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THE RADIO-ENHANCER HAFNIUM OXIDE NANOPARTICLE, NBTXR3 ACTIVATED BY RADIATION THERAPY IN PATIENTS WITH LOCALLY ADVANCED SOFT TISSUE SARCOMA: A PHASE II/III TRIAL

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Objective: A subset of locally advanced soft tissue sarcoma (STS) patients achieve significant therapeutic benefit from preoperative radiation therapy (RT) as shown by Pisters JCO 1996 and Yang JCO 2018. However, the impact of RT on pathological response (pR) and R0 resection is limited, highlighting the need for novel multimodal therapies aimed at local control.
NBTXR3 (hafnium oxide nanoparticles), injected intratumorally may represent such an option. Otherwise inert, NBTXR3 augments the effective RT dose deposited within tumor cells when activated by ionizing radiation to increase cancer cell death compared to RT alone.
We report here on the results of a phase II/III randomized clinical trial evaluating the preoperative efficacy and safety of NBTXR3 activated by RT in patients with locally advanced STS of the extremity and trunk wall [NCT02379845].

Methods: This is a multi-national phase II/III randomized, open-label clinical trial. Adults with locally advanced STS of the extremity or trunk wall, of any histologic grade, eligible for preoperative RT were randomly assigned 1:1 to receive NBTXR3 as a single intratumoral injection (volume corresponding to 10% of baseline tumor volume at 53.3g/L) followed by external beam RT (EBRT; 50 Gy as 25 fractions of 2 Gy, over 5 weeks) (arm A) or EBRT alone (arm B). Both arms had the chance to go on to receive post-RT surgical resection.

The primary objective was to compare the proportion of patients with pathological complete response (pCR; defined as <5% of residual viable cancer cells after surgery), as assessed by a Central Pathology Review Board based on the EORTC guidelines. Key secondary endpoints included negative surgical margin (R0), limb amputation rate and safety. Safety was evaluated in all subjects who received at least one puncture of NBTXR3 or at least one fraction of RT. Subjects are in continued long-term follow-up, focused on safety.

Results: Between March 3rd, 2015 and November 21st, 2017, 180 patients were randomized and 179 received treatment: n=89; arm A and n=90; arm B. The proportion of patients with pCR was 16.1% (14/87) compared with 7.9% (7/89) in arms A and B, respectively (p=0.044). The R0 resection rate was 77.0% (67/87) in arm A versus 64.0% (57/89) in arm B (p=0.0424). The most common grade 3-4 treatment emergent adverse event (AE) was post-operative wound complication, which occurred at a similar rate in each arm (8/89 and 8/90 in arm A and B, respectively). The most common grade 3-4 AE related to NBTXR3 administration was injection site pain (4/89, 4.5%) and hypotension (4/90, 4.4%). Skin injury was the most common grade 3-4 RT-related AE, which was shared between both arms (5/89, 5.6% and 4/90, 4.4% in arm A and B, respectively). Serious AEs were observed in 35 (39.3%) of 89 patients in arm A and 27 (30.0%) of 90 patients in arm B. There were no treatment-related deaths. Follow-up was conducted on 153 patients with a current median follow-up of 18.5 months. Currently 87 patients are still in long-term follow-up.

Conclusion: This registration trial of NBTXR3 combined with EBRT significantly achieved its primary and secondary endpoints of improving pCR and increasing R0 resection versus EBRT alone. NBTXR3 together with EBRT was well tolerated with a safety profile consistent with EBRT alone. Taken together, these results led to the EU approval (CE Mark) of NBTXR3 + RT for patients with locally advanced STS of the extremity and trunk wall.