Abstract for ASTRO 2018

Title:

Act.In.Sarc: An international randomized phase III trial evaluating efficacy and safety of first-in-class NBTXR3 hafnium oxide nanoparticles activated by preoperative radiotherapy in locally advanced soft tissue sarcoma

Authors:

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Purpose/Objectives(s):

A subset of soft tissue sarcoma (STS) patients achieve significant therapeutic benefit from preoperative radiotherapy (RT). Yet, this treatment paradigm may be associated with limited efficacy and increased toxicity, highlighting the necessity of novel multimodal therapies aimed at local control with few adverse events (AEs).

NBTXR3 is a first-in-class Hafnium-Oxide nanoparticle. Designed for cancer cell uptake, it is injected intratumorally (IT) and activated by ionizing radiation to yield a tumor-localized high energy deposit and increased cell death compared to the same dose of RT alone.

We report now the first phase II/III randomized clinical trial of NBTXR3 given as preoperative treatment to patients with locally advanced STS of the extremity and trunk wall.

Methods:

In this multicenter, open-label phase II/III trial [NCT02379845], patients (pts) were randomized 1:1 to receive a single IT preoperative NBTXR3 injection followed by RT or RT alone and then surgical resection. RT consisted of Intensity Modulated RT or 3D-RT of 2Gy*25 fractions (total 50 Gy).

The primary endpoint was pathological Complete Response Rate (pCRR) defined as the percentage proportion of pts presenting ≤5% of residual viable cancer cells (EORTC guidelines) evaluated by a blind Central Review Board. Key secondary endpoints included negative surgical margins (R0) and safety.

Results:

In 180 included pts, the pCRR was 16.1% in the NBTXR3 plus RT group compared with 7.9% in the RT alone group (p=0.0448) in the intent-to-treat full analysis set population, which included all pts who were randomized and stratified by STS histological subtype. In the same population, 77.0% in the experimental arm achieved an R0 versus 64.0% in the control arm (p=0.0424). NBTXR3 showed very good local tolerance without any modification of RT alone safety profile. In all the treated pts, who were randomly assigned and received any amount of NBTXR3 or at least one RT dose, the IT administration of NBTXR3 caused injection-site pain in 12 (13.5%) pts. NBTXR3 was also associated with grade 3-4 acute immune reactions in 7 (7.9%) pts, but these AEs were of short duration, manageable, and resolved spontaneously in some cases.

Conclusion:

This trial met its primary and secondary endpoints of pCRR and R0 rates, respectively. NBTXR3 with RT demonstrated an acceptable safety profile compared to RT alone.

As pCR is a known indicator of long-term treatment response with a positive correlation to both progression free and overall survival, NBTXR3 represent a new option for preoperative treatment for locally advanced STS. These data support ongoing studies investigating NBTXR3 in recurrent/metastatic HNSCC or metastatic non-small cell lung cancer [NCT03589339]; HNSCC [NCT01946867; NCT02901483]; prostate [NCT02805894], liver [NCT02721056] and rectal cancers [NCT02465593].