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Clinical Trials Corner

Dear Readers,

This month's issue of the Clinical Trials Corner of *Bladder Cancer* is devoted towards novel intravesical therapy trials for non-muscle invasive bladder cancer (NMIBC). Historically, we have not had any advances in the treatment of NMIBC since the approval of BCG. However, BCG has limited efficacy and management of BCG-refractory disease has been suboptimal consisting of further BCG, intravesical chemotherapy, or radical cystectomy. With the advent of checkpoint blockade inhibitors, it is common to forget that we have active ongoing trials in NMIBC that are evaluating novel intravesical therapies that are not checkpoint blockade inhibitors. In this issue, we specifically highlight some of these trials that are actively recruiting patients. We have described ABI-009, rAd-IFN/Syn3, mistletoe plant extract (AVF2), and MCNA in previous issues and so they will not be mentioned again here but please refer to previous issues for details of these agents. In the future, if you feel that you would like to draw attention to a specific trial, please feel free to email us at: piyush.agarwal@nih.gov and/or cnsternberg@corasternberg.com.

Sincerely,

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Study Title: VPM1002BC in Recurrent Non-muscle Invasive Bladder Cancer (NMIBC)

Clinicaltrials.gov identifier: NCT02371447

Sponsor: Swiss Group for Clinical Cancer Research

Enrollment: 39

Study Design: Phase I/II single arm trial of VPM1002BC in patients with recurrent high-risk non-muscle invasive bladder cancer after standard Bacillus Calmette Guerin (BCG) therapy. VPM1002BC is a genetically modified BCG designed to be more immunogenic and tolerable than standard intravesical BCG. Phase I of this trial evaluated safety and tolerability of intravesical instillations of VPM1002BC and determined the recommended Phase II dose. Results of Phase I showed that VPM1002BC was well tolerated and safe. Phase II of this trial has been recently opened for accrual. The primary endpoint for Phase II is the recurrence-free rate in the bladder. The secondary endpoints include time to recurrence, time to progression, overall survival, tolerability, the incidence of adverse events, and quality of life. The treatment schedule consists of a standard induction therapy of 6 weekly instillations followed by a maintenance regimen of 1 year (3 weekly instillations 3, 6 and 12 months after start of treatment.

Rationale: Despite the proven efficacy of BCG treatment in patients with NMIBC, recurrence-free and progression-free survival are still to be improved. VPM1002BC has an innovative mode of action with a unique potential of inducing tumor-specific immune responses.

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Comments: As consequence of the previous treatment and priming with standard BCG, VPM1002BC might induce an even stronger immune response in patients included in this trial. However, the treatment was well tolerated in Phase I. We eagerly await the results of the phase II portion of this trial.

Study Title: Safety and Tolerability of GemRIS 225 mg in Subjects With Non Muscle-Invasive Bladder Cancer (NMIBC)

Clinicaltrials.gov identifier: NCT02720367

Sponsor: Taris Biomedical LLC

Enrollment: 30

Study Design: Phase Ib multi-center single-arm study evaluating safety, tolerability, and efficacy of GemRIS 225 mg in patients with low or intermediate risk urothelial cell carcinoma of the bladder. Patients with any high grade disease and previous intravesical therapy with chemotherapy (e.g. gemcitabine) or BCG within the last 12 months are excluded from the trial. Patients will have insertion of GemRIS 225 into the bladder at day 0 and removal at day 7. Subsequent insertion will occur on day 21 and then will be removed on day 28 on the day of the TURBT. The primary endpoint is safety as determined by the number of patients with treatment emergent adverse events (TEAEs). Secondary endpoints include: tolerability of agent, plasma and urine levels of gemcitabine, and anti-tumor effects.

Rationale: Intravesical gemcitabine has been shown to be tolerable and active especially in BCG-refractory NMIBC. GemRIS, an investigational drug delivery method, is a passive gemcitabine-releasing system that is inserted into the bladder cystoscopically and releases gemcitabine for 7 continuous days. This technology involves the use of a proprietary drug eluting system that is inserted cystoscopically and can be retained in the bladder and can then be subsequently removed.

Comments: The "pretzel" technology of Taris has been successfully used to elute intravesical lidocaine in patients with intractable interstitial cystitis. This platform offers the ability to elute various drugs in the bladder in a sustained manner that goes well beyond 1-2 hour intravesical dwell time that can be achieved in an office setting. GemRIS is probably the beginning of many intravesical elutions that will be evaluated for NMIBC.

Study Title: Vicinium Treatment for Subjects With Non-muscle Invasive Bladder Cancer (NMIBC) Previously Treated With BCG (VISTA: Vicinium Study in Bladder Cancer)

Clinicaltrials.gov identifier: NCT02449239

Sponsor: Viventia Bio

Enrollment: 134

Study Design: Single arm non-randomized multi-center phase III study evaluating efficacy of intravesical Vicinium in patients with recurrent high grade NMIBC that is refractory or intolerant to BCG. Vicinium is given as an induction course (twice weekly for 6 weeks and then once weekly for 6 weeks) followed by a maintenance course (once every other week for up to 104 weeks). The primary endpoint is the complete response rate and duration of response in patients with CIS. The secondary endpoints include: recurrence rate, progression-free survival , cystectomy rate, and overall survival. In addition, the time to these events will also be noted.

Rationale: Vicinium is a recombinant fusion protein, VB4-845, that contains a humanized single-chain antibody fragment specific for the epithelial cell adhesion molecule (EpCAM) antigen linked to ETA (252-608), Pseudomonas aeruginosa exotoxin A. EpCAM is overexpressed on the surface of urothelial carcinoma cells and therefore represents a good target for Vicinium to bind to. In a previous phase II study with a less rigorous induction and maintenance schedule in BCG refractory or BCG intolerant patients with CIS, the 3-month

complete response rate was 40% and 16% of patients remained disease-free at 1 year. These results spurred the current phase III trial.

Comments: Fusion proteins are attractive in cancer therapy as they can deliver a cytotoxic payload to tumors provided that the receptor of interest is preferentially expressed in the tumor cells. EpCAM is one such target that appears to be over-expressed in bladder tumors and given that the fusion protein had activity in a difficult to treat population in the phase II study, perhaps a more rigorous regimen will have greater activity in the ongoing phase III study.