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) +

FOLFIRI or NIS793 + bevacizumab + modified FOLFOX6 on Days 1 and 15 of each 28-day cycle. Upon phase II dose confirmation for NIS793 + SOC, an additional safety run-in of NIS793 (starting at 2100 mg Q2W, with the potential for dose de-escalation to 2100 mg Q4W if required) + an anti−PD-1 antibody, tislelizumab (tisle; 300 mg Q4W) + SOC will be performed. Patients (N= ∼226) will then be randomized to continue the same investigational drug(s) + SOC (n= ∼150) or SOC (n= ∼76). In the case that the tisle safety run-in is concurrent with the randomized expansion of the NIS793 + SOC arm, randomization will be modified to also assign patients to the tisle safety run-in cohort. Treatment will continue until unacceptable toxicity, disease progression per RECIST 1.1 (or per iRECIST in the tisle arm), discontinuation by investigator, or withdrawal of consent. The primary objectives are to confirm the recommended phase II dose of NIS793 and to evaluate progression-free survival with NIS793 ± tisle + SOC vs SOC alone. Secondary objectives include assessing safety/tolerability, overall survival, and antitumor activity, as well as characterization of immunogenicity and pharmacokinetics. Efficacy will be assessed per RECIST 1.1 (or iRECIST in the tisle arm) every 8 weeks for 1 year, then every 12 weeks until disease progression. Blood will be obtained at baseline and during treatment for immunogenicity and pharmacokinetic assessments. This ongoing study will enroll patients from 87 sites across 20 countries. The study start date was November 15, 2021.

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P-24 Gender differences in overall survival in patients with metastatic pancreatic cancer

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Background: Pancreatic cancer is an aggressive cancer disease and bears a dismal prognosis. Data on gender differences in this tumor entity are scare.

Methods: In this single center, real-world retrospective analysis of our registry for pancreatic cancer, we investigated and compared the survival data and inflammatory parameters of male and female patients.

Results: In total, we included in this analysis 42 female and 63 male patients with metastatic pancreatic cancer. Liver metastasis was comparable between the genders (69.0% for female and 68.3% for male patients). Female patients were older at time of initial diagnosis (70.5 versus 69.7 years). Median overall survival (OS) rates from initial diagnosis were 13.4 months (95% CI: 7.6-19.1) and 7.0 months (95% CI: 3.2-10.9; $p = 0.013$), respectively. CRP/albumin ratio was significantly lower in female patients ($p = 0.039$). CRP/albumin ratio (HR = 7.7, $p = 0.012$) and CEA (HR = 1.0, $p = 0.821$) were independent prognostic factors for OS.

Conclusions: Based on our retrospective analysis, female patients had a significantly longer OS than male patients with metastatic pancreatic cancer, maybe due to a lower inflammatory activity as reflected by the CRP/albumin ratio.

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P-25 Tislelizumab monotherapy for patients with previously treated advanced hepatocellular carcinoma (HCC): RATIONALE-208 Chinese subpopulation

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Background: Tislelizumab, an anti-programmed cell death protein 1 monoclonal antibody, demonstrated clinical activity and was well tolerated in patients with previously treated advanced HCC in the phase 2 RATIONALE-208 study (NCT03419897). Here, we report results for the Chinese subpopulation.

Methods: Eligible patients who had received ≥ 1 prior line of systemic therapy for advanced HCC, excluding immune checkpoint inhibitors, received tislelizumab 200 mg intravenously once every three weeks. The primary endpoint was objective response rate by independent review committee (IRC) (ORR IRC) per Response Evaluation Criteria in Solid Tumors version 1.1. Secondary endpoints included ORR by investigator (INV) (ORR INV), duration of response by IRC (DoR IRC), DoR by INV (DoR INV), overall survival (OS), PFS by INV (PFS INV), PFS by IRC (PFS IRC), and safety.

Results: As of June 2021, 249 patients were enrolled, and the Chinese subpopulation comprised 122 patients; baseline demographic and disease characteristics were balanced between the Chinese and overall (N=249) populations. Median follow-up duration was 12.9 months for the Chinese subgroup and 12.7 months for the overall population. Response rates were not impacted by region: ORR IRC was 12.3% (95% CI: 7.1, 19.5) and ORR INV was 13.9% [95% CI: 8.3, 21.4) in the Chinese subpopulation, and ORR IRC was 12.9% (95% CI: 9.0, 17.7) and ORR INV was 14.5% (95% CI: 10.3, 19.5) in the overall population. Median DoR IRC in both populations was not reached. Median DoR INV was consistent between the Chinese (21.4 months [95% CI: 7.6, NE]) and overall (21.4 months [95% CI: 11.1, NE) populations. Median PFS IRC was 1.4 months (95% CI: 1.4, 2.6) and median PFS INV was 1.5 months (95% CI: 1.4, 2.7) for the Chinese subpopulation, while median PFS IRC was 2.7 months (95% CI: 1.4, 2.8) and median PFS INV was 2.8 months (95% CI: 2.6, 4.0) for the overall population. Median OS was 13.7 months (95% CI: 9.9, 17.0) vs 13.2 months (95% CI: 10.8, 15.2) for the Chinese vs overall population, respectively. Treatment-related adverse events (TRAEs) were similar between the Chinese and overall populations; 18.9% vs 15.5% of patients experienced ≥ Grade 3 TRAEs, and 4.9% vs 5.2% experienced TRAEs that led to treatment discontinuation in the Chinese vs overall population, respectively. The most common ≥ Grade 3 TRAEs were increased aspartate aminotransferase (4.1% vs 2.8%) and increased alanine aminotransferase (1.6% vs 1.2%) for the Chinese vs overall population, respectively.

Conclusions: Tislelizumab is clinically active and well tolerated in Chinese patients with previously treated advanced HCC, and the results are consistent with the overall study population. An ongoing phase 3 clinical trial will continue to investigate the impact of region on the efficacy and safety of tislelizumab monotherapy (NCT03412773).

Clinical trial identification: NCT03419897.

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