800TiP Meet-URO 12: A randomized phase II trial of niraparib versus best supportive care (BSC) as maintenance treatment in patients with locally advanced or metastatic urothelial cancer (UC) whose disease did not progress after completion of first-line platinum-based chemotherapy

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Background: Niraparib is an oral inhibitor of poly ADP-ribose polymerase (PARP) enzymes. PARP inhibitors induce synthetic lethality in cells with aberrations in BRCA1, BRCA2 or other genes impairing homologous recombination (HR). HR deficiency (HRD) is also implicated in the sensitivity to platinum-based chemotherapy, the backbone of perioperative and first-line treatment of UC patients. In preclinical models, a reduced capacity for HR repair is associated with increased sensitivity to PARP inhibitors, and the combination of PARP inhibitor and cisplatin causes a significant increase in DNA damage compared to cisplatin alone. The prevalence of somatic mutations in HR genes in UC and their association with platinum sensitivity represent a good rationale to test PARP inhibition in UC pts. Aim of this trial is to compare maintenance treatment with niraparib plus BSC vs. BSC alone in pts with locally advanced or metastatic UC obtaining objective response or stable disease with first-line platinum-based chemotherapy.

Trial design: Meet-URO 12 is a randomized phase II multicentre trial enrolling pts with locally advanced or metastatic transitional cell UC (either pure or mixed histology), who have received 4-6 cycles of first-line platinum-based chemotherapy without evidence of progression. Primary endpoint is progression-free survival (PFS). 77 pts will be randomized (2:1 ratio) to experimental arm (niraparib 300 or 200 mg daily according to body weight and baseline platelets, plus BSC) or control arm (BSC alone). Treatment will be continued until disease progression, or unacceptable toxicity. 65 PFS events are needed to detect Hazard Ratio 0.57 (median PFS increase from 4 to 7 months), with 80% power and one-tailed alpha 0.1. Secondary endpoints are 6-month PFS rate, objective response rate, duration of response, overall survival, safety and tolerability, patient reported outcomes. Exploratory endpoints are BRCA mutation and HRD test. The study is open, with 16 patients enrolled as of May 20, 2020. Clinical trial information: NCT03945084.

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Legal entity responsible for the study: Department of Oncology, University of Turin.

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801TiP A phase II study of cabozantinib in combination with atezolizumab as neoadjuvant treatment for muscle-invasive bladder cancer (ABATE)

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Background: ABACUS and PURE-01 trials demonstrated the activity of single-agent atezolizumab and pembrolizumab respectively as neoadjuvant therapy for muscle-invasive urothelial carcinoma (MIUC), however, downstaging to non-muscle invasive disease was noted in only 50 percent of patients. Resistance to programmed death (PD) 1/L-1 antibodies is likely multifactorial including factors such as impaired dendritic cell maturation/function, infiltration of T-Regs, impaired T-cell priming, and T-cell trafficking in tumors. Cabozantinib is a tyrosine kinase inhibitor whose targets include MET, AXL, and VEGFR2. Cabozantinib has a unique immunomodulatory profile and has demonstrated clinical activity as monotherapy and in combination with PD-1/L1 antibodies in metastatic UC and renal cell carcinoma. We hypothesize that the combination of cabozantinib and atezolizumab in a neoadjuvant setting for MIUC would improve rates of pathologic downstaging compared to single-agent checkpoint inhibitors.

Trial design: ABATE(NCT04289779) is an open-label, single-arm study to assess the efficacy and safety of cabozantinib with atezolizumab as neoadjuvant therapy for cT2-T4aN0/xM0 MIUC. An estimated 38 patients will be enrolled and receive cabozantinib 40 mg PO daily with atezolizumab 1200mg every 3 weeks for a total duration of 9 weeks followed by radical cystectomy. Adults ($\geq$18 years) with histologically confirmed, resectable UC who are either cisplatin-ineligible or decline cisplatin are eligible. Pts are required to have an ECOG PS of 0-2 and provide tumor tissue for PD-L1 analysis. Urothelial carcinoma should be the predominant component ($\geq$ 50%). Previous systemic anticancer therapies for MIUC are not permitted. CT/MRI will be performed before investigational therapy and cystectomy. Primary endpoint is pathologic response rate defined as the absence of residual muscle-invasive cancer in the surgical specimen ($<$ pT2). Secondary endpoints are safety and toxicity, pathologic complete response rate, and event-free survival. Exploratory endpoints include patient-reported outcomes and biomarkers. Accrual began May 2020. Clinical trial information: NCT04289779.

Clinical trial identification: NCT04289779.

Legal entity responsible for the study: HCRN.

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802TiP Immune tumor microenvironment (TME) in correlation with peripheral blood immune biomarkers as prognostic factor in metastatic renal cell carcinoma (mRCC) patients treated with nivolumab: The multicentric retrospective Meet-URO 18 study

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Background: Despite the survival advantage observed with nivolumab in pretreated mRCC patients, only a small percentage of them respond to the treatment (20-30%) and experience long-term clinical benefit. There is, therefore, an intense interest and still an unmet need in identifying prognostic and predictive biomarkers to select patients most likely to benefit from immunotherapy. Inflammatory biomarkers from peripheral blood, such as neutrophil-to-lymphocyte ratio (NLR), have shown promising results in retrospective analysis on cancer patients treated with immunotherapy, including mRCC patients.

Trial design: A multicentric retrospective translational study was designed and is ongoing to assess the correlation of immune TME of primary tumor and metastases

and peripheral blood inflammatory biomarkers with survival and response outcomes. The analysis of immune TME is conducted on two cohorts of mRCC patients treated with nivolumab as $\geq 2^{nd}$ line therapy: *responders* (PFS $\geq$12 months) and *non-responders* (PFS $\leq$ 3 months). It consists in the immunohistochemical, genomic and transcriptomic analysis of TME including morphological and immunophenotypic evaluation of tumor-infiltrating lymphocytes (TILs) (CD8+,CD4+, FOXP3+ T cells), tumor-associated macrophages polarization (pro-inflammatory M1 and anti-inflammatory M2 macrophages), tissue NLR and lymphocyte-to-monocyte ratio (LMR), population of NK cells and expression of the phosphorilated mTOR effectors S6K1 and 4E-BP. All the assessments of the immune TME are correlated, in terms of response and survival outcomes, with the peripheral blood biomarkers NLR, derived NLR [neutrophil / (white blood cells − neutrophils)], platelet-to-lymphocyte ratio (PLR), LMR and systemic inflammation index (SII; NLR x Platelets) at baseline and during the first four cycles of treatment.

Legal entity responsible for the study: Giuseppe Fornarini.

Funding: IRCCS Ospedale Policlinico San Martino of Genova; Azienda Ospedaliero Universitaria Integrata of Verona.

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803TiP Pilot study of cabozantinib efficacy, safety and tolerability in metastatic renal carcinoma in aged fragile patients

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Background: Aged fragile patients are not usually included in clinical trials and efficacy and tolerability of the different treatments in this population are unknown. In the METEOR trial efficacy was similar in all age groups. Conversely, ageing has been associated with a decrease in the efficacy of immune checkpoint inhibitors due to immunosenescenc, thus, TKis might be a better treatment option. However, the absence of data and concerns about possible secondary effects associated, can preclude clinicians to treat aged fragile patients with cabozantinib. A pilot phase II trial would help to have data on safety and efficacy of cabozantinib in this aged fragile population.

Trial design: Pilot open-label, multicenter study to evaluate cabozantinib safety and efficacy in previously untreated aged population with metastatic renal cell carcinoma. Patients will receive cabozantinib 40 mg p.o. once daily in 28-day cycles. Dose can be escalated to 60 mg to avoid suboptimal exposure to the drug if 40 mg is considered tolerated. Geratric evaluation scales will be performed to all patients and correlation between study outcomes and functionality, comorbidity and cognitive and social status will be evaluated. 50 patients is expected to be included in 2 years in ten spanish centers of SOGUG cooperative group. Mean inclusion criteria: Histological diagnosis of renal cell cancer. Metastatic and measurable disease per RECIST 1.1. ECOG 0-2. No previous treatment for mRCC. Patients aged >70 years old with SIOG (Society of Geriatric Oncology) defined fragile population or patients >75 years with or without SIOG defined fragility. Fragile patients are defined as those with G8 scale under 14 points and with one or two reversible deficiencies in ADL (activities in daily life) or CISR-G grade 2 comorbidities (a single grade 3 comorbidity may also be reversible) or weight loss of 5-10% during the last 3 months. All patients will be evaluated for geriatric assessment, comorbidities and dependence status with the following scales: CISR-G, ADL/IADL index, Barthel index, Mini-Cog test, Gijon's social-familial evaluation scale, Hospital anxiety and Depression Scale. HAD scale, Vulnerable Elders Survey 13 and Short Physical Performance Battery.

Legal entity responsible for the study: SOGUG cooperative group.

Funding: Ipsen.

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804TiP CaboPoint: A phase II study of second-line cabozantinib in patients with metastatic renal cell carcinoma (RCC)

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Background: Cabozantinib is an approved therapy for advanced RCC (in the USA) and in treatment-naïve patients with intermediate/poor risk, as well as following VEGF-targeted therapy (in Europe).

Trial design: CaboPoint (NCT03945773) is a phase II, open-label study of cabozantinib in adults with unresectable, locally advanced or metastatic clear-cell RCC, whose disease progressed after checkpoint inhibitor therapy with ipilimumab and nivolumab alone (cohort A) or in combination with VEGF-targeted therapy (cohort B). The primary endpoint is objective response rate. Secondary endpoints include time to response, duration of response, disease control rate, progression-free survival and overall survival. A target of 250 patients at 50 European sites will receive cabozantinib (60 mg once daily; self-administered at home) for $\leq$ 18 months after the last patient receives their first dose. Safety assessments will occur every 2 weeks up to week 4, then every 4 weeks. Patients may continue cabozantinib after disease progression if there is clinical benefit. During follow-up, patients who discontinue early will be contacted every 12 weeks to assess survival and subsequent therapy. Each cohort will have an interim analysis when 60% of patients reach 12 months of follow-up. CaboPoint has been adjusted to allow the trial to continue during the COVID-19 outbreak, protecting participants in compliance with the study protocol.[1] Alternative arrangements include: study drug dispensation to the participant's home if they cannot attend the study site; safety assessments at the study site or remotely at a local health care provider, within the protocol defined window; tumour assessments at a local radiology facility if they cannot attend the study site. Enrolment is permitted if the patient can be managed in compliance with the protocol and alternative arrangements.[1] The limitations, risks and impact on data privacy of such arrangements will be accounted for and documented.

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