PROJECT 1

DoS: Prof. Andrea Necchi

Title: Expanding the therapeutic options in muscle-invasive bladder cancer

Curriculum: Experimental and Clinical Medicine

Link to OSR/UniSR personal page: https://www.unisr.it/docenti/n/necchi-andrea

Project description (*Number of characters, including spaces*: 2.000 - 3.000):

Background: muscle-invasive bladder cancer (MIBC) is a systemic disease as >40% of patients (pts) ultimately develop recurrence after radical cystectomy (RC). For pts who cannot receive or refuse cisplatin-based chemotherapy there is no standar-of-care neoadjuvant therapy. Single-agent pembrolizumab (pembro), given neoadjuvantly in patients with T2-4N0M0 MIBC, documented a 42% pathologic complete response-rate (ypT0N0) in our previous trial (PURE-01, NCT02736266). However, there is a huge proportion of pts who do not benefit from single-agent immune-checkpoint inhibitors (ICI). Sacituzumab govitecan (SG) is an antibody-drug conjugate (ADC) composed by a humanized anti-Trop-2 antibody, SN-38 payload (a parent compound of irinotecan), and a hydrolysable linker for SN-38 release. Based on preliminary data from TROPHY-U-01 trial, SG got fast-track designation for urothelial carcinoma (UC) by the United States Food and Drug Administration (US-FDA). In SURE trial (Study sponsor: OSR) we aim to evaluate the efficacy of neoadjuvant SG either as a single-agent (SURE-01) or combined with pembro (SURE-02), before RC.

Methods: This phase 2, open-label trial will test the safety, tolerability, activity, of SG and SG+Pembro.
This study will enroll pts sequentially in the 2 cohorts. Pts should have a histopathologically-confirmed predominant UC, be fit and planned for RC, have a clinical stage T2-T4N0M0 MIBC, be ineligible (Galsky criteria) or refuse to receive cisplatin-based chemotherapy. Eligible pts will receive 4 cycles of 10 mg/Kg SG IV, on days 1, 8, of each 21 day cycle (SURE-01) and SG plus Pembro on day 1, every 21 days, at the standard dose of 200 mg intravenously (SURE-02). Surgery is planned at the time of study inclusion to be performed within 2 weeks of the last dose of study drug. After surgery patients will be managed and the surgical safety data will be recorded according to the European Association of Urology (EAU) guidelines. In SURE-02, an adjuvant phase of 13 postoperative cycles of pembrolizumab will be administered. The primary endpoint of the study is to assess the proportion of ypT0N0. The total sample size of SURE is of 77 pts, distributed as 56 pts in SURE-01 and 48 in SURE-02. The assumptions include a ypT0N0 $\leq$20% as H_0 and $\geq$45% as H_1 in a single-stage A'Hern's design for SURE-01 and a 2-stage design for SURE-02 assuming a ypT0N0 $\leq$30% as H_0 and $\geq$45% as H_1. In SURE-02 a safety lead-in phase will be conducted including 10 subjects. An external Review Committee will evaluate the safety outcomes in this phase and the occurrence of pre-defined study-limiting events.
Biomarker analyses will include assessment of transcriptomic clustering, immune-gene signature, next generation sequencing on tumor circulating tumor DNA (ctDNA), including single-cell RNA sequencing on frozen tumor samples, before and after treatment.

Study sponsor: IRCCS San Raffaele Hospital and Scientific Institute, Milan, Italy.
Collaborators (budget and funding): Gilead, Merck Inc.

Skills to be acquired by the student:

In this project, which includes a robust biomarker platform based on an academic clinical trial, the student will be able to learn the most advanced biomarker discovery platforms thanks to multiple collaborations we have set with Companies (e.g., Foundation Medicine Inc, Celsius Therapeutics Inc, Decipher Biosciences Inc.) within this clinical study. Among the most advanced technologies the student will be able to learn, applied to clinical trials, there will be the single-cell RNA sequencing, made possible through an ongoing collaboration with Celsius Therapeutics.

In particular, the student will be able to follow the entire process of tumor sample analyses, from the biopsy to the final biomarker report. He/she will be able to access the database we will generate from the planned analyses, and will have the possibility to independently propose original analyses after discussion with the DoS.

Finally, the student will work full time in a clinical research environment and will be able to learn the process of clinical trials submission, ethical discussion, approval and the start-up activities including the operational, management steps.

References (max. 3)

1. Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients With Muscle-Invasive Urothelial Bladder Carcinoma (PURE-01): An Open-Label, Single-Arm, Phase II Study. J Clin Oncol. 2018 Dec 1;36(34):3353-3360.
2. Necchi A, Raggi D, Gallina A, et al. Impact of Molecular Subtyping and Immune Infiltration on Pathological Response and Outcome Following Neoadjuvant Pembrolizumab in Muscle-invasive Bladder Cancer. Eur Urol. 2020 Jun;77(6):701-710
3. Necchi A, de Jong JJ, Raggi D, et al. Molecular Characterization of Residual Bladder Cancer after Neoadjuvant Pembrolizumab Eur Urol (2021), https://doi.org/10.1016/j.eururo.2021.03.014.