P-19 Subgroup analysis of the number of prior lines of systemic therapy and clinical outcomes associated with tislelizumab in patients with previously treated advanced hepatocellular carcinoma (HCC)

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Background: Tislelizumab, an anti-programmed cell death protein 1 (PD-1) monoclonal antibody, showed clinical activity and was well tolerated in patients with previously treated advanced HCC in the phase 2 RATIONALE-208 study (NCT03419897). This analysis examined the number of prior lines of systemic therapy and clinical outcomes associated with tislelizumab.

Methods: Patients who received ≥ 1 prior line of systemic therapy for advanced HCC, excluding immune checkpoint inhibitors, received tislelizumab 200 mg IV every 3 weeks. The primary endpoint was objective response rate by independent review committee (IRC) (ORR IRC) per RECIST version 1.1. Secondary endpoints included investigator-assessed (INV) ORR INV , duration of response by IRC (DoR IRC), DoR by INV (DoR INV), overall survival (OS), progression-free survival by IRC (PFS IRC), and safety.

Results: As of June 2021, 249 patients were enrolled; 138 had received 1 prior line of therapy and 111 patients had received ≥ 2 prior lines of therapy. Median (m) follow-up duration was 13.3 months and 11.9 months, respectively. Response rate assessed by IRC (1 prior line, ORR IRC =13.0% [95% CI: 7.9, 19.8]; ≥ 2 prior lines, ORR IRC =12.6% [95% CI: 7.1, 20.3]) and by INV (1 prior line, ORR INV =15.2% [95% CI: 9.7, 22.3]; ≥ 2 prior lines, ORR INV =13.5% [95% CI: 7.8, 21.3]) was generally consistent between subgroups. Number of prior lines of therapy did not impact OS (1 prior line, mOS=13.8 months [95% CI: 10.5, 19.1]; ≥ 2 prior lines, mOS=12.4 months [95% CI: 9.9, 15.2]) or PFS (1 prior line, mPFS IRC =2.6 months [95% CI: 1.4, 2.8]; ≥ 2 prior line, mPFS IRC =2.7 months [95% CI: 1.4, 2.8]). mDOR IRC was not reached in either subgroup. mDoR INV was not reached in the 1 prior line subgroup and was 14.6 months [95% CI: 7.6, 27.3] in the ≥ 2 prior lines subgroup. Treatment-emergent adverse events (TEAEs) were consistent between the 1 prior line and ≥ 2 prior lines subgroups; 94.2% vs 95.5% experienced any TEAE, 50.0% vs 48.6% experienced ≥ Grade 3 TEAEs, 38.4% vs 36.0% experienced serious TEAEs, 13.0% vs 9.0% experienced TEAEs that led to treatment discontinuation, 32.6% vs 30.6% experienced TEAEs that led to dose delay, and 11.6% vs 9.0% experienced TEAEs that led to death in the 1 prior line and ≥ 2 prior lines subgroups, respectively. Similarly, treatment-related adverse events (TRAEs) were consistent between the 1 prior line and ≥ 2 prior lines subgroups; 65.9% vs 60.4% experienced any TRAE, 17.4% vs 12.6% experienced ≥ Grade 3 TRAEs, 9.4% vs 4.5% serious TRAEs, 7.2% vs 2.7% experienced TRAEs that led to treatment discontinuation, 19.6% vs 17.1% experienced TRAEs that led to dose delay, and 0% vs 0% experienced TRAEs that led to death in the 1 prior line and ≥ 2 prior lines subgroups, respectively.

Conclusions: Effective second- and third-line treatment options are limited for patients with advanced HCC. This analysis indicates Tislelizumab is clinically active and well tolerated in patients with advanced HCC, regardless of the number (1 or ≥ 2) of prior lines of systemic therapy. Tislelizumab is being investigated further in a phase 3 study (NCT03412773).

Clinical trial identification: NCT03419897.

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P-20 Predictors of distant relapse in rectal cancer patients submitted to preoperative chemoradiotherapy

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Background: Neoadjuvant chemoradiotherapy (nCRT) is the standard treatment for locally advanced rectal cancer. nCRT improves local control, however, this does not translate into a survival benefit. Long-term survival is mostly affected by the development of distant metastases after local treatments. This study aimed to evaluate predictive clinical factors for the development of early metastatic disease after nCRT.

Methods: All patients with stage II and III rectal adenocarcinoma, who underwent nCRT from January 2013 to December 2019 were identified. Serum measurements of Hemoglobin, C-Reactive Protein (CRP), platelets, ratio neutrophils/lymphocytes, CEA and CA 19.9 were obtained before nCRT. Patients were divided into two groups: those who developed distant relapse (Group A) and patients without distant relapse (Group B). For the comparison of the groups calculated by the threshold predictors value, the Chi-square test and the Fisher's exact test were used. Logistic regression was performed to determine univariate relationships and multivariate logistic regression analysis, adjusted for factors possibly related to distant disease relapse.

Results: The study included 162 patients. Most of the patients were male (n=103, 63.6%), the median age of the studied cohort was 63 years (interquartile range 18 years) and the ECOG 0 was predominant (n=132, 81.5%). At initial presentation and radiologic examination, most of the patients had cT3 disease (n=118, 72.8%) and 127 (35%) were node positive. Thirty-nine (24.1%) had distant relapse from neoadjuvant treatment and surgery (Group A) and 123 (75.9%) did not (Group B). A higher rate of distant relapse was associated with CEA levels above 2.2 ng/dL (p=0.002) and CPR above 8.8 mg/L (p=0.002). Multivariate analysis confirmed these factors to be independently correlated with a higher risk of metastasis, CEA 2.2 ng/dL (OR 0.061; 95% IC 0.005-0.695; p=0.024) and PCR 8.8 mg/L (OR 0.163; 95% IC 0.041-0.650; p=0.010).

Conclusions: High serum CEA and CPR may be associated with unfavorable early oncological outcomes after nCRT and surgery for rectal cancer. Defining unfavorable clinical characteristics may permit us to correctly drive the appropriate therapy to the right patient, possibly improving the current staging and thus hopefully outcomes.

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P-21 Molecular subtypes (profile) of colorectal cancer and their correlation with clinical and pathological profile in a tertiary care centre in India

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Background: Colorectal cancer is a heterogeneous disease with 3 molecular carcinogenesis pathways and 2 morphologic multistep pathways. The varied response rates to the standard therapeutic regimens is due to its heterogeneous tumor biology. A lot of the literature is from the western world on this molecular heterogeneity. We aimed to study the molecular subtypes of colorectal cancer and the correlation with clinical and pathological characteristics in Indian population.Objectives: To evaluate the clinical and pathological profile of colorectal cancers, to determine the frequency of molecular subtypes of colorectal cancers, to correlate between the molecular

subtypes and their clinic-pathological features and to determine the association between different molecular subtypes of colorectal cancer.

Methods: It is a prospective non-invasive interventional study done in 50 patients (both outpatients and inpatients) with newly diagnosed colorectal cancers presenting to Rajiv Gandhi Cancer Institute and Research Centre, Rohini, Delhi from February 2019 to March 2020. Clinical and histopathological data was collected from case sheets as per study proforma- history and physical examination, non-invasive and invasive imaging and histopathological reports. Patients in whom tissue was insufficient or not available for testing for at least 3 molecular markers out of 5 (KRAS, NRAS, BRAF, MSI and MLH1methylation) were excluded. Molecular testing for MMR protein analysis was done using Immunohistochemistry (BenchMark XT, Ventana Medical Systems, Inc., Tucson, AZ, USA). Germline mutation analysis in MSH2, MLH1, PMS2 and MSH6 as dictated by the MMR protein analysis. KRAS, NRAS and BRAF V600E mutation analysis was done by RT-PCR. Methylation of CpG islands of MLH1 is done by pyrosequencing. Results were analyzed with SSPS 23.0 software. For comparison of the frequencies among groups, the Chi-square test and the Fisher exact test were used. P-value <0.05 was considered statistically significant.

Results: The median age was 53 years. Majority of males (54%) had CRC. 44% were right sided colon tumors. Of the 50 patients with CRC 40%, 4% and 22% had KRAS mutation, BRAF mutation and deficient MMR respectively. None of the patients was NRAS mutant. KRAS mutation was significantly associated with upfront liver metastases ($p=0.02$) and well/moderate differentiation ($p=0.02$). BRAF wild tumors were likely to be well-differentiated ($p=0.02$) and moreover, half of them (52%) had MLH1 promoter methylation. The proportion of dMMR was higher in male patients ($p = 0.04$). Deficient mismatch repair was associated with well/moderate differentiation ($p = 0.02$), early stage ($p=0.02$) and mild peri-tumoral lymphocytes ($p=0.01$). None of the MMR deficient patients had Stage IV CRC. 27% patients (3/11) with dMMR tumors had germline mutation of MMR genes. Majority of MMR deficient tumors (43%, 3 out of 7) had MLH1 promoter methylation. Overall, 45% (5/11) dMMR tumors harbored KRAS mutation.

Conclusions: In conclusion, this prospective study evaluated the correlations between RAS/BRAF mutation and MMR status with clinico-pathological characteristics in Indian CRC patients, which is mostly similar to worldwide reports with some exceptions. It paves way for future studies to include large populations for validation of the molecular heterogeneity and their prognostic value in Indian population.

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P-22 Phase III study (daNIS-2) of the anti–TGF-β monoclonal antibody NIS793 with nab-paclitaxel/gemcitabine vs nab-paclitaxel/gemcitabine alone in patients with first-line metastatic pancreatic ductal adenocarcinoma

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Background: Despite improving outcomes, current therapies for metastatic pancreatic ductal adenocarcinoma (mPDAC) have a modest impact on overall survival (OS) and new therapies are needed. PDAC is characterized by an abundance of intratumoral fibrosis, which may contribute to the lack of treatment efficacy and act as a mechanical barrier to effective penetration of therapeutics. TGF-β has a multifactorial role in tumorigenesis and maintaining an immunosuppressive tumor microenvironment (TME). Emerging evidence points to the role of TGF-β as a pivotal activator of cancer-associated fibroblasts that lead to the development of fibrotic networks. In preclinical models, TGF-β blockade alters the TME to facilitate an antitumor response, reduce stromal fibrosis, and augment the benefit of chemotherapy, providing rationale for combining TGF-β–targeting agents with chemotherapy. NIS793 is a potent, selective, human IgG2 monoclonal antibody (mAb) antagonist of TGF-β. This study investigates NIS793 in combination with nab-paclitaxel/gemcitabine (NG) vs NG alone in treatment-naïve patients with mPDAC.

Trial design: This is a phase III, randomized, double-blind, multicenter, two-arm study (NCT04935359) consisting of two stages: an initial safety run-in period followed by two-arm randomization. Eligible patients include adults with previously untreated mPDAC and an ECOG performance status ≤ 1. Patients with a tumor histology other than adenocarcinoma or with microsatellite instability-high tumors are ineligible. The aim of the safety run-in period is to assess the safety and tolerability of NIS793 + NG and confirm the recommended dose for the randomized phase of this study. Data will be analyzed once at least six evaluable patients have received NIS793 (intravenous [IV] 2100 mg every 2 weeks) + nab-paclitaxel (IV 125 mg/m2 on Days 1, 8, and 15) + gemcitabine (IV 1000 mg/m2 on Days 1, 8, and 15) for one 28-day cycle. Patients (N=480) will be randomized 1:1 to NIS793 + NG or placebo + NG. Treatment will continue until unacceptable toxicity, disease progression, discontinuation by investigator or patient choice, death, or withdrawal of consent. The primary objective is to evaluate the OS of patients receiving NIS793 + NG vs NG alone; secondary objectives include assessing progression-free survival, the overall response rate, disease control rate, duration of response, and time to response (assessed locally per RECIST v1.1), as well as safety and tolerability, immunogenicity, pharmacokinetics, and patient-reported outcomes such as health-related quality of life. Efficacy will be assessed at screening, every 8 weeks for 1 year, and then every 12 weeks until disease progression. Blood samples will be taken at baseline and during treatment for pharmacokinetic and immunogenicity assessments. This study is ongoing and will enroll patients from approximately 149 sites across 28 countries. The first patient was treated on October 20, 2021.

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P-23 Phase II study (daNIS-3) of the anti–TGF-β monoclonal antibody NIS793 and other new investigational drug combinations with standard-of-care therapy vs standard-of-care alone in patients with second-line metastatic colorectal cancer

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Background: Colorectal cancer (CRC) is the second leading global cause of cancer-related death. Despite recent improvements in chemotherapy + targeted agent combination therapies, treatment options for second-line, microsatellite-stable metastatic CRC (mCRC) remain suboptimal. TGF-β has a multifactorial role in tumorigenesis and maintaining an immunosuppressive tumor microenvironment. NIS793 is a potent, selective, human IgG2 monoclonal antibody (mAb) antagonist of TGF-β. This study investigates NIS793 in combination with standard-of-care (SOC) for second-line treatment of mCRC.

Trial design: This is a phase II, open-label, randomized, multicenter, platform study (NCT04952753) with an initial safety run-in to confirm the NIS793 dose with SOC before expansion to randomization vs SOC. Eligible patients are adults with histologically or cytologically confirmed mCRC not amenable to potentially curative surgery that has progressed within 6 months of one prior line of systemic anticancer therapy for mCRC. Exclusion includes microsatellite instability-high/mismatch repair-deficient and/or BRAFV600 mutation-positive CRC. Safety run-in data will be analyzed after at least six patients in each regimen have received NIS793 (intravenous [IV] 2100 mg every 2 weeks [Q2W] or 2100 mg every 4 weeks [Q4W]) + bevacizumab (5 mg/kg) +