) adenocarcinoma treated in the French AcSé program (5). Another study reported 18% of tumor response in MET-amplified oesogastric adenocarcinoma treated with AMG 337 specific MET-inhibitor (18). FISH and IHC testing provides information regarding MET amplification and protein expression, but cannot identify other MET pathway alterations. Comprehensive next-generation sequencing-based tumor profiling has the added benefit of interrogating all types of alteration in MET (substitutions, deletions/insertions, copy number changes and chromosomal rearrangements) and will probably further define the optimal patients for MET-directed therapy.

2.4 Description of the population to be studied and justification for the choice of participants

Several polychemotherapy regimens have demonstrated efficacy in first line for patients with oesogastric advanced or metastatic adenocarcinoma. In second line chemotherapy or antiangiogenic therapy improves modestly overall survival. Immunotherapy with anti-PD1 gives improves significantly survival but only in a small subset of patients. Improving efficacy of immunotherapy in second line is an urgent need.
Thus, chemorefractory patients after a first line is the target population for the present study.

2.5 Identification and description of the investigational medication or medications

Spartalizumab is a humanized IgG4 monoclonal antibody (mAb) that binds PD-1 with sub-nanomolar affinity and blocks interaction with PD-L1/PD-L2, thus preventing PD-1-mediated inhibitory signaling and leading to T-cell activation. The safety profile of spartalizumab is consistent with other PD-1 inhibitors.

Capmatinib is a highly selective and potent MET inhibitor with in vitro and in vivo activities against preclinical cancer models with MET activation. In non-small cell lung cancer capmatinib + gefitinib (EGFR inhibitor) demonstrated efficacy in patients with tumor with 50% of tumor cells IHC 3+ or MET Gene Copy Number (GCN) >4 (19).

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

The dosage of capmatinib recommended from previous phase II trials is 400 mg twice daily either in monotherapy or in association with other tyrosine kinase inhibitors.
The dosage of spartalizumab recommended from previous phase Ib trials is either 300 mg Q3W or 400 mg Q4W.
The schedule for the combination used in the ongoing NCT02795429 trial (hepatocellular carcinoma) is spartalizumab 300 mg Q3W + capmatinib 400 mg twice per day.
For the present study, the same dosage of spartalizumab 300 mg Q3W + capmatinib 400 mg twice per day will be used as in the NCT02795429 trial (resulting in treatment cycles of 3-week duration).

2.7 Summary of the known and foreseeable benefits and risks for the research participants

Spartalizumab
The risk of spartalizumab is comparable to those of other anti-PD1 monoclonal antibody already extensively evaluated in oesogastric adenocarcinoma.
The mains toxicity of spartalizumab observed in previous clinical study are consistent with and characteristic of agents that inhibit the PD-1 receptor in advanced cancer population

investigated in respective trials. Severe immune-related adverse events (irAEs) were infrequent and typically manageable with dose interruption and use of immunosuppressive treatment or other supportive therapy as clinically indicated; discontinuations due to irAEs were rare.
Patients have been treated with single agent spartalizumab across different regimens (400 mg Q4W [n=427], 300 mg Q3W [n=59] and 1- 10 mg/kg Q2W or Q4w [n=76]) and various advanced solid tumors types (i.e. mainly non- small cell lung cancer (NSCLC), melanoma, triple negative breast cancer (TNBC), anaplastic thyroid carcinoma (ATC), neuroendocrine tumors (NET) and nasopharyngeal carcinoma).
The most common AEs (>10%), all grades, regardless of relationship with study treatment included fatigue (26.7%), decreased appetite (23.7%), anaemia (23.5%), dyspnea (22.4%), nausea (21.2%), pyrexia (20.6%), cough (20.3%), constipation and diarrhea (18.0% each), vomiting (15.8%), asthenia (14.8%), back pain and abdominal pain (12.3% each), pruritus (11.4%). weight decreased (11.2%), AST increased (10.7%), oedema peripheral (10.3%) and rash (10.0%).
Most common AEs (>3%), all grades, suspected to be drug related included fatigue (13.3%), decreased appetite and pruritus (7.1% each), hypothyroidism (6.8%), diarrhea (6.6%), nausea and rash (6.0%), asthenia (5.5%), pyrexia (5.2%), anaemia (4.8%), AST increased (4.6%), ALT increased (4.1%), arthralgia (3.4%), pneumonitis (3.2%) and rash maculo-papular (3.0%).
Most common SAEs (>1%), all grades, regardless of relationship with study treatment were dyspnoea (4.8%), pneumonia (3.6%), abdominal pain (2.8%), pleural effusion (2.7%), pyrexia (2.7%), sepsis and pneumonitis (2.1% each), hypercalcaemia (2.0%), anaemia (each 1.6%), back pain and respiratory failure (1.4% each), cellulitis, vomiting and hyponatraemia (1.2% each), fatigue, diarrhoea, cardiac arrest, spinal cord compression and pneumonia aspiration (1.1%)
AEs of special interest (AESI) for spartalizumab include endocrinopathies, colitis, skin reactions, hepatitis, nephritis, pneumonitis and other irAEs, and infusion reaction.

Capmatinib
As of the cut-off date of 28-Sep-2020, more than 800 participants with solid tumors have been treated with capmatinib as a single agent, and 720 participants have received capmatinib in combination with other therapies. The recommended Phase II dose (RP2D) for capmatinib as a single agent has been determined to be 400 mg BID. The most frequent AEs suspected to be related to capmatinib of any grade reported in the [CINC280A2201] study, which remains as the reference study for the safety profile of INC280 monotherapy, were oedema peripheral (42.9%), nausea (34.3%), vomiting (18.7%), blood creatinine increased (18.4%), fatigue (13.7%), decreased appetite (12.6%) and diarrhea (12.4%), and the majority were Grade 1/2. The Grade 3/4 AEs suspected to be related to capmatinib in the [CINC280A2201] study included oedema peripheral (7.6%), alanine aminotransferase increased (5.5%), lipase increased (5.2%), amylase increased (3.0%), fatigue (2.7%), aspartate aminotransferase increased (2.5%), vomiting (1.9%), nausea (1.6%), decreased appetite (0.8%), constipation (0.5%), and diarrhea (0.3%).

Combination of spartalizumab and capmatinib
The study CINC280X2108 has assessed the combination of spartalizumab and capmatinib in 59 patients treated for a HCC. Fifty-eight patients, [98,3%] experienced AEs of any grade, regardless of causality. The most common AEs were peripherial oedema (31 patients, [52.5%]), nausea (24 patients, [40.7%]), pyrexia (21 patients [35.6%]) decreased appetite (20 patients [33.9%]), diarrhoea (18 patients [30.5%]), asthenia (17 patients [28.8%]), hypoalbuminemia (16 patients [27.1%]) , increased aspartate aminotransferase, increased blood bilirubin and vomiting (each in 15 patients [25.4%]), increased alanine aminotransferase (14 patients [23.7%]), pruritus and fatigue (13 patients [22%]) ascites and increased blood creatinine (each in 12 patients [20.3%]), abdominal pain (11 patients [18.6%]), rash (10 patients [16.9%]). The majority of AEs were Grade 1/2. Fifty-two patients (88%) experienced

AEs of any grade, suspected to be related to study treatment. The most frequent AEs suspected to be related to study treatment were nausea and peripherial oedema (each in 18 patients [30.5%]), vomiting (14 patients [23.7%]), decreased appetite and diarrhoea (each in 12 patients [20.3%]), asthenia and pyrexia (each in 11 patients [18.6%]), increased alanine aminotransferase, fatigue and pruritus (each in 10 patients [16.9%]), increased aspartate aminotransferase (9 patients [15.2%]), increased blood creatinine and rash (each in 8 patients [13.6%]. The majority of AEs were Grade 1/2. Forty-five patients (76,3%) experienced Grade 3/4 AEs regardless of causality. Thirty-two patients (54.2%) had Grade 3/4 AEs suspected to be related to study treatment: asthenia and increased lipase (each in 6 patients [10.2%]), increased aspartate aminotransferase (4 patients [6.8%]), increased alanine aminotransferase, increased amylase, cellulitis, diarrhoea, nausea, neutropenia, decreased platelet count (each in 2 patients, [3.4%]), abscess, acute myocardial infarction, anaemia, unstable angina, increased blood bilirubin, decreased blood corticotrophin, cardiac arrest, chronic kidney disease, decreased appetite, dehydration, fatigue, hyperlipasaemia, hypertransaminasaemia, hypotension, immune mediated hepatitis, lichen planus, liver injury, lymphocyte count decreased, peripherial oedema, pain, pyrexia, rash, maculo-papular rash, skin ulcer, stomatitis, systemic inflammatory response syndrome (each in 1 patient, [1.7%]).
Another trial (CINC280J12201) has evaluated the combination of spartalizumab and capmatinib in first line treatment of patients with lung cancer. An increased risk of hepatotoxicity was observed in this study that lead Novartis to edict new recommendation for inclusion criteria, follow-up of hepatotoxicity and dose adaptation for capmatinib and spartalizumab. This new safety rules are applied in the present protocol.

3 OBJECTIVES

3.1 Primary objective

To evaluate the tumor response to the regimen at 6 months after inclusion

3.2 Secondary objectives

- To evaluate the safety of the regimen during the first and second cycles of administration (up to day 42 (D42))
- To evaluate the safety and tolerability of the regimen during the whole course of treatment for all kind of toxicities and up to 2 years for immunotherapy-related toxicity
- To characterize the tumor response to the regimen (duration, time to response)
- To estimate the progression free survival, up to 2 years after inclusion
- To estimate the overall survival, up to 2 years after inclusion
- According to the results of interim analysis: to evaluate tolerance and efficacy of spartalizumab monotherapy in patient with non-amplified MET tumor

3.3 *Objective of any potential ancillary study*

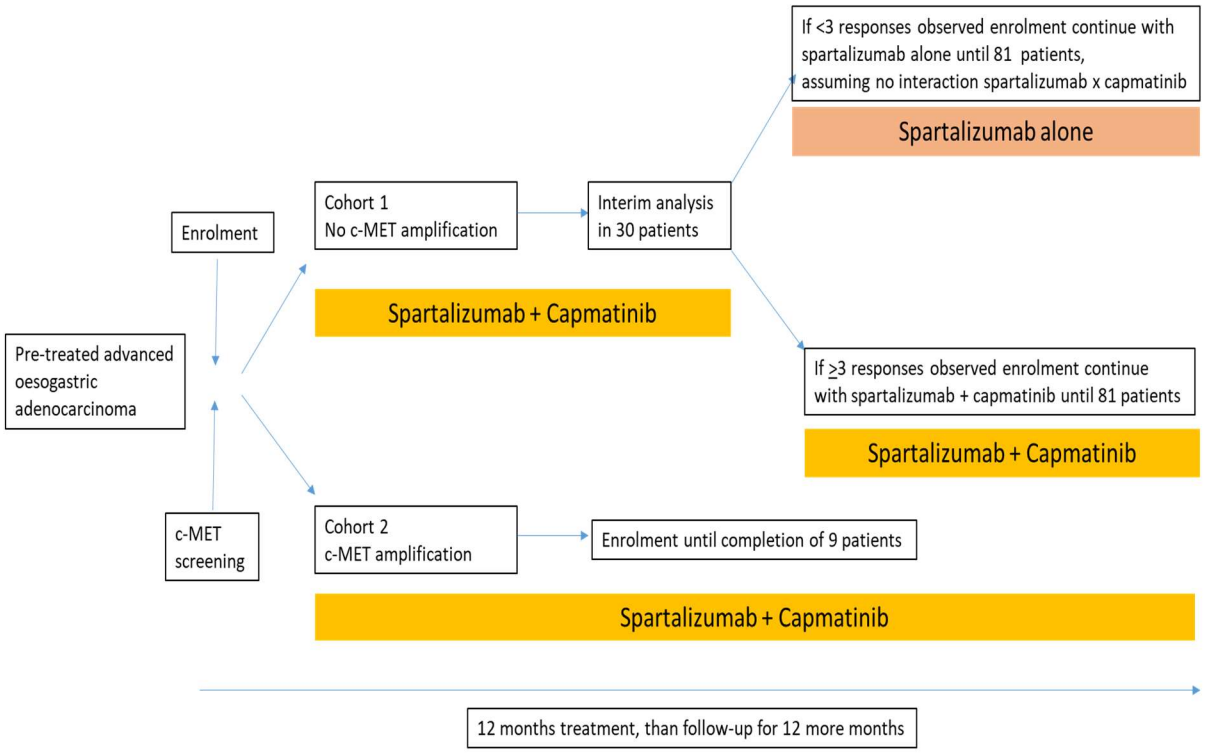
- To evaluate pharmacokinetics of capmatinib according to the presence of a gastrectomy and of a concurrent treatment with a proton pump inhibitor
- To evaluate the tumor response in specific subgroups:
 a) According to the residual level of capmatinib at Cycle 2 Day1 (C2D1)
 b) According to MET amplification level in FISH on the archival tumor sample
 c) According to the baseline and C2D1 neutrophil count and circulating HGF level

4 STUDY DESIGN

The design incudes an interim analysis after the inclusion of 30 patients. The advantage of the TOP design is to handle pending responses. Thus, the go/no-go efficacy rules are presented in following table.

Patients treated	Observed responses	Pending patients	Action
30	≤3	≥12	Suspend inclusion
	≤2	≤ 11	Conclude to futility of combination, continue with spartalizumab monotherapy
	3	≤ 11	Go if ESS < 23.03*
	≥ 4	≤ 26	Go
81	≤ 17	0	Conclude to insufficient efficacy
	≥ 18	0	Conclude to efficacy

It means that if 3 responses is observed and 12 patients or more are pending, one should wait for new responses before be able to decide if we conclude to futility or if we continue the trial. Thus, in summary when only 11 patients remains pending if we observed 3 or more responses the trial continue with spartalizumab + capmatinib, if less than 3 responses is observed (<3) the trials is stopped for futility.



4.1 Study endpoints

4.1.1 Primary endpoint

Primary endpoint: Overall response rate (ORR) defined as the proportion of patients with at least one objective tumor response (complete or partial) according RECIST v1.1 criteria, within 6 months (8 treatment cycles) after inclusion. Response will be evaluated by thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT-scan without injection if contraindication) CT-scan every 9 weeks, with independent centralized reading. Patients who discontinue the trial without tumor evaluation will be consider with no response in intent to treat analysis.

4.1.2 Secondary endpoints

- Unacceptable toxicity within the first and second treatment cycle (occurrence of the event between D1 to D42 included), defined using the NCI-CTCAE v5 criteria, as follows:
- Adverse event which is considered a toxicity ≥ grade 3 at least possibly related to the study treatment.
AND - Adverse event ≥ grade 3 which is unrelated to disease, disease progression, intercurrent illness, or concomitant medications
AND - Any of the following events:
- Any non-hematological toxicity ≥ grade 3 (except for nausea, vomiting, fatigue)
- Recurring grade 2 pneumonitis
- Myocarditis grade ≥2
- Autoimmune hemolytic anemia, hemolytic uremic syndrome, or acquired hemophilia grade ≥3
- Guillain-Barre, severe peripheral or autonomic neuropathy, or transverse myelitis
- Encephalitis or aseptic meningitis
- Laboratory abnormality ≥ grade 3 lasting >7 consecutive days (except for Nephritis (Grade 3 and 4: Creatinine >3x ULN), for combined elevations of AST or ALT and Total Bilirubin (see

details in section 7.1.2 «Criteria for dose reduction / interruption») and for hyperglycaemia and changes in serum electrolytes/enzymes without clinical impact)

- Hematological toxicities defined as: Febrile neutropenia (absolute neutrophil count [ANC] <1.0 x109/L and fever ≥38.5°C) and/or documented infection with ANC <1.0 x 109/L, grade 3 neutropenia lasting >7 consecutive days, grade 4 neutropenia, grade 4 thrombocytopenia or bleeding requiring a platelet transfusion
- Adverse event requiring permanent treatment discontinuation more than 21 days
- Any other study drug related toxicity considered significant enough to be qualified as unacceptable toxicity in the opinion of the investigators after discussion with the sponsor.

Unacceptable toxicity during the whole treatment course (occurrence of the event between D1 to treatment discontinuation), defined using the NCI-CTCAE v5 criteria as above (see below).

All adverse events during the whole treatment course, graded according to the NCI-CTCAE v5 criteria before each cycle.

Duration of overall response (DOR), defined as the time between the first occurrence of tumor objective response, partial or complete (as defined in the primary endpoint above, using RECIST 1.1) and the first radiological progression, with response assessment every 9 weeks, up to 24 months.

Time to response (TTR) defined as the time between inclusion and the first occurrence of tumor objective response (complete or partial, as defined in the primary endpoint above, according to RECIST 1.1) or the end of the study, with response assessment every 9 weeks, up to 24 months.

Progression-free survival up to 24 months after inclusion, defined as the time between inclusion and the date of the first radiological progression (according to RECIST 1.1), death (any cause), or last follow-up (max=24 months), whichever occurs first.

Overall survival (OS) up to 24 months after inclusion, defined as the time between inclusion and death (any cause) or last follow-up (max=24 months), whichever occurs first. Patients alive will be censored at date of last record.

Exploratory endpoints

Following pharmacokinetics parameters of capmatinib in patients after gastrectomy will be determined using non-compartmental analysis: maximum plasma concentration (Cmax), maximum plasma concentration time (Tmax), area under the plasma concentration time curve (AUC), clearance (Cl), mean residence time (MRT), and distribution volume (Vd/F).

Pre-defined subgroups analyses: ORR, as defined above in the primary endpoint, and PFS will be assessed according to residual level of capmatinib at day 1 of Cycle 2 (C2D1), baseline MET amplification level in FISH, baseline and C2D1 neutrophil count and circulating HGF level.

4.2 Description of research methodology

4.2.1 Design of the study

The study will be multicenter single-arm adaptive phase II trial.

Patients will be receiving the investigational combination regimen until progression, patient's refusal or unacceptable toxicity, and for a maximum of 12 months (Capmatinib 400 mg BID and 16 spartalizumab cycles of 3 weeks). The primary efficacy endpoint will be assessed at 6

months after treatment initiation (see next section below for detailed definition). Toxicity will be monitored sequentially during the trial allowing a toxicity stopping rule in case of high probability of unacceptable toxicity risk [Ivanova-Clin. Invest-2015].

Associated translational researches

Pharmacokinetics of capmatinib

The solubility of capmatinib is poor (BCS class II compound) and pH-dependent. Capmatinib absorption has a 37.5% decrease in Cmax and a 25.2% decrease in AUC inf with proton pump inhibitor (PPI) in healthy subjects. The pharmacokinetics in patients with partial or total gastrectomy has never been assessed.

Pharmacokinetic profiling will be conducted on the first 20 patients included: 10 patients with total gastrectomy and 10 patients with partial gastrectomy or no gastrectomy treated with PPI in order to assess the impact of gastrectomy and drug-drug interaction with PPI.

The pharmacokinetics of capmatinib will be investigated during phase II study, at cycle 2 day 1 (steady state). Following PK parameters of capmatinib will be determined using noncompartmental analysis (WinNonlin Pharsight Corporation: maximum plasma concentration (Cmax), maximum plasma concentration time (Tmax), area under the plasma concentration time curve (AUC), clearance (Cl), mean residence time (MRT), and distribution volume (Vd/F).

A second pharmacokinetics study for trough and peak plasma levels will be conducted on all patients (90) included in this study. The concentrations of capmatinib will be investigated at cycle 2 day 1 for 70 patients and at cycle 3 day 1 for all patients.

Blood sampling schedule

Pharmacokinetic profiles

Blood sampling for this study will be taken according to the schedule provided in the following table:

<table>
<tr><td>Visit</td><td colspan="2">Time point</td><td>Sample type</td></tr>
<tr><td rowspan="5">Cycle 2 Day 1</td><td colspan="2">Prior to doses of capmatinib</td><td>1 blood sample *</td></tr>
<tr><td>0.5</td><td rowspan="4">Hours after doses of capmatinib</td><td>1 blood sample *</td></tr>
<tr><td>1</td><td>1 blood sample *</td></tr>
<tr><td>2</td><td>1 blood sample *</td></tr>
<tr><td>4</td><td>1 blood sample *</td></tr>
</table>

Trough and peak plasma levels

A second pharmacokinetics study will be performed on all patients (90) included in this study at C2D1 and C3D1.

Visit	Time point	Sample type
Cycle 2 Day 1	Prior to doses of capmatinib	1 blood sample *
	2 hours after capmatinib intake	1 blood sample *

Cycle 3 Day 1	Prior to doses of capmatinib	1 blood sample *
	2 hours after capmatinib intake	1 blood sample *

* Patients will be alerted not to take capmatinib in the morning before the sampling. On those days intake will occur at the hospital after the sampling.

Blood samples of 5.0 mL will be collected into heparinized tubes before the morning intake of capmatinib and before perfusion of spartalizumab. Immediately after collection, tubes will be inverted several times and kept at approximately 4 °C until centrifugation. The tubes will be centrifuged for 10 min at 1500×g at 4 °C within 60 min of collection to separate plasma. The plasma will be separated into 2 aliquots in polypropylene screw-cap tubes and placed at -80°C until analysis.

All samples will be labeled with patient identification, study identification, sample number, and actual date and time at which the sample was collected.

All blood samples will be shipped at the end of the study to Pr. S. Mourah - Laboratoire de Pharmacologie Biologique, Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75475 Paris Cedex 10. 0142494325 / 0142499336

420 blood collections in 5.0 mL heparinized tubes

Pharmacokinetic profiles Pharmacokinetics plasma assays : 20 patients; 5 pharmacokinetics per patient (100 plasma samples)
Trough and peak concentrations of capmatinib (320 plasma samples): 70 patients C2D1 90 patients C3D1

Moreover, ORR and PFS will be analyzed according to mean trough plasma concentrations and mean peak plasma concentrations of capmatinib over the follow-up.

MET expression and amplification study

A previous study has shown that MET inhibitors have a direct action in MET driven tumors (independent of the immunomodulatory action of MET inhibitor). ORR and PFS will be analyzed according to baseline expression of *MET* amplification level in FISH on archival diagnosis tumor sample.

The *MET* amplification will be determined previous the enrollment in each participating center. The patients will be enrolled in cohort 1 if the tumor present < 6 *MET* gene copies and in cohort 2 if the tumor present ≥ 6 *MET* gene copies.
Both cohorts will be pooled and analyzed for the primary endpoint to evaluate different threshold of *MET* gene copies number.

Ancillary studies of PD-L1, MMR/MSI and EBV expression

The determination of PD-L1 expression, MMR/MSI status and EBV status will be routinely performed on the different investigational site.

Local tumor phenotyping data at investigational site will be collected to allow pooled analysis without to have to perform supplementary sample processing.

- Contradictory findings have been reported about the predictive value of PD-L1 level of expression for efficacy of immune checkpoint inhibitors in gastric adenocarcinoma. No data have been reported for spartalizumab. The Combined Positive Score (CPS) will be assessed on archival diagnosis tumor sample.

- Consistent data suggest that Mismatch Repair deficiency (dMMR) is a strong predictor of efficacy of immune checkpoint inhibitors in gastric and colorectal adenocarcinoma. dMMR will be assessed by IHC of MMR protein and microsatellite status in PCR analysis on archival diagnosis tumor sample. Extracted DNA may be further analyzed with NGS.

- EBV status has been reported as predictive factor for immune checkpoint inhibitors. In situ hybridization will be performed to determine EBV tumor status on archival diagnosis tumor sample.

ORR and PFS will be analyzed according to these candidate predictive factors: PD-L1 expression, MMR and EBV status.

If the determination of these status were not performed on investigational site, an archival tumor bloc will be collected at the end of the study for each patient and stored in the Centre de Ressource Biologique of Saint Louis hospital (Pr Philippe Bertheau / Jihene Benlagha) in order to allow planned ancillary studies. The IHC (PDL-1 and MMR) and FISH (EBV) studies will be performed by the anatomo-pathologic team of Saint Louis hospital (Pr P Bertheau). The MSI status determination by PCR will be performed in the Molecular Oncology Unit of Saint Louis hospital, Paris (Pr J Lehmann-Che).

Predictive value of neutrophil count and circulating Hepatocyte Growth Factor (HGF) level

It has been suggested that high serum levels of the MET ligand HGF correlated with increasing neutrophil counts and poor responses to checkpoint blockade therapies. We will explore baseline neutrophil count and circulating HGF level and also evolution of both parameters after 3 weeks of treatment with the combination of capmatinib and spartalizumab.

ORR and PFS will be analyzed according to baseline neutrophil count and circulating HGF and to evolution of both parameters after one month of treatment.

Blood samples of 5.0 mL will be collected into dry tubes with separator (*Heparin plasma is not recommended for use in HGF immunoassay)* before the beginning of treatment with capmatinib at inclusion and at C2D1,

The dosage of HGF will be performed using a human HGF Quantikine ELISA kit (RnD) at laboratory of pharmacogenomic of Saint Louis hospital (Pr S Mourah).

4.2.2 Number of participating sites

This is a multicentric French National study
Number of centers: 10 clinical centers of 7 public hospitals or institute located in France

- **Recruitment centres**

  - Saint Louis Hospital, APHP (Paris): Gastroenterology and Digestive Oncology department, CLIPP and CIC
  - Centre Léon Bérard (Lyon): Medical Oncology, CLIPP
  - Centre Georges Francois Leclerc (Dijon): Medical Oncology, CLIPP and Unité de phase précoce

- Gustave Roussy (Villejuif): Digestive Oncology, CLIPP
- Institut universitaire du cancer de Toulouse (Toulouse): Medical Oncology, CLIPP
- Hôpital Haut Levêque , (Bordeaux) : Hepato-Gastroenterology and Unité de recherche clinique
- Centre Hospitalier Régional Universitaire Jean Minjoz de Besançon : Medical Oncology

4.2.3 Identification of participants

The participants in this research will be identified as follows:
Site number. (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

5 IMPLEMENTATION OF THE STUDY

Before any examination or intervention related to the study may be carried out, the investigator must obtain the *freely given, informed and written consent of the participant, or of his/her legal representative* where applicable.

Individuals liable to participate in studies stipulated in line 1° of article L. 1121-1 of the *Code de la Santé Publique* (French Public Health Code) benefit from a preliminary medical examination adapted to the study.

5.1 Screening visit

The screening visit takes place 1 month maximum before the Inclusion visit, during a consultation or an hospitalization of the usual medical follow-up of patients with investigator of gastroenterology or oncology departments.

Whose consent must be obtained	Who informs the individuals and collects their consent	At what point the individuals are informed	At what point the consent is obtained
The individual participating in the study	*The principal investigator or collaborating physician declared and trained in the study: gastroenterologist and oncologist*	*Screening visit*	*After a reflection period of minimum 1 hour during the screening visit*

The procedure for informing participants and obtaining their consent should be described in detail in the section on: Ethical and legal considerations.

During this visit, the investigator will:

- verify the eligibility criteria,
- interview the patient and record:
    - patient demographics information, patient medical history and tumor characteristics
    - histories of intercurrent disease and current treatments,
- perform a physical examination (ECOG Performance status, weight, height, blood pressure, neurological examination)
- inform the patient about the protocol, and collect the free and informed written consent of the patient after reflection period. For collection of subject's consent, see Chapter 15.1.
- **Once the consent will be signed by the patient and investigator the "Patient Screening Form" will be registered by investigator by connecting into the eCRF web site (CleanWeb). The patient identification number will be allocated.**
- arrange the following evaluation and laboratory tests:

    - Determination of tumor MET amplification by FISH on an archived tumor sample. If MET amplification determination has already been performed as part of the care, it does not need to be repeated during the screening for patient inclusion.

    - Check the biologic examination according to inclusion criteria:
        - hemoglobin, polynuclear neutrophil, leucocyte, lymphocyte, platelet, sodium, potassium, creatinine clearance, calcium, magnesemia, lipase, Amylase, AST, ALT, GGT, glycemia, alkaline phosphatase, bilirubin, CRP, TSH, albumin, troponin, urinary dipstick, HIV serology, C hepatitis status, B hepatitis status (may be performed 12 months before enrolment, in case of B hepatitis viral B DNA should be checked before enrolment), CEA, CA 19-9, Coagulation (Prothrombin Time (PT) and partial thromboplastin time (PTT)).
    - Electrocardiogram
    - Radiological evaluation may have been performed a maximun of 21 days before treatment start: thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT-scan not injected if contraindication)
    - Collecting the biologic data of a previous NGS (MSI, mutation profile, mutation load if available)

The treatment will be started at inclusion visit.

5.2 Inclusion and subsequent visits: Baseline (Day 1 of cycle 1) to Month 12 (D1 of Cycle 16)

Inclusion and starting treatment

This visit takes place at Day 1 of cycle 1.
At this visit, investigator will:

- Review eligibility criteria
- Review the results of the following evaluation and laboratory tests:
    - Determination of tumor MET amplification by FISH on an archived tumor sample
    - The following test should be repeated if they were performed more than 2 weeks before inclusion: hemoglobin, polynuclear neutrophil, leucocyte, lymphocyte, platelet, sodium, potassium, creatinine clearance, calcium, magnesemia, lipase, Amylase, AST, ALT, GGT, glycemia, alkaline phosphatase, bilirubin, CRP,
    - TSH, albumin, troponin, urinary dipstick, HIV serology, C hepatitis status, B hepatitis status (may be performed 12 months before enrolment, in case of B

hepatitis viral B DNA should be checked before enrolment), CEA, CA 19-9 Coagulation (Prothrombin Time (PT) and partial thromboplastin time (PTT)).
    - Electrocardiogram
    - Radiological evaluation: thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT-scan not injected if contraindication), baseline images for disease evaluation must have measurable target tumors according to RECIST v1.1 (see inclusion criteria).

- Perform a physical examination (ECOG Performance status, weight, height, blood pressure, neurological examination)
- Perform a *Pregnancy test (urinary or blood)* if applicable
- **When the patient meets all eligibility requirements, investigator will insure the inclusion by registration of the "Patient Inclusion Form" on eCRF web site (CleanWeb).** A patient will be allocated to one of two cohorts constituted:
    - Cohort 1 to enrol patients with no MET amplification.
    - Cohort 2 to enrol patient with MET amplification
- Perform blood samples for ancillary studies (HGF), see Chapter 4.2.1. Blood samples will be sent to Saint Louis at the end of the study.
- Assure the prescription of study treatment by using eCRF
- Provide the first treatment and patient card to patient. All patients will receive treatment by Capmatinib 400 mg mg-BID + Spartalizumab-300 mg-Q3W for a maximum of 12 months or until progression, patient's refusal or unacceptable toxicity.
- A patient diary will be given to the patient during the treatment period. It contains practical information to help them take their treatment at home and will allow them to keep track of their capmatinib treatment. Patients should be instructed to bring the patient diary and all treatment packs, including empty packs and unused treatments, with them to each visit to allow assessment of trial compliance. The investigator will review the subject's diary at each subject's hospital visit. At that time, a new diary will be given to the subject if necessary. All subject diaries should be stored with the medical file of the subject for reconciliation with the trial drug accountability.

Days 8 and 15 of Cycle 1:

Toxicities will be assessed by clinical evaluation (ECOG Performance status, weight, blood pressure, neurological examination) and blood tests (hemoglobin, polynuclear neutrophil, leucocyte, lymphocyte, platelet, sodium, potassium, creatinine, calcium, magnesemia, lipase, Amylase, AST, ALT, GGT, glycemia, alkaline phosphatase, bilirubin, troponin, urinary dipstick, Coagulation (Prothrombin Time (PT) and partial thromboplastin time (PTT)) during the first cycle at days 8 and15

Day 1 Cycle 2 to D1 Cycle 16:

- Before each cycle, every 3 weeks*+/- 3 days*:
    - Complete clinical evaluation: ECOG Performance status, weight, blood pressure, neurological examination
    - Laboratory assessments: hemoglobin, polynuclear neutrophil, leucocyte, lymphocyte, platelet, sodium, potassium, creatinine, calcium, magnesemia, lipase, Amylase, glycemia,TSH, albumin, troponin, CRP urinary dipstick, Coagulation (Prothrombin Time (PT) and partial thromboplastin time (PTT)).
    - ALT, AST GGT, alkaline phosphatase and bilirubin should to be performed every two weeks during the first 3 months and then every 3 weeks at D1 of each cycle until the end of the treatment

- Electrocardiogram
- Pregnancy test (urinary or blood)
- At D1 of cycle 2 and cycle 3: blood samples for ancillary studies (pharmacokinetic cycle 2 and 3, HGF cycle 2) see Chapter 4.2.1
- Toxicities: evaluated by NCI-CTC 5.0 classification, adverse events
- Compliance
- Dispensation of treatments. Spartalizumab should be administered on Day 1 of each cycle after all assessments have been completed, and may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Treatment administration out of the 3-day window must be reported as a protocol deviation.

- Efficacy assessments every 9 weeks:
  - Radiological evaluation: thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT-scan not injected if contraindication)
  - ACE, CA 19-9

5.3 Follow-up visits

During the second part of the study (Follow up: between Month 12 and Month 24) the following assessment will be performed:

After the end of the treatment at M12

Within 30 days after treatment stop:

- Complete clinical evaluation: ECOG Performance status, weight, neurological examination
- Laboratory assessments: hemoglobin, polynuclear neutrophil, leucocyte, lymphocyte, platelet, sodium, potassium, creatinine, calcium, magnesemia, lipase, AST, ALT, GGT, glycemia, alkaline phosphatase, bilirubin, TSH, albumin, troponin, CRP urinary dipstick, Coagulation (Prothrombin Time (PT) and partial thromboplastin time (PTT)).
- Toxicities: evaluated by NCI-CTC V5 classification

Every 9 weeks to collect follow-up data until Months 24:

- Radiological evaluation: thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT-scan not injected if contraindication) until progression
- Tumor biomarkers: CEA and CA 19-9 until progression
- Further line treatments will be recorded
- Late toxicities of immunotherapy (notably hepatitis, pancreatic, nephrology, colitis, thyroiditis) evaluated by NCI-CTC V5 classification

After early termination of treatment

Within 30 days after treatment stop and subsequently at approximately 30-day intervals, until resolution or stabilization of an adverse event:

- Complete clinical evaluation: ECOG Performance status, weight, neurological examination
- Clinical laboratory assessments: hemoglobin, polynuclear neutrophil, leucocyte, lymphocyte, platelet, sodium, potassium, creatinine, calcium, magnesemia, lipase, amylase, AST, ALT, GGT, glycemia, alkaline phosphatase, bilirubin, TSH, albumin, troponin, CRP urinary dipstick, Coagulation (Prothrombin Time (PT) and partial thromboplastin time (PTT)).

- Toxicities: evaluated by NCI-CTC V5 classification

Every 9 weeks (if treatment stopped without radiological progression):
- Complete clinical evaluation: ECOG Performance status, weight, neurological examination
- Radiological evaluation: thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT-scan not injected if contraindication) until progression
- Tumor biomarkers: CEA and CA 19-9 until progression
- Late toxicities of immunotherapy (notably hepatitis, pancreatic, nephrology, colitis, thyroiditis) evaluated by NCI-CTC V5 classification
- Further line treatments will be recorded

If treatment stopped for radiological progression:
- Patients will be followed-up according to investigator's decision until death with a minimum follow-up every 3 months for 24 months.
- Late toxicities of immunotherapy (notably hepatitis, pancreatic, nephrology, colitis, thyroiditis) evaluated by NCI-CTC V5 classification will be recorded
- Further line treatments will be recorded
- State at least follow-up alive or deceded

Patients whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week for 30 days, and subsequently at approximately 30-day intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.
If an AE is suspected to be immune-related the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed.

5.4 End of study visit: Month 24

The end of study visit will be done at month 24. Late toxicities: evaluated by NCI-CTC V5 classification, date of tumor progression and state at the last follow-up will be collected.

5.5 Expected length of participation and description of the chronology and duration of the study.

In accordance with the Declaration of Helsinki a trial subject has the right to withdraw from the study at any time and for any reason. Patients will receive treatment for a maximum duration of 12 months (16 cycles) or until unacceptable toxicity, progression or patient's refusal.

If the patient stopped the treatment because of intolerance, he/she should be under medical supervision as long as deemed appropriate by the treating physician. If the patient discontinued due to an adverse event, the event will be followed until resolution or stabilization.

The patients that have received at least one dose of spartalizumab or capmatinib will have a follow-up until a maximum of 24 months after the end of the treatment.

Duration of enrolment period	18
The length of participation for participants, of which:	25
Maximum period between screening and enrolment	1 month
• Treatment duration:	12 months

- Duration of follow-up period: 12 months

Total study duration: 43 months

5.6 Table summarising the chronology of the study

Actions	***Screening visit:*** *Between D-14 and D-1 of inclusion visit*	***Baseline/ inclusion visit:*** *D1 of Cycle 1*	*D 8 and D15 of Cycle 1*	*21 +/- 3 days Cycle 1 to Cycle 16*	*63 +/- 6 Days Cycle 1 to Cycle 16*	***End of the treatment (month 12)***	***Follow-up visits: Every 9 weeks (month 12 to 24)***	***After Early termination of treatment***	***End of study (month 24)***
Information	X								
collect the free and Informed written consent	X								
Verification of inclusion and exclusion criteria	X	X							
History	X								
*Clinical examination**	X	X	X	X	X	X		X	X
Electrocardiogram	X			X	X				X
Determination of tumor MET amplification by FISH on an archived tumor sample	X								
*Test 1**	X	X	X	X	X	X		X	X
*Test 2**	X								
Test 3	X				X		X	X	
Pregnancy test (urinary or blood)		X		X					
*Radiological evaluation**	X	X			X		X	X	X
*Ancillary biologic studies **		X		X					
Dispensation of treatments		X		X	X				
Compliance		X		X	X			X	X
Adverse events			X	X	X	X	X	X	X

Physical examination: blood pressure, weight, ECOG performance status

Test 1: hemoglobin, polynuclear neutrophil, leucocyte, lymphocyte, platelet, sodium, potassium, creatinine, calcium, magnesemia, lipase, amylase, AST, ALT, GGT, glycemia, alkaline phosphatase, bilirubin, TSH, albumin, troponin, CRP, urinary dipstick, Coagulation (Prothrombin Time (PT) and partial thromboplastin time (PTT)) :

- **At baseline/ inclusion visit** those test should be repeated if they were performed more than 2 weeks before inclusion. At the *end of the treatment at M12* those test should be done *within 30 days after treatment stop*
- **At D8 and D15 of Cycle 1** the following items are not done: TSH, albumin and CRP.
- **During the first 3 months** ALT, AST GGT, alkaline phosphatase and bilirubin should to be performed every two weeks (The liver function tests will be assessed in city laboratory or during scheduled visits to the hospital)

Test 2: HIV serology, C hepatitis status, B hepatitis status may be performed 12 months before enrolment. In case of B hepatitis, viral DNA
Test 3: CEA, CA 19-9
Radiological evaluation*: baseline may have been performed 21 days before treatment start
Ancillary biologic studies:
1) Pharmacokinetic of capmatinib: residual level of capmatinib at day 1 of Cycle 2 (C2D1) and Cycle 3 (C3D1) collected before the morning intake of capmatinib and before perfusion of spartalizumab.
2) Baseline and C2D1 circulating HGF level.

After Early termination of treatment: for details see section 5.3 Follow-up visits

5.7 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatments	None	Capmatinib + spartalizumab 1 ambulatory hospitalization every 3 weeks during 12 months
Visits	Every 3 weeks	Baseline (inclusion) visit and Days 8 and 15 of Cycle 1
Blood samples	Every 3 weeks	<u>For pharmacokinetic</u> At C2D1 : for the first 20 patients 5 samples of 5ml and for 70 patients 2 samples of 5ml At C3D1 : for all patients : 2 samples of 5ml <u>For HGF</u> At baseline (inclusion visit) and C2D1:for all patients 1 samples of 5 ml - Blood tests during the first cycle at days 8 and15
Biological assessment	<u>At inclusion visit:</u> *Pregnancy test (urinary or blood),* HIV	At screening visit: determination of tumor MET amplification by FISH

	serology, C hepatitis status, B hepatitis status Every 3 weeks: hemoglobin, polynuclear neutrophil, leucocyte, platelet, glycemia, sodium, potassium, creatinine clearance, calcium, magnesemia, lipase, AST, ALT, GGT, alkaline phosphatase, bilirubin, CRP,TSH, albumin, troponin, urinary dipstick, Coagulation (Prothrombin Time (PT) and partial thromboplastin time (PTT)). Every 9 weeks: CEA, CA 19-9	
Medical procedure	ECG Every 3 weeks during treatment visit	
Imaging	Scanner or MRI every 9 weeksl	Centralized imaging assessment

5.8 Biological samples collection

The serum samples and the tumor sample (only if the tumor phenotyping was not routinely performed at local site) collected if necessary for the purpose of ancillary studies will be stored in a biological sample collection.

During the study the serum collection will be stored at -80°C in the laboratory of Pharmacology of Saint Louis hospital under the supervision of Pr Samia Mourah. The tumor DNA will be stored in the Molecular Oncology department of Saint Louis Hospital in the supervision of Pr Lehman-Che, The tumor sample will be store in the Centre de Ressource Biologique of Saint Louis hospital under the supervision of Pr Philippe Bertheau and Ms Jihene Belhaga (see table below).

At the end of the study, the samples will be kept. For the storage duration see table below.

At the end of the study, the samples may be used for further analysis not described in the initial protocol but which may be useful for investigation in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form.

If the samples are kept at the end of the study, the sample collection will be declared to the ministry of research (Article L. 1243-3 of the *Code de la Santé Publique* [French Public Health Code]).

Type of sample	Quantity	Storage location (name and entity)	Supervisor of the sample collection (name and entity)	Purpose of the sample collection	Storage duration	End use/Future

Tumor sample (only if the the tumor phenotyping was not routinely performed at local site)	1 tumor block by patient	Hôpital Saint Louis, APHP	Pr Bertheau, Anatomo-pathology department and CRB Ms Benlagha	Determination of PD-L1 expression, MMR/MSI status and EBV status	5 years	Kept for future research of predictive factor of efficacy of immunotherapy
Tumor DNA (only if MSI was not performed at local site)	1 sample by patient	Hôpital Saint Louis, APHP	Pr Lehman-Che, Molecular Oncology department	Determination of MSI status	5 years	Idem
Serum sample	<u>For pharmacokinetic</u> At C2D1: for the first 20 patients 5 samples of 5ml and for 70 patients 2 samples of 5ml At C3D1: for all patients : 2 samples of 5ml <u>For HGF</u> At baseline and C2D1:for all patients 1 samples of 5 ml	Hôpital Saint Louis, APHP	Pr Mourah, Pharmacology department	HGF level, capmatinib pharmacokinetics	5 years	Idem

6 ELIGIBILITY CRITERIA

6.1 Inclusion criteria

- Histologically or cytologically documented locally advanced or metastatic oesogastric adenocarcinoma.
- Unresectable tumor.
- Patients must have received at least one prior systemic chemotherapy based on platinium salt and fluoropyrimidine with documented progression during or after chemotherapy.
- Patients must have received trastuzumab in case of HER2 positive tumor (HER2 +++ or HER2++ and FISH or SISH+)
- Determination of tumor MET amplification by FISH available
- ECOG Performance Status ≤ 1.
- Measurable tumoral disease according to RECIST 1.1 criteria.
- Patients must be willing and able to swallow and retain oral medication.
- Age ≥18 years.

- Women of childbearing potential and males who are sexually active must agree to follow instructions for method(s) of contraception for the duration of study treatments with Capmatinib and Spartalizumab until 7 days after the last dose of Capmatinib and 150 days after the last dose of Spartalizumab
- Consent to participate in the trial after information
- Affiliated to a social security system

6.2 Exclusion criteria

- Previous treatment with immunotherapy or MET inhibitor
- Impossibility to take oral medication
- Persistent toxicities related to prior treatment of grade greater than 1, except for alopecia any grade and grade 2 neuropathy related to previous treatment with platinium salt.
- Presence or history of another malignant disease that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
- Use of any live vaccines within 4 weeks of initiation of study treatment.
- History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs).
- History or current interstitial lung disease or non-infectious pneumonitis
- Active autoimmune disease or a documented history of autoimmune disease (Patients with vitiligo, controlled type I diabetes mellitus on stable insulin dose, residual autoimmune-related hypothyroidism only requiring hormone replacement or psoriasis not requiring systemic treatment are permitted).
- Allogenic bone marrow or solid organ transplant
- Uncontrolled active infection
- Human Immunodeficiency Virus (HIV) infection
- Untreated active Hepatitis B infection (HBsAg positive) (Patients with active hepatitis B (HBsAg positive) may be enrolled provided viral load (HBV DNA) at screening is <100 UI/mL. Patients may receive antiviral treatment with lamivudine, tenofovir, entecavir, or other antiviral agents before the initiation of study treatment to suppress viral replication).
- Untreated active hepatitis C (HCV RNA positive) (patients that achieved a sustained virological response after antiviral treatment and show absence of detectable HCV RNA ≥6 months after cessation of antiviral treatment are eligible)
- Untreated or symptomatic central nervous system (CNS) lesion. However, patients are eligible if: a) all known CNS lesions have been treated with radiotherapy or surgery and b) patient remained without evidence of CNS disease progression ≥4 weeks after treatment and c) patients must be off corticosteroid therapy for ≥2 weeks
- Clinically significant, uncontrolled heart diseases.
- Recent acute coronary syndrome or unstable ischemic heart disease
- Congestive heart failure ≥ Class III or IV as defined by New York Heart Association
- Long QT syndrome (> 480 ms in women and 470 ms in men), family history of idiopathic sudden death or congenital long QT syndrome.
- Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 150 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.
- Surgery less than 4 weeks
- Radiotherapy less than 2 weeks
- Pregnancy or breastfeeding or women of child-bearing potential, unless they are using highly effective methods of contraception.

- Sexually active males unless they use a condom during intercourse while taking capmatinib and for 7 days after stopping treatment and should not father a child in this period.
- Participants receiving treatment with strong inducers of CYP3A and could not be discontinued ≥ 1 week prior to the start of treatment.
- Systemic chronic steroid therapy (>10 mg/day prednisone or equivalent) or any immunosuppressive therapy 7 days prior to planned date of first dose of study treatment.
- Patient having out of range laboratory values defined as:
  - Total bilirubin ≥ 1.5 x Upper Limit of Normal (ULN) - Alkaline phosphatase (ALP) ≥5 x ULN
  - Alanine aminotransferase (ALT) > 3 x ULN
  - Aspartate aminotransferase (AST) > 3 x ULN
  - Coagulation: Prothrombin Time (PT) > 4 seconds more than the ULN or International Normalized Ratio (INR) >1.7
  - Absolute neutrophil count (ANC) <1.5 x 10^9/L
  - Platelet count <75 x 10^9/L
  - Hemoglobin <9 g/dL
  - Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) <45 mL/min
  - Serum lipase >2 ULN
  - Cardiac troponin I (cTnI) elevation >2 x ULN
  - Potassium, Magnesium, Phosphorus, total Calcium (corrected for serum albumin) outside of normal limits (patients may be enrolled if corrected to within normal limits with supplements during screening)
- Patients under legal protection
- Participation to another interventional study whith treatment

6.3 Recruitment procedure

The recruitment of patient will came directly from gastroenterology or oncology departments of the participating center but also from network of the participating center that referred chemorefractory patients

	Number of participants
Total number of participants to be included	90
Number of centres	7
Enrolment period (months)	18
Number of participants/centre	12,8
Number of participants/centre/month	**0,7**

6.4 Termination rules

6.4.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible
- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

The investigator must:
- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 12 months following the premature discontinuation of treatment. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

6.4.2 Temporary interruption of the study treatment

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events) or toxicity reasons as describe on clinical management guidelines of adverse events (point 7.1.1 and 7.1.2). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The patients will start the next cycle after the interruption.
In the cohort 1, if capmatanib is definitively stopped the treatment with spartalizumab should continue but if the treatment with spartalizumab is definitively stopped than the capmatinib should be stopped also.
In the cohort 2, if capmatinib or spartalizumab is interrupted, the other treatment should continue

The reason for interruption should be documented in the patient's study record.
In case of treatment interruption not related to study therapy, the duration of the treatment should be prolong of the same duration of the treatment interruption or until definitive termination of the study treatment.

6.4.3 Permanent termination of the study treatment

- For each participant, a maximum of two consecutive dose level reductions of capmatinib is allowed after which the participant must be discontinued.

- A participant must discontinue treatment with capmatinib if, after treatment is resumed at the lowest allowed dose (200 mg b.i.d.), the toxicity recurs with the same or worse severity despite use of maximal preventive measures as per the institution guidelines for toxicity prevention and management.
- If the treatment with capmatinib is withheld for more than 21 consecutive days (counting from the first day when a dose was interrupted), then study treatment should be permanently discontinued.

A subject must be permanently discontinued the treatment for any of the following reasons:

- Progression disease
- Any toxicity inducting permanently discontinuation of treatment as describe on Mandatory dose modification / discontinuation requirements and recommended clinical management guidelines for adverse events (see section 7.1.1 and 7.1.2)
- Any life-threatening adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy)
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to <= Grade 1 within 12 weeks
- Inability to reduce the dose of steroids (for the management of irAE) to 10 mg/day or less of prednisone or equivalent within 12 weeks
- Any severe or Grade 3 recurring treatment-related adverse reaction after 3 weeks
- Active uncontrolled autoimmune disease.
- Clinically significant, uncontrolled heart diseases.
- Pregnancy or breastfeeding.
- The subject withdraws consent.
- Intercurrent illness that prevents further administration of treatment
- Investigator’s decision to withdraw the subject
- The subject is lost to follow-up.

If all target lesions require palliative radiotherapy

Participants will continue to be monitored for the study according the timetable visits of protocol except in case of the subject withdraws consent and lost to follow-up.

6.4.4 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant’s best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).

- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.4.5 Follow-up of participants following premature withdrawal from the study

Disease progression or death will be assessed according the timetable for the collection of data as stipulated by the protocol at the time participation in the study is discontinue, if the participant agrees.
If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 6.4.1

6.4.6 Procedures for replacing participants

A patient will be replace if he did not receive any study treatment

6.4.7 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board, according the results of the toxicity monitoring:

Toxicity monitoring
We will perform close toxicity monitoring during the trial based on all available information. We plan scheduled safety analyses every 5 completed observations in cohort 1 + 2 (after 5 patients have either completed the two first treatment cycles (C1+C2) or experienced an unacceptable toxicity during C1 or C2) for the 20 first patients than approximately every 10 observations.

Safety stopping rules

Number of included patients	**5**	**10**	**15**	**20**	**30**	**40**	**50**	**60**	**70**	**80**	**90**
Stop the trial if unacceptable toxicity in ≥n patients	3	5	7	9	12	15	18	21	24	27	30

Definition of unacceptable toxicity
Unacceptable toxicity defined using the NCI-CTCAE v5 criteria, as follows:

- Adverse event which is considered a toxicity ≥ grade 3 at least possibly related to the study treatment.
AND
- Adverse event ≥ grade 3 which is unrelated to disease, disease progression, intercurrent illness, or concomitant medications
AND
- Any of the following events:
    - Any non-hematological toxicity ≥ grade 3 (except for grade 3 nausea, vomiting, fatigue)
    - Recurring grade 2 pneumonitis
    - Myocarditis grade ≥2
    - Autoimmune hemolytic anemia, hemolytic uremic syndrome, or acquired hemophilia grade ≥3
    - Guillain-Barre, severe peripheral or autonomic neuropathy, or transverse myelitis
    - Encephalitis or aseptic meningitis
    - Laboratory abnormality ≥grade 3 lasting >7 consecutive days (except for Nephritis (Grade 3 and 4: Creatinine >3x ULN), for combined elevations of AST or ALT and Total Bilirubin (see details in section 7.1.2 «Criteria for dose reduction / interruption») and for hyperglycaemia and changes in serum electrolytes/enzymes without clinical impact)
    - Hematological toxicities defined as: Febrile neutropenia (absolute neutrophil count [ANC] <1.0 x109/L and fever ≥38.5°C) and/or documented infection with ANC <1.0 x 109/L, grade 3 neutropenia lasting >7 consecutive days, grade 4 neutropenia, grade 4 thrombocytopenia or bleeding requiring a platelet transfusion
    - Adverse event requiring treatment discontinuation more than 21 days
    - Any other study drug related toxicity considered significant enough to be qualified as unacceptable toxicity in the opinion of the investigators after discussion with the sponsor.

- The steering committee will have a meeting every 3 months (meeting on site (or TC for those who cannot join) and receive every month a report on enrolments, evaluations and side effects from the sponsor) and the DSMB will have a meeting every 6 months in order to analyse the safety data.

Efficacy interim analysis

An interim efficacy analysis will be performed in cohort 1 when the number of enrolled patients reaches 30. The rules for stopping or continuing the trial are specified in Table 1 of paragraph 12.1.

Similarly, AP-HP, as the sponsor, or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved**.**

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

In all cases in which a study is discontinued, the participants included in the study be monitored until the end of their participation, as set forth in the protocol. The patients enrolled in the study will receive the treatment for the 12 months even in case of early closure of the research.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

All patients will be treated with Capmatinib-400mg-BID + Spartalizumab-300mg-Q3W.

7.1 Description of the investigational medicinal product(s)

7.1.1 Spartalizumab

Spartalizumab is a humanized mAb which belongs to a class of agents known as immune-checkpoint inhibitors, specifically anti-PD-1. This class of compounds has demonstrated significant improvement in efficacy combined with a tolerable and manageable safety profile, supporting regulatory approvals in various indications.
The Spartalizumab will be administered on Day 1 of each cycle every 3 weeks at a dose of 300 mg (3 x 100 mg vials), administered via intravenous infusion over 30 minutes. The Spartalizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Treatment administration out of the 3-day window must be reported as a protocol deviation.
The treatment duration is fixed to 12 months.
If treatment was stopped temporarily due to adverse event, subjects should be placed back on study therapy within 3 weeks of the interruption.
Subjects will resume treatment at the next cycle.
The reason for interruption should be documented in the patient's study record.

Spartalizumab is presented as concentrate for solution for infusion in 4 mL vials containing 100 mg of spartalizumab. It shall be stored at 2-8°C.

Spartalizumab vials are provided free of charge by Novartis and then labelled, packaged for clinical trials and sent to the investigational sites by the Clinical Trial Department (DEC) of AGEPS.

Infusion must take place in a facility with appropriate resuscitation equipment available at the bedside and a physician readily available during the period of drug administration.
Patients should be closely observed for potential infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Signs and symptoms usually develop during or shortly after drug infusion and resolve completely within 24 hours of completion of infusion. Subjects do not need to be observed for any specific period of time after the infusion, but should be provided instructions to notify study personnel if symptoms of infusion reaction occur after any Spartalizumab infusion.

General dose modification instructions:
No changes in dose of Spartalizumab are allowed.
Overall, patients with AEs suspected to be related to Spartalizumab including those of potential immune-mediated etiology (irAE) may need to interrupt or permanently discontinue study treatment. In general, study treatment must be permanently discontinued in case of:

- Progression disease
- Any toxicity inducting permanently discontinuation of treatment as describe on Mandatory dose modification requirements and recommended clinical management guidelines for adverse events (see below)
- Any life-threatening adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy)
- Myocarditis grade ≥2 or cardiac event grade ≥3
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to <= Grade 1 within 12 weeks

- Inability to reduce the dose of steroids (for the management of irAE) to 10 mg/day or less of prednisone or equivalent within 12 weeks
- Any severe or Grade 3 recurring treatment-related adverse reaction after 3 weeks
- Active uncontrolled autoimmune disease.
- Clinically significant, uncontrolled heart diseases.
- If all target lesions require palliative radiotherapy

Dose Modification and management requirements for potential immune-mediated adverse events (irAEs)

Adverse events of special interest (AESI) include AEs of a potential immune-mediated etiology (irAE) that are associated with Spartalizumab treatment. Investigators must be vigilant and carefully identify AEs that may be suggestive of potential irAEs as their appearance may be sub-clinical and early diagnosis is critical for its adequate management and resolution. Collaboration with disease-specific subspecialties is encouraged; corticosteroids are the mainstay of treatment for most irAEs.
An irAE may be of low grade and self-limited, most frequently involving the GI tract (e.g. diarrhea/colitis), skin (e.g. rashes, pruritus), liver (e.g. immune mediated liver injury or liver laboratory alterations), lung (e.g. pneumonitis), kidneys (e.g. nephritis) and endocrine systems (e.g. hypothyroidism, hyperthyroidism, type I diabetes, hypophysitis including hypopituitarism and adrenal insufficiency). Other immune-mediated AEs may rarely include the nervous system (e.g. encephalitis, Guillain-Barre syndrome, myasthenia gravis), eye (e.g. uveitis, vision changes), musculo-skeletal system (e.g. myositis, arthritis), pancreas (e.g. pancreatitis), cardio-vascular system (e.g. vasculitis, myocarditis) or blood system (e.g. anemia, cytopenias), and severe skin reactions such as toxic epidermonecrolysis or Steven Johnson syndrome. Furthermore, complications in patients with bone marrow or solid organ transplant have been reported (e.g. organ rejection, severe graft-versus-host disease). However, nearly all organs can be affected by immune-mediated toxicities. irAEs often occur relatively early (mostly within weeks to 3 months after treatment initiation), however, may develop at any time during treatment (even after several months), and may also occur after the treatment discontinuation. Serological, immunological and histological assessments should be performed as deemed appropriate by the investigator, to verify the potential immune-related nature of the AE, and exclude a neoplastic, infectious or metabolic origin of the AE.
Severe grade or persistent lower grade irAEs typically require interrupting or permanently discontinuing treatment and administration of systemic steroids, and sometimes other immunosuppressive medications (i.e. tumor necrosis factor alpha (TNFa) antagonists, mycophenolate or tacrolimus, etc.). Early recognition and work-up of irAEs and initiation of treatment are critical to reduce the risk of complications, since the majority of irAEs are reversible with the use of steroids and other immune suppressants. Some events like endocrinopathies may require life-long hormonal replacement.
Tapering of steroids should not be too rapid (i.e. >4 weeks) to avoid recurrence or worsening of irAEs. The management of irAEs may further include initiation of antibiotics for prophylaxis against opportunistic infections.
Patients should be instructed to return to the study site as soon as possible (instead of waiting for their next scheduled visit) if they experience symptoms consistent with an irAE. Patients who experience a new or worsening irAE should be contacted and/or evaluated by the study site more frequently.
Investigators are encouraged to contact the Sponsor as needed to discuss cases that warrant separate discussion outside of the scope of the current instructions.

Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related diarrhea/colitis

Diarrhea/Colitis (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 (< 4 stools per day over baseline)	• May continue Spartalizumab treatment • Symptomatic treatment (loperamide, hydration, diet) • Monitor closely	
Grade 2 (4 to 6 stools per day over baseline)	• Consult with GI specialist • Stool evaluation, imaging and endoscopy as clinically indicated • Symptomatic treatment (loperamid, hydration, diet) • Commence steroids (0.5-1 mg/kg/d prednisone or IV equivalent) until recovery to Grade 1, particularly in case of persisting/worsening symptoms, ulcerations or bleeding seen on endoscopy, or blood in stool. If no improvement within few days, manage as per Grade 3. • Slowly taper steroids once symptoms improve to Grade 1 (i.e. over 4-6 weeks)	• Interrupt Spartalizumab until diarrhea/colitis recovers to Grade ≤1 or baseline
Grade 3 Diarrhea: Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care ADL; Grade 3 Colitis: Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	• Consider hospitalization; rule out bowel perforation and initiate IV hydration as needed • Consultation with GI specialist; consider endoscopy and biopsy • In addition to symptomatic treatment, initiate treatment with IV steroids (1 to 2 mg/kg/d of methylprednisolone or equivalent) • Consider antibiotics as appropriate • If no improvement in 2-3 days: consider initiating infliximab 5 mg/kg and continue steroids. (infliximab is contraindicated in patients with sepsis/perforation) • Slowly taper steroids once symptoms improve to Grade 1 (4 to 6 weeks) • If symptoms worsen during steroid reduction, re-escalate as needed followed by more prolonged taper and consider infliximab	• Interrupt Spartalizumab until diarrhea/colitis recovers to Grade ≤1 or baseline

Diarrhea/Colitis (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 4: Life-threatening consequences; urgent intervention indicated	Same as Grade 3	Permanently discontinue Spartalizumab

Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related liver laboratory alterations / immune mediated liver injury

Abnormal liver function tests		
Severity	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 2: AST or ALT >3x ULN to ≤ 5.0x ULN and/or bilirubin > 1.5x ULN to ≤ 3x ULN	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values • Rule-out alternative causes (e.g. concomitant medications, infection, disease progression) • Consider prednisone (0.5-1 mg/kg/d) if liver tests worsen and/or significant symptoms	• Interrupt Spartalizumab treatment until recovery to Grade ≤1 or baseline • Patients with baseline grade 2 AST/ALT value (>3.0-5.0 ULN) may continue Spartalizumab treatment
Grade 3: AST or ALT >5x ULN to ≤ 20x ULN ; or >5x ULN during more than 2 weeks and/or bilirubin >3x to10x ULN Grade 4: AST or ALT >20x ULN and/or bilirubin >10x ULN	• Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to baseline values • Consult with hepatologist; consider hospitalization and liver biopsy to establish etiology • Initiate treatment with steroids (prednisone 1-2 mg/kg/d or IV equivalent) • Add prophylactic antibiotics for opportunistic infections as appropriate • Once symptoms/liver tests improve to Grade ≤1, taper steroids over at least 4 weeks • If no improvement or steroid refractory after 3 days, consider oral mycophenolate as per local treatment guidance • Infliximab is not recommended due to its hepatotoxicity potential	• Permanently discontinue Spartalizumab • Patients with baseline grade 2 AST/ALT value (>3.0-5.0 ULN) will discontinue spartalizumab treatment if value increased to grade 3 with increase >=2x baseline, or to grade 4

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Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related skin events

Skin Events (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 (e.g. rash, pruritus)	• Continue Spartalizumab treatment • Initiate prophylactic and symptomatic treatment • Consider mild/moderate potency topical steroids or urea containing creams in combination with oral antipruritics • Reassess after 2 weeks	
Grade 2 (e.g. rash, pruritus)	• Consider dose interruption • Consider initiating systemic steroids (e.g. oral prednisolone 0.5-1mg/kg daily). • In addition, treat with topical emollients, oral antihistamines, and medium/high-potency topical steroids • If symptoms persist or recur consider skin biopsy	• In case of bullous dermatitis, acute generalized exanthematous pustulosis or DRESS, interrupt spartalizumab until recovery to Grade ≤1 or baseline
Grade 3 (e.g. rash, pruritus) Other severe cutaneous adverse reactions Bullous dermatitis	• Consult with dermatologist and consider skin biopsy. • Initiate systemic steroids (1 mg/kg/d prednisone or IV equivalent); consider increasing if no improvement • High-potency topical steroids • Topical emollients, oral antihistamines as indicated • Consider GABA agonists or aprepitant in case of severe pruritus	• Interrupt Spartalizumab until recovery to Grade ≤1 or baseline For patients with severe cutaneous adverse reaction or bullous dermatitis, risk/benefit before resuming treatment should be carefully considered.
Grade 4: Life-threatening	• Urgent dermatologic consultation and additional measures as per local guidelines	Permanently discontinue Spartalizumab
Stevens-Johnson syndrome, toxic epidermal necrolysis	• Hospitalization and urgent dermatology consultation • Institute supportive care immediately as per institutional guidelines	Permanently discontinue Spartalizumab

Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related nephritis

Nephritis (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Creatinine >ULN to ≤1.5x ULN; >1 to ≤1.5x baseline	• Continue Spartalizumab treatment • Monitor creatinine weekly • Rule-out other causes (e.g. fluids, medications, IV contrast) • Promote hydration and consider cessation of nephrotoxic drugs	
Grade 2: Creatinine >1.5 to ≤3x ULN; >1.5 to ≤3x baseline	• Monitor creatinine every 2 to 3 days and consult with nephrologist • Rule-out other causes (e.g. fluids, medications, IV contrast) • Initiate 0.5 to 1 mg/kg/d prednisone or equivalents if other causes are ruled-out • If worsening or no improvement: 1 to 2 mg/kg/d prednisone or equivalents • Promote hydration and cessation of nephrotoxic drugs • Consider renal biopsy	• Interrupt Spartalizumab until serum creatinine recovers to ≤ Grade 1 or baseline.
Grade 3 and 4: Creatinine >3x ULN	• Monitor creatinine every 1 to 2 days and consider hospitalization • Consult with nephrologist and consider renal biopsy • Start 1 to 2 mg/kg/d prednisone or equivalents • Once event improves to Grade ≤1, slowly taper steroids over at least 4-6 weeks	Permanently discontinue Spartalizumab

Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related pneumonitis

Pneumonitis (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1: Radiographic changes only- Asymptomatic	• interrupt Spartalizumab • Chest imaging/CT scan; repeat imaging in 3-4 weeks or as clinically indicated	Permanently discontinue Spartalizumab in case of interstitial lung disease/pneumonitis

Pneumonitis (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	• Monitor symptoms every 2-3 days; clinical evaluation and laboratory work-up for infection: pulse oximetry • Consultation with pulmonologist recommended	
Grade 2: Symptomatic-medical intervention indicated; limits instrumental ADLs	• Chest imaging/CT scan; repeat imaging in 3-4 weeks or as clinically indicated • Monitor symptoms daily, consider hospitalization • Clinical evaluation and laboratory work up for infection, pulse oximetry • Consult pulmonologist • Pulmonary function tests • Bronchoscopy with biopsy and/or BAL to rule out infection and/or disease progression/lung infiltration • Initiate steroids (1 to 2 mg/kg/d prednisone or equivalent) • Consider empirical antibiotics • If no improvement within 2-3 days, or worsening, treat as grade 3	Permanently discontinue Spartalizumab treatment in case of grade 2 pneumonitis Permanently discontinue Spartalizumab in case of interstitial lung disease
Grade 3: Severe symptoms; limits self-care ADLs; oxygen indicated Grade 4: Life- threatening respiratory compromise; urgent intervention required	• Same as Grade 2; in addition: • Hospitalization and pulmonary and infectious disease consultation • Methylprednisolone (1-2 mg/kg/d or equivalent) until symptoms improve to Grade ≤1, then slow taper over ≥4-6 weeks • If no improvement within 48 hours, consider infliximab and/or other immune-suppressive therapy, or IVIG as per local guidelines • Empiric antibiotics	Permanently discontinue Spartalizumab

Mandatory dose modification requirements and recommended clinical management guidelines for potential immune-related endocrine events

Endocrine events (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Asymptomatic, intervention not indicated (e.g. hyperthyroidism or hypothyroidism)	• Continue Spartalizumab treatment • If TSH <0.5x LLN, or TSH >2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated • Consider endocrinologist consult • If hypophysitis is suspected, consider pituitary gland imaging (MRIs with gadolinium and sellar cuts); evaluate hormone levels as clinically indicated • Repeat labs in 1 to 3 weeks/MRI in 1 month if laboratory abnormalities persist but normal lab/pituitary scan	
Symptomatic endocrinopathy (e.g., hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)	• Endocrinology consultation • Rule out infection/sepsis and other alternative causes with appropriate cultures/imaging • Evaluate hormone levels (e.g. ACTH, cortisol, FSH/FH, TSH, free T4, testosterone/estrogen), metabolic panel (e.g. Na, K, CO2, glucose), and imaging (e.g. brain MRI) as clinically indicated • Initiate hormone replacement therapy as appropriate • Consider steroids (methylprednisolone 1 to 2 mg/kg/d or equivalent) in case of severe hypophysitis or thyrotoxicosis • Consider beta-blocker in case of severe hyper-thyroidism • Consider hospitalization (e.g. in case of severe adrenal insufficiency/crisis), fluid replacement, and	• Interrupt Spartalizumab until recovery to mild or no symptoms, and controlled with hormone replacement therapy • Hypothyroidism may be managed with replacement therapy without treatment interruption (unless life-threatening) Permanently discontinue Spartalizumab for life-threatening endocrinopathies (i.e. hyperthyroidism, adrenal insufficiency, hypophysitis) or recurring severe/life-threatening events not controlled by hormone replacement therapy.

Endocrine events (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
	other supportive measures as clinically indicated	
Autoimmune diabetes (Grade 3 or symptomatic hyperglycemia) Autoimmune diabetes (Grade 4 hyperglycemia or life-threatening complications)	• Initiate anti-glycemic therapy (i.e. insulin) as medically indicated and monitor glucose levels regularly until metabolic control is achieved • Evaluate for ketoacidosis as medically indicated • Consultation with endocrinologist • Consider hospitalization (e.g. in case of ketoacidosis)	• Interrupt Spartalizumab until recovery to grade 1 or baseline • Permanently discontinue Spartalizumab in case of recurring severe/life-threatening events not controlled by anti-glycemic therapy.

Mandatory dose modification requirements and recommended clinical management guidelines for "other" potential immune-related AEs of special interest

Other (e.g. Autoimmune neuropathy, demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis-like syndrome, encephalitis, non-infectious myocarditis, pericarditis, pancreatitis, grade 3 fatigue with rapid onset in absence of disease progression, etc.)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Mild (Grade 1)	• Provide symptomatic treatment evaluate/monitor adequately • Continue Spartalizumab treatment	
Moderate (Grade 2)	• Consider interruption of Spartalizumab until recovery to ≤ Grade 1 or baseline • Ensure adequate evaluation to confirm etiology or exclude other causes • Provide symptomatic treatment • Systemic corticosteroids may be indicated • Consider biopsy or additional tests for confirmation of diagnosis • A specialist should be consulted	
Severe (Grade 3)	• Initiate systemic corticosteroids (prednisone at a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate • Monitor closely and consult with a specialist	• Interrupt Spartalizumab until recovery to ≤ Grade 1 or baseline o May restart Spartalizumab treatment at the same dose and schedule taking into account the risks and benefits • Permanently discontinued Spartalizumab in case of recurrent Grade 3

Other (e.g. Autoimmune neuropathy, demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis-like syndrome, encephalitis, non-infectious myocarditis, pericarditis, pancreatitis, grade 3 fatigue with rapid onset in absence of disease progression, etc.)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 4	• Hospitalization and consult with specialist • Initiate systemic corticosteroids (prednisone a dose of 1-2 mg/kg/d or equivalent) and other therapies as appropriate	Permanently discontinue Spartalizumab
Encephalitis or aseptic meningitis	• Rule out infectious or other causes of moderate to severe neurologic deterioration, and consult with specialist. • If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents.	Permanently discontinue Spartalizumab
Guillain-Barre Severe peripheral or autonomic neuropathy, or transverse myelitis	• Hospitalization and consult with specialist	Permanently discontinue Spartalizumab.
Myasthenia gravis	• Consult with specialist • Consider pyridostigmine and systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d; other therapies as appropriate (e.g. IVIG) • Hospitalization in case of severe cases	Grade 2 • Interrupt Spartalizumab until recovery to ≤ Grade 1 or baseline Grade ≥3 • Permanently discontinue
Myocarditis grade ≥2 or cardiac event grade ≥3	• Initiate systemic corticosteroids (prednisone or equivalent) at a dose of 1-2 mg/kg/d • Consult with specialist; hospitalization as indicated	Permanently discontinue Spartalizumab.
Pancreatitis Amylase/lipase elevation	• Evaluate for pancreatitis (clinical assessment, abdominal imaging and/or MRCP as appropriate) • PDR001 may be continued in case of asymptomatic, isolated enzyme elevations without evidence for pancreatitis • Initiate steroids in case of ≥ grade 2 acute pancreatitis	Grade 2 acute pancreatitis • Interrupt Spartalizumab until recovery to ≤ Grade 1 or baseline Grade ≥3 acute pancreatitis: • Permanently discontinue
Autoimmune hemolytic anemia, hemolytic uremic syndrome, or acquired hemophilia grade ≥3	• Consult with specialist • Consider systemic corticosteroids and other therapies as appropriate (e.g. transfusion) per local institutional guidelines	Permanently discontinue Spartalizumab.

Other (e.g. Autoimmune neuropathy, demyelinating polyneuropathy, Guillain Barre, Myasthenia Gravis-like syndrome, encephalitis, non-infectious myocarditis, pericarditis, pancreatitis, grade 3 fatigue with rapid onset in absence of disease progression, etc.)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Ocular events	• Consult with ophthalmologist	• Grade 2: interrupt Spartalizumab until recovery to ≤ Grade 1 or baseline • Grade 3 and 4: permanently discontinue Spartalizumab

Mandatory dose modification requirements and recommended clinical management guidelines for infusion-related reactions

Infusion reaction (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs/pulse oximetry as medically indicated until patient is deemed medically stable • Consider slowing infusion rate until recovery of symptoms • May continue Spartalizumab	
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	• Stop infusion and keep line open • Additional medical therapy as per local institutional guidelines that may include : o IV fluids o Antihistamines o NSAIDS, acetaminophen o Narcotics o Oxygen and corticosteroids as indicated • Increase monitoring of vital signs/pulse oximetry as medically indicated until patient is deemed medically stable • If symptoms resolve, the infusion may be restarted at 50% of the original infusion rate • Pre-medicate patients approximately 1.5 hours prior to next infusion with: o Diphenhydramine (50 mg po or equivalent) o Acetaminophen (500-1000 mg po or equivalent) o Or as per local institutional guidelines	Spartalizumab should be permanently discontinued in case of recurring infusion reaction despite adequate premedication and prolonged infusion/slow infusion rate

Infusion reaction (NCI-CTCAE v5)		
Grade	**Recommended Adverse Event management guidelines**	**Mandatory Dose Modification requirements**
Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	• Stop Infusion • Additional medical therapy as per local institutional guidelines that may include: o IV fluids o Antihistamines o NSAIDS, acetaminophen o Narcotics o Oxygen o Corticosteroids o Epinephrine • Close monitoring of vital signs, pulse oximetry and ECG as medically indicated until the patient is deemed medically stable • Hospitalization as indicated	Permanently discontinue Spartalizumab

Guidance for corticosteroids tapering for management of immune-related AEs:
Consultation with disease-specific experts is recommended. Steroids should be tapered slowly and based on response/recovery of clinical symptoms. Consider complete tapering over a period of at least 4 weeks (sometime 6-8 weeks or longer) to present recurrent irAEs. Slower tapering or re-escalation of corticosteroids therapy may be needed if the adverse event is not showing improvement. Once corticosteroid tapering is achieved at a level of 10 mg of prednisone/day (or equivalent) or less, Spartalizumab can be restarted as indicated in the dose modification tables.

Follow-up for toxicities
Patients whose treatment is interrupted or permanently discontinued due to an irAE, AE or clinically significant laboratory value, must be followed-up at least once a week for 30 days, and subsequently at approximately 30-day intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary.
If an AE is suspected to be immune-related the relevant immunological assessments (e.g. rheumatoid factor, anti-DNA Ab, etc.) should be performed. All patients must be followed-up for AEs and SAEs for 150 days following the last dose of spartalizumab or 30 days after the last dose of the capmatinib, whichever is later. However, if the patient begins post treatment antineoplastic medication before the 150-Day safety visit the collection of new SAEs and AEs unrelated to study medication will stop and thereafter only suspected SAEs and suspected AEs will continue to be collected up to Day 150. If SAEs suspected to be related to study medication occur beyond Day 150, information should also be collected.

7.1.2 Capmatinib

The capmatinib is presented in bottles of 30 tablets, (3 strengths: 100 mg 150 mg and 200 mg). Bottles shall be stored at room temperature, below 25°C.

Capmatinib bottles are provided free of charge by Novartis. 150 mg tablets will be used solely for dose reduction. For full dose treatments, 200 mg tablets will be used preferentially however, 100 mg could be used alternatively depending on products availability.

The capmatinib bottles are labelled for clinical trials, packaged and sent to the investigational sites by the Clinical Trial Department (DEC) of AGEPS.
The initial posology is 400 mg b.i.d. everyday *per os*. The capmatinib may be delivered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Treatment administration out of the 3-day window must be reported as a protocol deviation.
The treatment duration is fixed to 12 months.

For capmatinib, a specific notice for the trial will be provided to subjects. It describes how to take the tablets: twice a day, same hour, during meal. This notice specifies to subject what to do if they missed a dose or if they vomited. It also specifies the particular administrations related to PK days (as described in 4.2.1).

If treatment was stopped temporarily due to adverse event, subjects should be placed back on study therapy within 3 weeks of the interruption.
Subjects will resume treatment at the next cycle.
The reason for interruption should be documented in the patient's study record.

Dose modifications
For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions, and/or reductions are either recommended or mandated in order to allow participants to continue the study treatment.
The following guidelines should be considered:
Dose reductions are allowed for capmatinib and should follow the dose reduction steps. For each participant, a maximum of two consecutive dose level reductions is allowed after which the participant must be discontinued. Dose reductions of capmatinib below 200 mg b.i.d. are not permitted. The lowest dose allowed, 200 mg b.i.d. in tablets is expected to be pharmacologically active, as the observed steady state plasma trough concentrations were above the concentration associated with full MET inhibition in xenograft mice models (IC90, 120 nM total concentration).
For participants who do not tolerate the protocol-specified dosing schedule, dose interruptions are permitted in order to allow participants to continue the study treatment. All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 5.0). Any changes must be recorded on the dosage administration eCRF page.
A participant must discontinue treatment with capmatinib if, after treatment is resumed at the lowest allowed dose (200 mg b.i.d.), the toxicity recurs with the same or worse severity despite use of maximal preventive measures as per the institution guidelines for toxicity prevention and management.
If the treatment with capmatinib is withheld for more than 21 consecutive days (counting from the first day when a dose was interrupted), then study treatment should be permanently discontinued. Under exceptional circumstance, when the investigator believes that continuing treatment may still derive clinical benefit for the participant, study treatment may be resumed. However, the investigator must discuss and receive approval from the sponsor prior to continuing study treatment and rationale should be captured in the source documents.
Dose re/escalation of study treatment to previous dose level is allowed only once, and if no AE leading to dose modification is observed after at least 1 cycle (3 weeks) of study treatment at the reduced dose.
If all target lesions require palliative radiotherapy, the patient shall discontinue the treatment with capmatinib.
Events not included in the study protocol or the reference guidance documents should be managed according to local practices.

Dose reduction steps for capmatinib

	Starting dose level 0	Dose level -1	Dose level -2
Capmatinib	400 mg b.i.d.	300 mg b.i.d.	200 mg b.i.d.
Note: dose reduction should be based on the worst toxicity demonstrated at the last dose.			

Criteria for dose reduction / interruption and re-initiation / permanent discontinuation of capmatinib treatment for adverse drug reactions

Worst toxicity CTCAE Grade[a] during a cycle of therapy	
No toxicity	Maintain dose level
HEMATOLOGICAL	
Neutrophil count decreased (ANC) Neutropenia	
Grade 1 (ANC < LLN - 1500/mm^3; < LLN - 1.5 x 10^9/L)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3; < 1.5 - 1.0 x 10^9/L)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3; < 1.0 - 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 500/mm^3; < 0.5 x 10^9/L)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level
Platelet count decreased (Thrombocytopenia)	
Grade 1 (PLT < LLN - 75,000/mm^3; < LLN - 75 x 10^9/L)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3; < 75 - 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3; < 50 - 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm^3; < 25 x 10^9/L)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
Febrile neutropenia (ANC < 1000/mm^3 (< 1.0 x 10^9/L), fever > 38.3°C)	Omit dose, then: If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level If resolved in > 7 days, permanently discontinue participant from capmatinib treatment
Hemoglobin decreased (Anemia)	
Grade 1 (Hemoglobin [Hgb] < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Maintain dose level
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 – 4.9 mmol/L; < 100 - 80 g/L)	Maintain dose level
Grade 3 (Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level

Grade 4 (Life-threatening consequences; urgent intervention indicated)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level If toxicity recurs, permanently discontinue participant from capmatinib treatment.
RENAL	
Serum creatinine	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at the same dose level.
Grade 3 (> 3.0 - 6.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at ↓ 1 dose level.
Grade 4 (> 6.0 x ULN)	Permanently discontinue participant from capmatinib treatment
HEPATIC	
Isolated Total Bilirubin elevation*	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN)	Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to ≤ grade 1 Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, maintain dose level. If resolved in > 7 days, ↓1 dose level
Grade 3 (> 3.0 - 10.0 x ULN)	Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to ≤ grade 1 Omit dose until resolved to ≤ grade 1, then If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days, permanently discontinue participant from capmatinib treatment
Grade 4 (> 10.0 x ULN)	Mandatory: Permanently discontinue participant from capmatinib treatment
Isolated AST or ALT elevation	
Grade 1 (> ULN - 3 x ULN)	Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN)	Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to ≤ grade 1 Omit dose until resolved to ≤ grade 1
Grade 3 (> 5.0 - 20.0 x ULN)	Monitor hepatic laboratory tests more frequently (every 2-3 days) until returned to ≤ grade 1 Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if grade 2 elevation at baseline) then If resolved in ≤ 7 days, then resume treatment at the same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Grade 4 (> 20.0 x ULN)	Mandatory: Permanently discontinue participant from capmatinib treatment
Combined elevations of AST or ALT and Total Bilirubin [b,c,d]	
For participants with normal baseline ALT and AST and total bilirubin value: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN without evidence of cholestasis or hemolysis OR	Mandatory: Permanently discontinue participant from capmatinib treatment

For participants with elevated baseline AST or ALT or total bilirubin value: [AST or ALT > 3 x baseline] OR [AST or ALT > 8.0 x ULN], whichever is lower, combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN] without evidence of cholestasis or hemolysis	
METABOLIC	
Amylase and/or lipase elevation	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN; > 2.0 - 5.0 x ULN and asymptomatic)	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms; > 5.0 x ULN and asymptomatic)	Omit the dose until resolved to ≤ grade 2, then If resolved in ≤ 14 days, resume treatment at the same dose level If resolved in > 14 days, then ↓ 1 dose level
Grade 4 (> 5.0 x ULN with signs or symptoms)	Permanently discontinue participant from capmatinib treatment
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTcF 450-480 ms)	Maintain dose level
Grade 2 (QTcF 481-500 ms)	Maintain dose level
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (QTcF ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue participant from capmatinib treatment
GASTROINTESTINAL	
Pancreatitis	
Grade 2	Maintain dose level
Grade ≥ 3	Mandatory: Permanently discontinue participant from capmatinib treatment
Diarrhea**	
Grade 1 (despite appropriate anti-diarrheal medication)	Maintain dose level
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Grade 3 or 4 (despite appropriate anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Vomiting	
Grade 1 (despite appropriate anti-emetics)	Maintain dose level
Grade 2 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then maintain dose level.

	If vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Nausea	
Grade 1 or 2 (despite appropriate anti-emetics)	Maintain dose level
Grade 3 (despite appropriate anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash/photosensitivity* **	
Grade 1	Maintain dose level
Grade 2	Maintain dose level
Grade 3, despite skin toxicity therapy	Omit dose until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, then resume treatment at ↓ 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then permanently discontinue participant from capmatinib treatment
Grade 4, despite skin toxicity therapy	Omit dose and permanently discontinue participant from capmatinib treatment
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	
ILD /Pneumonitis	
Monitor participants for pulmonary symptoms indicative of ILD/pneumonitis. In addition, withhold capmatinib for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for ILD/pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage.	
Grade 1	Interrupt capmatinib during diagnostic workup for ILD/Pneumonitis. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib may be restarted at the same dose. If it recurs after resumption of study drug, permanently discontinue capmatinib.
Grade 2	Mandatory: Interrupt capmatinib dose during diagnostic workup for ILD until improvement to ≤ Grade 1. Exclude infections and other etiologies. In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue capmatinib. Only in the absence of a diagnosis of ILD/Pneumonitis, capmatinib may be restarted following these guidelines: · If resolves to ≤ Grade 1 in ≤ 7 days reduce study drug by 1 dose level · If fails to resolve to ≤ Grade 1 within 7 days or recur after resumption of study drug at decreased dose, permanently discontinue capmatinib

Grade 3 and Grade 4	Mandatory: Permanently discontinue capmatinib. Treat with IV steroids as clinically indicated. Oxygen therapy as indicated
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue/ Asthenia	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, resume treatment at same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Grade 4	Permanently discontinue capmatinib
Peripheral edema	
Grade 1 or 2	Maintain dose level.
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, reduce capmatinib ↓ 1 dose level and resume spartalizumab/placebo at same dose level. Consider conservative measures such as leg elevation, compression stockings and dietary salt modification as clinically indicated and treat per local/institutional guidelines.
Grade 4	Permanently discontinue study treatment. Intensify as per Grade 3 above and manage per local/institutional guidelines.
Other adverse events	
Grade 1 or 2	Maintain dose level, consider to initiate appropriate support medication. For any intolerable grade 2 (e.g. limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then then restart either at same dose or ↓ 1 dose level.
Grade 3	Omit dose until resolved to ≤ grade 1, then↓ 1 dose level
Grade 4	Permanently discontinue capmatinib
All dose modifications should be based on the worst preceding toxicity. [a] Common Toxicity Criteria for Adverse Events (CTCAE version 5.0). [b] "Combined" defined as: total bilirubin increase to the defined threshold concurrently with ALT/AST increase to the defined threshold [c] "Cholestasis" defined as: ALP elevation (> 2.0 x ULN and R value (ALT/ALP in x ULN) < 2.0) in participants without bone metastases, or elevation of ALP liver fraction in participants with bone metastases [d] If combined elevations of AST or ALT and total bilirubin do not meet the defined thresholds, please follow the instructions for isolated elevation of total bilirubin and isolated elevation of AST/ALT, and take a conservative action based on the degree of the elevations (e.g. discontinue treatment at the situation when omit dose is needed for one parameter and discontinue treatment is required for another parameter). After all elevations resolve to the defined thresholds that allow treatment re-initiation, re-start the treatment either at the same dose or at one dose lower if meeting a criterion for dose reduction	

* Note: If total bilirubin > 3.0 x ULN is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator. ** Note: antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea *** During the whole duration of treatment with capmatinib, the participant is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing and avoid sunbathing or using a solarium intensively).

Treatment interruption and treatment discontinuation
If the administration of capmatinib is temporarily interrupted for reasons other than toxicity, then treatment with capmatinib may be resumed at the same dose. If the treatment with capmatinib is withheld due to toxicity, the dose modification guidelines in Table 1-4 should be followed. An interruption for more than 21 days for toxicities reason mean a definitive interruption of capmatinib. In any case, scheduled visits and all assessments (including tumor assessments) should continue to be performed

7.2 Description of Additional medicinal product(s) (treatments required to conduct the study)

If a patient experiences an infusion reaction after Spartalizumab, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care, at the discretion of the treating physician.
Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status.

7.3 Description of traceability elements accompanying the investigational medicinal product(s)

The treatments will be delivered by the pharmacy of each participating center every 3 weeks upon presentation of a study specific prescription. Traceability of batch number and expiry date will be made by the pharmacist.
The specific notice, provided by the sponsor, for capmatinib allows collecting data on medication intake.

7.4 Authorised and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications

<u>Spartalizumab</u>

Permitted concomitant therapy
In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed.
- Medications to prevent or treat nausea or vomiting
- Anti-diarrheal medications (e.g. loperamide) for patients who develop diarrhea
- Pain medication to allow the patient to be as comfortable as possible
- Treatment with bisphosphonates or denosumab for pre-existing, painful bone/liver metastases, and limited-field palliative radiotherapy or surgery is permitted. Patients requiring initiation of such treatment during the course of the study must be evaluated for disease progression; radiotherapy like any concomitant medication must be listed on the CRF.

Spartalizumab should be held for ≥1 week prior to radiotherapy or surgery, and be resumed ≥2 weeks after radiation or surgery, provided the patient has recovered from radiation or surgery related toxicity. Caution is advised for radiation to fields that include lung tissue (potentially increased risk of pneumonitis).

- Immunosuppressive agents to treat suspected irAEs
- Hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents as per local or published guidelines; in case of anemia, thrombocytopenia or neutropenia, potential immune-mediated etiology should be ruled out
- Oxygen therapy and blood products or transfusions
- Inactivated vaccines
- The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications.

Permitted concomitant therapy requiring caution and/or action

Anticoagulation and anti-aggregation agents are permitted if the patients are already at stable doses for > 2 weeks at time of first dose and International Normalized Ratio (INR) should be monitored as clinically indicated per investigator's discretion. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor sample according to the institutional guidelines.

Prohibited concomitant therapy

During the course of the study, patients must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies) except those specified in the protocol, or any other therapies that may be active against cancer or modulate the immune responses. However, limited-field palliative radiotherapy may be allowed as concomitant therapy (see above). Caution is advised for radiation to fields that include lung tissue.

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed except for the treatment of infusion reaction, irAEs, and for prophylaxis against imaging contrast dye allergy, or replacement-dose steroids in the setting of adrenal insufficiency (providing this is ≤ 10 mg/day prednisone or equivalent), or transient exacerbations of other underlying diseases such as COPD requiring treatment. If systemic corticosteroids are required for the control of infusion reactions or irAEs, it must be tapered and be at non-immunosuppressive doses (≤10 mg/day of prednisone or equivalent) before the next administration of study treatment. If the dose of prednisone or equivalent cannot be reduced to less than or equal to 10 mg/day before the administration of next dose of study treatment then spartalizumab must be discontinued). Additionally, for adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed.

There are no prohibited therapies during the post-treatment follow-up period.

<u>Capmatinib</u>

Permitted concomitant therapy requiring caution and/or action

The following medications should be used with caution when concomitantly used with capmatinib treatment in this study:

- Coadministrating capmatinib with CYP3A inhibitor increased capmatinib AUC_{inf} by 42%. There was no change in capmatinib Cmax. Closely monitor patients for adverse reactions during coadministration of capmatinib with CYP3A inhibitors.

- Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that coadministration of capmatinib with the moderate CYP3A inducer efavirenz (600 mg once daily for 20 days) would result in a 44% decrease in capmatinib $AUC_{0\text{-}12h}$ and 34% decrease in C_{max} at steady-state compared to administration of capmatinib alone. Caution should be exercised during concomitant use of capmatinib with moderate CYP3A inducers. Use an alternative medication with no or minimal potential to induce CYP3A during coadministration with capmatinib.
- Capmatinib is a moderate CYP1A2 inhibitor. Coadministration of capmatinib increased sensitive CYP1A2 probe substrate (caffeine) AUC_{inf} by 134%. Avoid coadministration of capmatinib with CYP1A2 substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, decrease the CYP1A2 substrate dosage in accordance with the approved prescribing information.
- Coadministration of capmatinib increased P-gp substrate (digoxin) exposure (AUC_{inf} and C_{max} by 47% and 74%, respectively) and BCRP substrate (rosuvastatin) exposure (AUC_{inf} and C_{max} by 108% and 204%, respectively). Avoid coadministration of capmatinib with P-gp and BCRP substrates where minimal concentration changes may lead to serious adverse reactions. If coadministration is unavoidable, decrease the P-gp or BCRP substrate dosage in accordance with the approved prescribing information.
- Coadministration of capmatinib with proton pump inhibitor (rabeprazole) decreased capmatinib AUC_{inf} by 25% and C_{max} by 38%. Exercise caution during concomitant use of capmatinib with proton pump inhibitors.
- As an alternative to proton pump inhibitors, an H2-receptor antagonist or antacid can be taken. Capmatinib should be administered at least 3 hours before or 6 hours after an H2-receptor antagonist. Capmatinib should be administered at least 2 hours before or 2 hours after an antacid.

Capmatinib should not be administered for 48 hours prior to surgery and should be restarted 48 hours after the patient has resumed feeding and fully recovered from surgery.

Localized palliative radiotherapy for pre-existing, painful bone/liver metastases is permitted. If all target lesions require palliative radiotherapy, the patient shall discontinue the investigational treatments. If only part of the target lesions require palliative radiotherapy, the patient may continue to receive investigational treatments; target lesions under palliative treatment will be excluded from response assessment to the investigational treatments there on. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out. The study treatment must be interrupted on the days of radiotherapy and can be resumed the day after its completion. Caution is advised for radiation to fields that include lung tissue. After documented progression by RECIST 1.1, radiotherapy is allowed following the same dose adjustment guidance in case capmatinib is continued beyond PD.

Drugs to be used with caution during coadministration with capmatinib

Mechanism of Interaction	Drug Name
CYP3A inhibitor	ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak), indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat, indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, eltegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole, mibefradil, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, idelalisib, boceprevir, atazanavir/ritonavir, darunavir/ritonavir

Mechanism of Interaction	Drug Name
Moderate CYP3A inducer	bosentan, dabrafenib, efavirenz, etravirine, genistein, modafinil, nafcillin, tipranavir/ritonavir, lopinavir, telotristat, thioridazine
CYP1A2 substrate with NTI	theophylline, tizanidine
P-gp substrates	afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, atorvastatin, azithromycin, boceprevir, bosentan, carvedilol, caspofungin, ceritinib, citalopram, colchicine, cyclosporine, dabigatran, digoxin, docetaxel, doxepin, doxorubicin, eribulin, everolimus, fentanyl, fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, irbesartan, lacosamide, lapatinib, levetiracetam, linagliptin, linezolid, loperamide, losartan, maraviroc, mirabegron, moxifloxacin, nadolol, naloxegol, nateglinide, nevirapine, nintedanib, olodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, posaconazole, pravastatin, proguanil, quinidine, ranolazine, riociguat, risperidone, ritonavir, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voriconazole
BCRP substrates	atorvastatin daunorubicin, dolutegravir, doxorubicin, ethinyl estradiol, hematoporphyrin, imatinib, irinotecan, methotrexate, mitoxantrone, paritaprevir, pitavastatin, rosuvastatin, simvastatin, sofosbuvir, sulfasalazine, tenofovir, topotecan, venetoclax
Proton pump inhibitor	Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole
H_2-receptor antagonists	cimetidine, famotidine, nizatidine, ranitidine
Antacids	aluminum carbonate, aluminum hydroxide, calcium carbonate, calcium hydroxide, bismuth subsalicylate
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (https://drug-interactions.medicine.iu.edu/Main-Table.aspx), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies". This list may not be exhaustive and could be updated periodically. Please refer to the above mentioned databases. NTI: narrow therapeutic index	

Prohibited medication

Coadministration of capmatinib with strong CYP3A inducer (rifampicin) decreases capmatinib AUCinf by 67% and Cmax by 56%, which may decrease capmatinib anti-tumor activity. Therefore, concurrent use of strong CYP3A inducers are prohibited. Capmatinib prohibited medications are listed below.

Participants enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies while on treatment.

There are no prohibited therapies during the post-treatment follow-up period.

Mechanism of Interaction	Drug Name
Strong CYP3A inducer	carbamazepine, enzalutamide, lumacaftor, mitotane, phenobarbital, phenytoin, rifabutin, rifampicin, St. John's wort (*Hypericum perforatum*)

Mechanism of Interaction	Drug Name
Source: The list is adapted from the Novartis Institutes for Biomedical PK Sciences internal memorandum (v01, 2018): drug-drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (https://drug-interactions.medicine.iu.edu/Main-Table.aspx), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies" This list may not be exhaustive and could be updated periodically. Please refer to the above mentioned databases.	

7.5 Methods for monitoring compliance with the treatment

The capmatinib not taken by the patient will be counted at each cycle by the pharmacy of each participating center.

8 EFFICACY ASSESSMENT

8.1 Description of efficacy endpoints assessment parameters

Primary endpoint:

Overall response rate (ORR) defined as the proportion of patients with at least one objective tumor response (complete or partial) according RECIST v1.1 criteria, within 6 months (8 treatment cycles) after inclusion. Response will be evaluated by thoraco-abdomino-pelvic CT-scan (or abdominal MRI and thoracic CT-scan without injection if contraindication) CT-scan every 9 weeks, with independent centralized reading. Patients who discontinue the trial without tumor evaluation will be considered with no response in intent to treat analysis.

Secondary endpoints:

- Unacceptable toxicity within the first and second treatment cycle (occurrence of the event between D1 to D42 included), defined using the NCI-CTCAE v 4.0 criteria: and will be evaluated by:
• Complete clinical evaluation
• Laboratory assessments
• Electrocardiogram

-**Unacceptable toxicity during the whole treatment course** (occurrence of the event between D1 to treatment discontinuation), defined using the NCI-CTCAE v5 criteria as above (see below).

-**All adverse events during the whole treatment course**, graded according to the NCI-CTCAE v 4.0 criteria before each cycle.

-**Duration of overall response** (DOR), defined as the time between the first occurrence of tumor objective response, partial or complete (as defined in the primary endpoint above, using RECIST 1.1) and the first radiological progression, with response assessment every 9 weeks, up to 24 months.

-**Time to response** (TTR) defined as the time between inclusion and the first occurrence of tumor objective response (complete or partial, as defined in the primary endpoint above,

according to RECIST 1.1) or the end of the study, with response assessment every 9 weeks, up to 24 months.

-**Progression-free survival** up to 24 months after inclusion, defined as the time between inclusion and the date of the first radiological progression (according to RECIST 1.1), death (any cause), or last follow-up (max=24 months), whichever occurs first.

-**Overall survival (**OS) up to 24 months after inclusion, defined as the time between inclusion and death (any cause) or last follow-up (max=24 months), whichever occurs first. Patients alive will be censored at date of last record.

8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy data

The efficacy data will be recorded at each evaluation every 9 weeks. The result of the radiological examination will be send for centralized review by the radiologist of the department of Radiology of Saint Louis hospital to assess the primary endpoint (best response rate at 6 months).

The centralized review will be performed every 3 months in order to perform interim analysis and final analysis without delay.

9 SPECIFIC STUDY COMMITTEES

9.1 Steering Committee

- Committee members: Pr T. Aparicio (coordinator), Pr R. Guimbaud (PI, Toulouse), Pr F. Ghiringhelli (PI, Dijon), Dr L. Biard (biostatistician), N. Raked (URC Saint Louis), C. Kedzia (DRCI, sponsor)
- Roles: oversee the study notably safety data
- Operating procedures: meeting on site (or TC for those who cannot join) every 3 months and receive every month a report on enrolments, evaluations and side effects from the sponsor

9.2 *Scientific Committee*

- Committee members: Pr T. Aparicio (coordinator), Pr R. Guimbaud (PI, Toulouse), Pr F. Ghiringhelli (PI, Dijon), Dr L. Biard (biostatistician), Pr S. Mourah (Pharmacologist), Pr P. Bertheau (Pathologist), Pr J. Lehman-Che (Biologist)
- Roles: protocol writing,study oversee and eventually decide any modification
- Operating procedures: meeting every 6 months to oversee the study notably for recruitment, data collection (primary endpoint and samples collection for ancillary studies)

9.3 Endpoint Adjudication Committee

- Committee members: Pr T. Aparicio (coordinator), Pr E de Kerviller (radiologist) + 2 radiologist
- Roles: Radiological centralized reading for tumour response assessment
- Operating procedures: review of all radiological evaluation until tumor progression during the first 6 months. Meeting every 3 months.

10 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

10.1 Description of Safety endpoints assessment parameters

The safety endpoints are describe in 4.1.2.

10.2 Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints

Toxicities will be assessed by clinical evaluation and blood tests according NCI-CTC V5 classification during the first cycle at days 8, 15 and 22 (=D1 of cycle 2) and before each cycle, every 3 weeks.
A monitoring of toxicity will be performed every months in each participating center.
The Data Safety Monitoring Board will have sequential meeting to evaluate toxicities and SAE collected allowing a toxicity stopping rule in case of high probability of unacceptable toxicity risk [Ivanova-Clin. Invest-2015]. We plan scheduled safety analyses every 5 completed observations in cohort 1 + 2 (after 5 patients have either completed the two first treatment cycles (C1+C2) or experienced an unacceptable toxicity during C1 or C2) for the 20 first patients than approximately every 10 observations. At least the DSMB will have a meeting every 6 months to evaluate SAE.

10.3 Recording and reporting adverse events

10.3.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

An adverse event occurring in a study involving human participants when this event is related to the study or to the product being studied.

- **Adverse reaction to an investigational medicinal product**

Any untoward and unwanted reaction to an investigational medication regardless of the dose administered.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the participant enrolled in the study, requires hospitalisation or prolongs existing hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity, and in the case of a medication, regardless of the dose administered.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product whose nature, severity, frequency or outcome is inconsistent with the standard safety information described in the summary of the product characteristics, or in the investigator's brochure if the product is not authorised.

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for sponsors of clinical trials (ANSM):

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, modifications in the investigational medicinal product use, the

conduct of the clinical trial or the clinical trial documents, or a suspension, interruption or modification of the clinical trial or of similar trials.
For studies involving the first administration of a health product in healthy volunteers: any serious adverse reaction.
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction;
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial which have been notified to by the investigator to the sponsor, as well as potential follow-up reports;
c) any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety
Examples:

- a serious adverse event likely to be related to the trial's interventions and diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk for the trial participants such as a lack of efficacy of the investigational medicinal product used in the treatment of a life-threatening disease,
- significant safety results from a recently completed study on animal subjects (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted with the same investigational medicinal product in another country, for safety reasons
- an unexpected serious adverse reaction related to a non-investigational medicinal product required to conduct the trial, (e.g.: "challenge agents", rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, if they are relevant to the safety of the participants
e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a clinical trial carried out in a different country but relating to the same medication

10.3.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF).
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events using Common Terminology Criteria for Adverse Events [National Cancer Institute]

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal products.

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following 4 causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC causality categories (excerpt)

Causality term	Assessment criteria*
Certain to occur	· Event or laboratory test abnormality, with plausible time relationship to drug intake** · Cannot be explained by disease or other drugs

Causality term	Assessment criteria*
	· Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable/Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
**Or study procedures

10.3.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies the sponsor without delay on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the Code de la Santé Publique, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

10.3.2.2 Specific features of the protocol

10.3.2.2.1 Other events that require the investigator to notify without delay the sponsor

- Adverse events deemed "medically significant"

The following adverse event of grade 3-4 CTCAE:
- endocrinopathies, colitis, skin reactions, Immune mediated liver injury, nephritis, interstitial lung disease/pneumonitis, pancreatitis and other immune-related AEs (irAEs)
- infusion reactions,
- hepatotoxicity
- renal dysfunction,
- febrile neutropenia, anemia
- prolonged QTc
- peripheral oedema.
- infection
- Secondary tumour/cancer

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- ***In utero* exposure**

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.
If the investigational medicinal product is genotoxic, every case of maternal or paternal exposure must be notified.

10.3.2.2.2 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report forms. A data retrieval of the case report forms will be implemented for serious adverse events every months

- *Normal and natural course of the condition*:
  - planned hospitalisation for monitoring the condition under investigation [no deterioration in the participant's condition compared to baseline],
  - hospitalisation for routine treatment or for monitoring of the condition under investigation, not associated with a deterioration in the participant's condition,
  - emergency hospitalisation at inclusion or prolongation of hospitalisation after inclusion for monitoring the condition under investigation
  - worsening of the condition under investigation

- *Adverse events potentially related to treatments prescribed as part of the care provided during the study follow-up*

The investigator must report these adverse events to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV).

10.3.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:
- from the date on which the participant begins treatment with an investigational medicinal product specific to the study.
- throughout the whole follow-up period required for the trial
- until 150 days following the last dose of spartalizumab or 30 days after the last dose of the capmatinib, whichever is later.

10.3.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.).

These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies which use e-CRFs
- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

10.3.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

10.3.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:
- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product added by the study and any other treatments,
  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions

Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the investigator's brochure if the product is not authorised, is considered unexpected.
The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal products:
- refer to the Investigator's Brochure of spartalizumab and capmatinib enclosed in appendix.

❖ For serious adverse events likely to be related to the additional medicinal products:
- refer to SmPc of the product administered

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM:
- The sponsor must send the initial report without delay upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 8 calendar days starting from when the sponsor had this information.

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

10.3.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

10.3.3.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:
- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the study,

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

10.3.4 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) may be established by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of such a committee to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee).

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the CPP (Research Ethics Committee).
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB members are: DSMB Committee members: Sophie Gourgou (Montpellier, Sophie.Gourgou@icm.unicancer.fr), Mélanie Dos Santos (Caen, m.dossantos@baclesse.unicancer.fr); Anthony Turpin (Lille, Anthony.TURPIN@CHRU-LILLE.FR)

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11 DATA MANAGEMENT

11.1 Data collection procedures

The data will be collected prospectively in an electronic Case Report Forms (e-CRF) via a Cleanweb internet browser
The investigator will permit the sponsor's representatives to monitor the study at the frequency defined in the contract, depending on enrolment at each centre.
Case Report Forms (CRFs) and related source documents will be reviewed in detail during monitoring visit (completeness, adherence to the guidelines, accuracy compared to source documents). The sponsor's representative will also review regulatory documents, drug storage and accountability.
The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by sponsor's monitors or representatives of other regulatory agencies.

11.2 Right to access data and source documents

11.2.1 Data access

In accordance with GCPs:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the

statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

11.2.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

The source document are: medical file, original biological examination results, summary from imaging examinations, anonymized CD-rom from the 6 first months radiological evaluation.

11.2.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.3 Data processing and storage of research documents and data

11.3.1 Identification of the data processing manager and location(s)

The management of data processing is held by Clinical Research Unit of Saint Louis hospital under the responsibility of Pr Matthieu Resche-Rigon, SBIM, Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75010 PARIS.
The data analysis will be performed by Dr Lucie Biard (Statistic department of Saint Louis hospital, APHP)

11.3.2 Data entry

Data entry will be performed by specially-trained staff *in non-identifying e-case report forms.*
Non-identifying data will be entered electronically via a web browser.

11.4 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Description of statistical methods to be used including the timetable for the planned interim analyses

Summary

Two cohorts will be constituted for this trial:

- **Cohort 1** to enroll patients with no MET amplification. Cohort 1 will primarily follow the time-to-event Bayesian optimal phase 2 (TOP) design [Lin, Coleman and Yuan, 2018, Zhou, Lee and Yuan, 2017] for the efficacy assessment of the combination treatment (spartalizumab + capmatinib). Specifically, a maximum total of 81 patients will ensure 90% power with a 5% type I error rate to detect a 30% response rate compared to reference 15%, including an interim analysis after 30 patients have been included with a futility stopping rule of the combination treatment. If the interim futility stooping boundary is crossed for the combination treatment, the inclusion of a 51 additional patients, treated by spartalizumab monotherapy, will ensure >80% power to detect a desirable 20% response rate in these 51 patients treated with spartalizumab monotherapy (against 8% as unacceptable), with a 5% type I error rate (one-sided), using an exact binomial comparison.
- **Cohort 2** to enroll patients with MET amplification for exploratory purpose only. The enrollment in cohort 2 will be ongoing until cohort 1 is completed. Around 9 patients are expected to be enrolled in cohort 2. The proportion of response (primary endpoint) will be estimated using Bayesian inference.
- Across both cohort, an additional close **toxicity monitoring** will be performed jointly across both cohorts [Ivanova et al.-Clin Invest-2015].

Design

In cohort 1, we will primarily monitor the efficacy endpoint using the time-to-event Bayesian optimal phase 2 (TOP) design (Lin, Coleman and Yuan, 2018, Zhou, Lee and Yuan, 2017). Specifically, let n denote the interim sample size and N denote the maximum sample size.
Let $peff$ denote the probability of efficacy (response rate) of the evaluated treatment.

For the combination treatment, spartalizumab+capmatinib, we define the null hypothesis H_0: p_{eff}≤0.15, representing that the combination treatment is inefficacious. We will stop enrolling patients and claim that the treatment is not promising if (p_{eff}>0.15|$data$)<$\lambda(n/N)\alpha$, where λ=0.92 and α=1 are design parameters optimized to maximize the power under the alternative hypothesis H_1: p_{eff}=0.3, while controlling the type I error rate at 0.05 (i.e., controlling that the chance of incorrectly claiming that an inefficacious treatment is promising is no more than 5%). Assuming a Beta (0.15,0.85) prior distribution for p_{eff}, the above decision rule corresponds to the following go/no-go rules during the trial and yields a maximum statistical power of 0.9476 under H_1:

Table 1: Go/no-go efficacy rules for cohort 1

Patients treated	Observed responses	Pending patients	Action
30	≤3	≥12	Suspend inclusion
	≤2	≤ 11	Conclude to futility of combination, continue with spartalizumab monotherapy
	3	≤ 11	Go if ESS < 23.03*
	≥ 4	≤ 26	Go
81	≤ 17	0	Conclude to insufficient efficacy
	≥ 18	0	Conclude to efficacy

**ESS: effective sample size= number of complete observations + (total duration of incomplete observations)/(Duration of observation window, 6 months).*

As reported in Table 1, we will perform the interim efficacy analysis when the number of enrolled patients, treated with the combination therapy, reaches 30 in cohort 1 and decide on the early stopping rule according to table 1 rules., We will reject the null hypothesis and conclude that the combination treatment is promising if the number of responses becomes 18 or more during the trial. Otherwise, and if the combination trial has not been stopped early, we conclude that the combination treatment is not promising if we observe 17 or less responses among the total sample size n=81.

Table 2 shows the operating characteristics of the TOP design, under the assumption of p_T=0 (no risk of unacceptable toxicity), based on 10000 simulations using the TOP web application, which is available at http://www.trialdesign.org. In the simulation, the assessment window is 6 months, and the patient arrival is uniformly distributed with an accrual rate of 5 patients per month. The time to response is simulated from a Uniform distribution by controlling 50% of the responses occurring in the latter half of the response assessment window.

Table 2: Operating characteristics of the design (under the assumption of ρ_T=0, e.g. no risk of unacceptable toxicity) with N=30 + 51

Response rate	Early stopping (%)	Claim promising (%)	Sample size	Average trial duration (month)
0.15	38.86	4.72	61.18	18.76
0.30	1.72	94.37	80.12	22.88
0.20	17.04	33.75	72.31	21.60
0.25	5.72	74.00	78.08	22.77

In case the combination trial is stopped early for futility, we will resume enrolment in cohort 1 for 51 more patients treated spartalizumab monotherapy (up until a total sample size N=81 in cohort 1). From this monotherapy sample of 51 patients, an exact binomial design will allow to conclude to a promising monotherapy with 80% power and 5% one-sided type I error rate, assuming a response rate ≥ 20% as promising and ≤ 8% response rate as undesirable. Specifically, the spartalizumab monotherapy will be claimed promising if 8 or more responses are observed among the 51 patients receiving monotherapy.

In **cohort 2**, we will enroll patients with MET amplification for exploratory purpose only. The enrollment in cohort 2 will be ongoing until cohort 1 is completed. Around 9 patients are expected to be enrolled in cohort 2. The proportion of response (primary endpoint) will be estimated using Bayesian inference.

Additionally, we will perform close **toxicity monitoring** during the trial based on all available information across both cohorts [Ivanova et al.-Clin Invest-2015]. The posterior probability of unacceptable toxicity will be evaluated based on the beta-binomial model $y| p_T \sim \text{binomial}(p_T)$ with prior $p_T \sim \text{Uniform}(0,1)$, where y is the number of patients who experienced unacceptable toxicity under treatment. We plan scheduled safety analyses every 5 completed observations from cohort 1 + 2 (after 5 patients have either completed the two first treatment cycles (C1+C2) or experienced an unacceptable toxicity during C1 or C2) for the 20 first patients than approximately every 10 observations. If at any of the interim safety analyses, the posterior

probability that p_T>0.25 becomes greater than 0.95 [Prob(p_T > 0.25 |data) > 0.95], the trial will be terminated. Table 3 below presents the safety stopping rules at the different analyses.

The impact of this additional safety monitoring on the operating characteristics of the design in terms of efficacy conclusions was evaluated by simulation (n=10000) and is limited when the probability of unacceptable toxicity is low: if the true probability of toxicity is $p_T \leq 0.20$, the probability of concluding to efficacy using the TOP design as defined in table 1 is close 0.05 under H_0:p_{eff}=0.15, and greater than 0.90 under H_1:p_{eff}=0.3. Nevertheless, when the probability of unacceptable toxicity is higher, e.g. p_T =0.30, the trial will be stopped in approximately 49%, and 95% if p_T =0.40.

Endpoints will be described with count and percentage for categorical endpoints (toxicity, AEs), and with mean, median, 95% confidence interval (or 95% credibility interval if appropriate), interquartile range for continuous endpoints. Time-to event endpoints (PFS and OS) will be estimated using the non-parametric Kaplan Meier estimator, to obtain the survival estimates up to 24 months after inclusion.

Analyses will be performed using R statistical platform. Along with data-management, analyses will be conducted in the Department of Biostatistics and Medical Information of Hôpital Saint Louis, Paris (Pr Sylvie Chevret), which is a labelled *Centre de Traitement des Données INCa.*

12.2 Calculation hypotheses for the number of participants required and the result

The sample size is mainly driven by **cohort 1** requirements. Overall, we plan to include a maximum of n=81 patients in cohort 1. An interim analysis will be conducted after n=30 patients have been included. .
Specifically, a maximum total of 81 patients will primarily ensure 90% power with a 5% type I error rate to detect a 30% response rate to the combination treatment compared to reference 15%, including an interim analysis after 30 patients have been included with a futility stopping rule.
If the interim futility stopping boundary is crossed for the combination treatment, the inclusion of 51 additional patients, treated by spartalizumab monotherapy, will ensure >80% power to detect a desirable 20% response rate in these 51 patients treated with spartalizumab monotherapy (against 8% as unacceptable), with a 5% type I error rate (one-sided), using an exact binomial comparison.

For **cohort 2,** we expect approximately 9 patients enrolled, given the prevalence of c-Met amplification. We will include all consecutive cohort 2- eligible patients up until cohort 1 enrollment is completed.

The total sample of the whole study will be close to 90 patients.

12.3 Anticipated level of statistical significance

For the primary analysis, in cohort 1, the design will rely on Bayesian methods for the evaluation of spartalizumab + capmatinib combination, and on an exact binomial comparison for the evaluation of spartalizumab monotherapy (in case the combination has been found unpromising). Operating characteristics of the Bayesian TOP design were evaluated in a simulation study and design parameters were calibrated to ensure a 5% risk of erroneously concluding to efficacy. The binomial exact comparison will also have a one-sided 5% type I error risk.
No test on the primary endpoint will be performed in cohort 2.

12.4 Statistical criteria for termination of the study.

In cohort 1, early termination rules will be implemented, both on efficacy and toxicity.
For efficacy, an interim analysis will be performed after 30 patients have been included. The stopping criteria are detailed in table 1 above, section 13.1.
For safety, sequential monitoring analyses will be performed accounting for both cohorts, every 5 completed observations from cohort 1 + 2 (after 5 patients have either completed the two first treatment cycles (C1+C2) or experienced an unacceptable toxicity during C1 or C2) for the 20 first patients than approximately every 10 observations. If at any of the interim safety analyses, the posterior probability that pT>0.25 becomes greater than 0.95 [Prob(pT > 0.25 |data) > 0.95], the trial will be terminated. Table 3 below presents the safety stopping rules at the different analyses.

Table 3: Safety stopping rules

Number of included patients	5	10	15	20	30	40	50	60	70	80	90
Stop the trial if unacceptable toxicity in ≥ n patients	3	5	7	9	12	15	18	21	24	27	30

12.5 Method for taking into account missing, unused or invalid data

Missing data will be described, and method of handling them according to their frequencies and nature will be used. Sensitivity analyses will confirm reliability of conclusions upon various hypotheses on missing values.

12.6 Choice of individuals to be included in the analyses

Only patients that have received one day of treatment will be enrolled in the analyses. The patients who did not received any treatment will be replaced.

References

- Ivanova A, Song G, Marchenko O, Moschos S. Monitoring rules for toxicity in Phase II oncology trials. Clinical investigation. 2015; 5(4):373-81
- Lin, R., Coleman, R. L., & Yuan, Y. (2019). TOP: Time-to-event Bayesian optimal phase II trial design for cancer immunotherapy. JNCI: Journal of the National Cancer Institute, djz049, https://doi.org/10.1093/jnci/djz049.
- Zhou, H., Lee, J. J., & Yuan, Y. (2017). BOP2: Bayesian optimal

13 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

13.1.1 Strategy for centre opening

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan.
The opening of the different participating center will be performed on site by the CRA from the URC-DRCI from Saint Louis hospital.

13.1.2 Scope of centre monitoring

In the case of this D risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: High Risk level

These various levels are defined in the monitoring charter for research involving human participants

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

13.3 Case report forms

Electronic CRF:
All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.

A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

13.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

13.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing research participants and obtaining their consent

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a person

without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period of minimum 1 hour is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study at the screening visit**.**

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

14.2 Prohibition from participating in another clinical study or exclusion period set after the study.

An exclusion period of participation after the participant has finished this study is defined in the context of this research. It will last for 14 days in order to collect safety data from the last investigational drug administration.

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study. The participants can however participate in other non-interventional studies

14.3 Compensation for participants

Each participant will receive financial compensation for transportation costs for the J8 and J15 visits in Cycle 1. A flat rate of 50 euros maximum (for the round trip) for patients in Ile de France and 150 euros maximum (for the round trip) for patients in the others districts.

14.4 Registration on the National Register of study participants to studies involving human participants concerning the products mentionned in Article L. 5311-1 of the Code de la santé publique

Not applicable.

14.5 Authorisation for the research location

Units participating in the study must have specific authorisation for the location.
The study requires interventions other than those usually performed at the unit.: the administration of treatment and follow-up of patient are performed in the CLIP^2 i.e. Inca labeled early phase center which has a specific authorization

14.6 Legal obligations

14.6.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique (French Public Health Code)*. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

14.6.2 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

14.6.3 Request for authorisation from ANSM

Prior to starting the study, AP-HP, as sponsor, must obtain authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants concerning a medicinal products for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

14.6.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Commitment to comply with “Reference Methodology” MR-001

This research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this “Reference Methodology”

14.6.5 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

14.6.6 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

14.6.7 Archiving

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
  - the successive versions of the protocol (identified by the version number and its date), and any appendices
  - the ANSM authorisations and CPP (Research Ethics Committee) decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - final study report
- The data collection documents

15 FUNDING AND INSURANCE

15.1 Funding sources

Institut National du Cancer (AAP_CLIPPMI2019-007)

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

16 PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must name the sponsor AP-HP (DRCI) and the source of funding (Institut National du Cancer, AAP_CLIPPMI2019-007); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming of the sponsor and funders).

16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be “AP-HP”
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym “**AP-HP**” first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

16.2 Mention of the AP-HP manager (DRCI) in the acknowledgements of the text

- "The sponsor was *Assistance Publique – Hôpitaux de Paris* (Clinical Research and Innovation Delegation)"

16.3 Mention of the financial backer in the acknowledgements of the text

“The study was funded by a grant from Institut National du Cancer, AAP_CLIPPMI2019-007”.

This study has been registered on the website http://clinicaltrials.gov/ under number *(add the registration number when the study is registered)*.

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18 LIST OF ADDENDA

Each addendum and the log of addenda versions are attached, independently of the protocol. Each addendum can be modified (change of addendum version) without modifying the protocol version.

18.1 List of investigators

Cf. addendum

18.2 Serious Adverse Events notification form

18.3 Pregnancy notification form

18.4 Investigator's Brochure

Specify here that the SmPC must have been obtained from the EMA website (http://www.ema.europa.eu/ema/), if absent from this site, the SmPC must have been obtained from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php) and if absent from the ANSM website, use the SmPC from the Vidal compendium.

18.5 Questionnaire or scale

RECIST 1.1

"New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)" E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij;
Eur J Cancer, 4 5 (2 0 0 9) 2 2 8 –2 4 7.

Lesions on inclusion:
Lesions and lymph nodes are classed individually as being measurable or non-measurable.

Measurable disease
A lesion is measurable if it can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be reported).
To be measurable, lesions must have a minimum size of
≥ 10 mm on CT (CT scan slice thickness no greater than 5 mm)
≥ 10 mm on clinical examination (measured using a caliper); lesions that cannot be accurately measured with calipers should be classed as non-measurable
20 mm on chest X-ray
For a malignant lymph node to be considered pathological and measurable, its short axis must measure ≥ 15 mm (the short axis is the axis perpendicular to the largest dimension of the lymph node). Only the length of this short axis is reported on inclusion and during follow-up.

Non-measurable disease
All other lesions, including small lesions (longest diameter < 10 mm on CT or lymph nodes with ≥ 10 mm and < 15 mm short axis) as well as truly non-measurable lesions: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic

involvement of skin or lung, abdominal masses identified by physical examination but unconfirmed by imaging techniques, and cystic lesions.
NB: bone lesions, simple cystic lesions and lesions that have received prior local treatment require special consideration (see comments below).

Target lesions
Target lesions are selected from the measurable lesions presented by the patient on entry into the study. A maximum of five target lesions are selected, with no more than two target lesions per organ. Target lesions will be selected so as to be representative of all involved organs. The largest lesions (in the longest dimension) that may be repeatedly and reproducibly measured throughout the trial using the initial examination method are to be chosen. Lymph nodes may be considered as target lesions if their short axis as measured on CT is ≥ 15 mm.

The sum of the diameters of these target lesions (the longest diameter for lesions, and short axis for lymph nodes) is what is followed throughout the trial for assessing response or progression.

Non-target lesions
All other lesions are identified as non-target lesions and are also recorded on inclusion. They are not measured but they are followed throughout the trial.

Criteria for response to treatment:
Target lesions:

Complete response (CR) Disappearance of all lesions, and all lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Note: lymph nodes selected as target lesions must always be measured (in the same anatomical plane as the baseline examination), even if they decrease in size during the study to a short axis of < 10 mm. Therefore, when lymph nodes are used as target lesions, the sum of the lesions' dimensions is not necessarily zero even if there is CR since a normal lymph node is defined as having a short axis < 10 mm. To qualify for CR, every lymph node must achieve a short axis of < 10 mm.

Partial response (PR) At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive disease (PD) At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum, or nadir, in the study (this includes the baseline sum if that is the smallest in the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Note: the appearance of one or more new lesions is also considered progression.
However, if there is progression compared with the nadir and response compared with the baseline examination, this is considered progression.

Stable disease (SD) Neither PR, CR or PD.

Non-target lesions

CR Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must have reached a short axis of < 10 mm.
Non-CR/SD Persistence of one or more non-target lesions and/or tumor marker levels above the normal limits.

PD Unequivocal increase in size of existing non-target lesions or appearance of one or more new lesions.

Overall response:

Target lesions	Non-target lesions	New lesion		Overall response
CR	CR	No	=	**CR**
CR	Non-CR/Non-PD	No	=	**PR**
CR	Not assessed	No	=	**PR**
PR	Non-PD or not all assessed	No	=	**PR**
SD	Non-PD or not all assessed	No	=	**SD**
Not all assessed	Non-PD	No	=	**Unassessable**
PD	Any	Yes or no	=	**PD**
Any	PD	Yes or no	=	**PD**
Any	Any	Yes	=	**PD**

Comments on lesion measurability on entry
Bone lesions:
Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered as measurable lesions if they can be evaluated by cross-sectional imaging techniques such as CT or MRI and if the soft tissue component meets the definition of measurability described above.
Cystic lesions:
Lesions that meet the criteria for radiographically defined simple cysts are not considered as malignant lesions (be it measurable or non-measurable).
Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
Lesions with prior local treatment:
Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion since the local therapy. Study protocols should detail the conditions under which such lesions may be considered measurable.