

Clinical Trials Corner Issue 8(1)

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Dear Readers,

In this issue, we highlight recently published and presented clinical trials in the treatment of localized bladder cancer. In the future, please reach out to us directly in order to highlight any specific clinical trials at pkagarwal@uchicago.edu or cns9006@med.cornell.edu and/or at BLC@iospress.com.

Sincerely,

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Study Title: ONCOFID-P-B (PACLITAXEL-HYALURONIC ACID) in the Intravesical Therapy of Patients With Non-muscle Invasive Cancer of the Bladder

Clinicaltrials.gov identifier: NCT04661826

Sponsor: Fidia Farmaceutici S.p.A.

Enrollment: 60

Rationale: The urothelial membrane resists penetration of chemotherapeutic agents preventing effective therapy of non-muscle invasive bladder cancer (NMIBC). Oncofid-P-B is a novel intravesical agent consisting of paclitaxel conjugated to hyaluronic acid (HA). It is postulated that the HA moiety binds selectively to CD44 which is over-expressed on the surface of urothelial tumors allowing for increased paclitaxel activity. In vitro studies demonstrate greater cytotoxicity in cell lines with Oncofid-P-B compared to paclitaxel alone. A previous Phase I study established good tolerability and efficacy in a BCG-refractory CIS cohort treated with a weekly 6-week course. This study is a Phase II, single-arm trial evaluating the effects of an intensive or induction phase followed by a maintenance phase of treatment with Oncofid-P-B in patients with high risk, BCG unresponsive CIS +/- Ta or T1 disease.

Study Design: Oncofid-P-B is a novel compound under development by Fidia Farmaceutici S.p.A. with specific binding to the CD44 receptor. This is a single-arm, multicenter European study consisting of weekly intravesical instillation of Oncofid-P-B for 12 weeks (intensive phase) followed by 12 monthly instillations (maintenance phase). Patients with CIS ± Ta-T1, unresponsive or intolerant to BCG, unwilling or unfit for cystectomy were

enrolled. Patients were deemed BCG-refractory and were not BCG-unresponsive by current standards. Patients with muscle invasive bladder cancer (MIBC) and/or concomitant cancer of the upper urinary tract were excluded.

Endpoints: The safety and tolerability profile was the primary endpoint. The secondary endpoints were the antitumor activity of Oncofid-P-B measured at the end of the intensive phase and every three months during the maintenance phase, compliance with treatment, and evaluation of systemic absorption of Oncofid-P-B. The complete response rate was defined as a negative cystoscopy, negative biopsy of the urothelium (performed after the intensive phase or whenever a suspicious area was found) and a negative cytology.

Results: Twenty-one patients were enrolled and twenty completed treatment and were evaluable. At study entry, 85% of patients had CIS only and 80% of all patients were unresponsive to BCG whereas 20% of all patients were intolerant to BCG. The compliance rate with the intensive treatment regimen was 91.6%. The complete response rate was 75% at the end of the intensive phase. The complete response rate was 65% at month 3 of maintenance therapy and was 40% at the end of the maintenance phase (15 months after treatment start). Ultimately, twelve patients did not respond and two had disease progression (one with lamina propria invasion and one with muscle invasion). Median time to failure (e.g. persistent CIS, disease relapse or progression) was 14.1 months in all patients. Eighteen (90%) patients experienced AEs and SAEs were only reported in two (10%) patients. One patient experienced death but not related to Oncofid-P-B and felt to be secondary to concomitant disease with squamous lung carcinoma. There was no systemic absorption of the drug.

Comments: This phase II study is promising and demonstrated good safety and tolerability and early efficacy results on par with other investigational agents in the BCG-unresponsive NMIBC clinical space. Of note, seven patients only received a single induction course of BCG followed by additional chemotherapy and were enrolled in order to mitigate the future risk of disease progression and so it is conceivable that the response rates seen are higher than what would be seen in a truly BCG-unresponsive cohort. The initial results warrant further evaluate in Phase II/III studies.

Reference: Hurlle R, Guazzoni G, Colombo P, et al. Oncofid-P-B: a novel treatment for BCG unresponsive carcinoma in situ (CIS) of the bladder: Results of a prospective European Multicentre study at 15 months from treatment start. *Urol Oncol.* 2021 Oct 11:S1078-1439(21)00308-2. doi: 10.1016/j.urolonc.2021.07.007.

Study Title: NIMBUS Trial

Clinicaltrials.gov identifier: N/A

Sponsor: European Association of Urology Research Foundation

Enrollment: 345

Rationale: BCG is the standard treatment for high risk non-muscle invasive bladder cancer (NMIBC) and given recent data suggesting comparable efficacy and improved tolerability with reduced dosing as well as recent challenges in administration given BCG shortages, this trial evaluated whether a reduced number of standard dose BCG instillations were non-inferior to the standard number and dose of BCG instillations for patients with high grade NMIBC.

Study Design: BCG naïve patients with high grade Ta or T1, primary or recurrent, single or multiple papillary urothelial cancer with or without CIS after adequate resection of papillary component (with muscle present in the specimen) were randomized to standard BCG frequency (SF) or reduced BCG frequency (RF). The SF arm consisted of 15 total instillations: a) induction course of weekly BCG for 6 weeks followed by b) maintenance courses of weekly BCG for 3 weeks at month 3, 6, and 12. The RF arm consisted of 9 total instillations: a)

induction course of BCG at week 1, 2, and 6 followed by b) maintenance courses of BCG at only weeks 1 and 3 at month 3, 6, and 12. Cystoscopy and cytology were performed every 3 months for the first two years and every six months afterwards. Patients completed study at first recurrence or after occurrence of new CIS, upper tract urothelial carcinoma, prostatic urethral disease, distant metastases, or requiring systemic chemotherapy. The study was designed to establish therapeutic equivalence defined as the lower part of the confidence interval (CI) (using one-sided 2.5% level of significance) being higher than a hazard ratio of 0.75 for recurrence. The sample size was calculated to be 412 per arm after recruitment delay due to BCG shortage led to re-definition of statistical assumptions.

Endpoints: The primary endpoint was time to first recurrence. Secondary endpoints included progression to muscle-invasion, number and grade of recurrent tumors, and side effects.

Results: As of November 2021, 359 patients were randomized with 177 to the RF arm and 182 to the SF arm. Majority of tumors were T1 and concomitant CIS seen in 28% of the RF arm and 29% of the SF arm. After fourteen months of median follow-up for all patients, ITT analysis demonstrated disease recurrence in 85 (24%) of the 359 patients: 55 (31%) of the 177 RF patients and 30 (16%) of the 182 SF patients. Univariate Cox regression demonstrated a HR of 0.47 (95% CI: 0.30-0.74) for first recurrence favoring the SF arm. The trial closed early due to inferiority of the RF arm. Interestingly, seven patients progressed to muscle invasive bladder cancer with one in the RF arm and six in the SF arm.

Comments: NIMBUS was designed based on animal data demonstrating profound Th1-mediated cytokine responses at weeks 1 and 6 of induction BCG equivalent to an entire 6-week induction phase. The maintenance course was also shortened in the RF arm based on data from CUETO 98013 demonstrating that one maintenance instillation is sufficient. However, the results in this randomized trial demonstrated an increased recurrence rate in the RF arm. There are obvious limitations to this trial (lack of central pathology review, stopping maintenance at 1 year) but the trial did factor in BCG shortages and 90% of patients had a re-TUR. Despite data in animal models, current SF BCG protocols result in lower recurrence rates and should remain the standard of care. This trial does not address the common practice of maintaining standard frequency BCG administration but with reduced dosing (e.g. one-half to one-third dose) for maintenance instillations.

Reference: Grimm MO, van der Heijden AG, Colombel M, Muilwijk T, Martínez-Piñeiro L, Babjuk MM, Türkeri LN, Palou J, Patel A, Bjartell AS, Caris C, Schipper RG, Witjes WPJ; EAU Research Foundation NIMBUS Study Group. Treatment of High-grade Non-muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations: Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial "NIMBUS". *Eur Urol.* 2020 Nov;78(5):690-698. doi: 10.1016/j.eururo.2020.04.066. Epub 2020 May 20. PMID: 32446864.

Personal communication with Grimm MO (January 26, 2022) from his presentation at the EMUC 2021 Annual Meeting

DISCLOSURES

Cora N. Sternberg

Consultant: Pfizer, Merck Ga, MSD, AstraZeneca, Astellas Pharma, Sanofi-Genzyme, Roche/Genentech, Immunomedics now Gilead, Clovis Oncology, Bayer, Foundation Medicine, UroToday, Medscape,

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