Conclusion: Apatinib in combination with IMRT was safe and effective in improving PFS and DCR, and suggested an encouraging anti-tumor activity in patients with unresectable advanced HCC.

Author Disclosure: S. Ke: None. H. Qiu: None. J. Peng: None. Y. Chen: None.

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Analysis of Radiation Therapy Quality Assurance in NRG Oncology RTOG 0848

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Purpose/Objective(s): NRG/RTOG 0848 is a two-step randomized trial to evaluate the benefit of the addition of concurrent fluoropyrimidine and radiotherapy (RT) following adjuvant gemcitabine-based chemotherapy (2^{nd} step) for patients with resected pancreatic head adenocarcinoma. Real-time quality assurance (QA) was performed for each patient who underwent RT. QA findings were reviewed, frequencies & reasons for resubmissions are reported.

Materials/Methods: Patients were treated using either a 3D-conformal RT (3DCRT) or intensity-modulated RT (IMRT) technique. In addition to a web-based contouring atlas, the protocol outlined step-by-step instructions for generating the clinical treatment volume (CTV) through the creation of specific regions of interest. The planning target volume (PTV) was established by expanding the CTV by 0.5 cm in all directions. Treatment planning data, including pre-operative imaging, surgical and pathology reports, simulation images with isodose lines, structure set, and dose volume histograms were submitted for review. One of two radiation oncology study chairs independently reviewed each plan. Plans with unacceptable deviations were returned for revision and then resubmitted for review until approved. Treatment started after final approval of the RT plan.

Results: Of the 354 patients who underwent second randomization, 180 were randomized to the RT arm. Of these, 160 received RT and were included in the QA analysis. Most patients (86%) were treated using IMRT. Resubmissions were more common for patients planned with 3D-CRT (43%) than with IMRT (31%). In total, at least one resubmission of the treatment plan was required for 33% of patients (see Table 1). Among patients requiring resubmission, the majority only needed to be resubmitted once (87%). The most common reasons for resubmission were unacceptable deviations with respect to the pre-operative gross target volume (GTV, 61%) and the pancreatojejunostomy (48%), leading to unacceptable deviations of the contours of the CTV and PTV (70% for each). Most patients requiring a resubmission had 5-9 unacceptable deviations (46%). Unacceptable deviations were similar for the few treatment plans that needed to be resubmitted more than once.

Conclusion: One third of patients required resubmission to meet protocol compliance criteria, demonstrating the continued need for expending resources on pretreatment QA for adjuvant pancreas cancer trials. Rigorous QA is of critical importance for clinical trials involving RT to ensure that the true impact of RT can be assessed. Moreover, RT QA serves as an educational process by training radiation oncologists on best practices.

Abstract 76 — Table 1

Resubmissions (Yes vs. No) and # Resubmissions for Contour by Modality

	3D-CRT (n = 23)		IMRT (n = 137)		Total (n = 160)	
	n	%	n	%	n	%
Resubmissions						
Yes	10	43	43	31	53	33
No	13	57	94	69	107	67
# Resubmissions out of patients requiring a resubmission	n = 10		n = 43		n = 53	
1	8	80	38	88	46	87
2	2	20	4	9	6	11
3	0	0	1	2	1	2

Author Disclosure: L. Tchelebi: None. K. Winter: None. R.A. Abrams: None. H. Safran: None. W.F. Regine: None. S. McNulty: None. A.J. Wu: Research Grant; CivaTech Oncology, Inc. Honoraria; 1199SEIU. Consultant; AstraZeneca, MORE Health. Advisory Board; Simphotek, Inc. Travel Expenses; AlphaTau Medical. Stock; Simphotek, Inc. K.L. Du: Independent Contractor; Albert Einstein Health System. Consultant; ACR, Dopf, PC. Travel Expenses; ACR. S.A. Seaward: None. S.X. Bian: None. R. Aljumaily: None. A.T. Shivnani: Stock; Gradalis. T. Moore: None. T. Crocenzi: None. T.A. DiPetrillo: Patent/License Fees/Copyright; Thomas DiPetrillo. A. Kuykendal: None. C.H. Crane: None. K.A. Goodman: Consultant; RenovoRx, Syntactx. NCI.

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Study of Novel Radioenhancer NBTXR3 Plus Radiotherapy in Patients With Locally Advanced Soft Tissue Sarcoma: Results of the Long-Term Evaluation in the Phase II/III Act.In.Sarc Trial

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Purpose/Objective(s): NBTXR3, a novel radioenhancer activated by radiotherapy (RT) demonstrated superior efficacy, as preoperative treatment in patients with locally advanced soft tissue sarcoma (LA STS) compared to RT alone. Primary endpoint of pCR rate (16% vs 8%; $P = 0.044$)

and main secondary endpoint of R0 margin rate (16% vs 8%; $P = 0.042$) were met while no modification of the early RT-associated safety profile was observed, leading to market authorization. Here we report on the long-term safety, limb function and quality of life.

Materials/Methods: This phase II/III randomized (1:1), international trial included adult patients with LA STS of the extremity or trunk wall, requiring preoperative RT. Patients received either a single intratumoral injection of NBTXR3 (equivalent to 10% of tumor volume, at 53.3g/L), plus EBRT (arm A) or EBRT alone (arm B) (50 Gy in 25 fractions), followed by surgery. Here we report on safety of NBTXR3+RT which was evaluated as secondary endpoint. Data were recorded on the "all treated population" during at least a two-year follow-up. Important parameters related to HR-QoL including functional outcome were studied using the EQ-5D, RNLI, TESS and MSTS questionnaires.

Results: Patients had at least two-year follow-up and the lost to follow-up rate was very low (1.9%). RT-related SAEs were observed in 11.2% (10/89) vs 13.3% (12/90) in A vs B. Post-treatment AEs, any grade, were observed in 51.7% (46/89) vs 57.8% (52/90) and serious post-treatment AEs in 13.5% (12/89) vs 24.4% (22/90) of patients in A vs B. Long-term safety continues to demonstrate that NBTXR3 plus RT has no impact on post-surgical wound complications (24.7% vs 36.7%, A vs B). Furthermore, the evaluation of radiation late toxicities in limbs such as fibrosis, arthrosis and edema that may alter limb function showed no difference between arms (4.5% vs 7.7%, 2.2% vs 0.0% and 6.7% vs 2.2% respectively in A vs B). In addition, sequelae or chronic tissue disturbances at the former tumor localization were similar in both treatment arms, confirming that the increase of energy dose deposit and the physical presence of NBTXR3 did not impact post-treatment limb functions. Accordingly, HR-QoL evaluation yielded no difference in functional outcome. Finally, second primary cancer was observed in 1 patient in arm A and 6 patients in arm B and the intratumoral injection of NBTXR3 did not induce cancer cell seeding at the former tumor site.

Conclusion: These results demonstrate that the use of NBTXR3 did not change the late onset toxicity profile of EBRT, nor modified its bystander effect. Taken together, the long-term safety data presented here, and the previously published efficacy data reinforce the favorable benefit-risk ratio of the use of NBTXR3 in patients with LA STS. NCT02379845

Author Disclosure: S. Bonvalot: Honoraria; Nanobiotix, Pharmamar. Consultant; Nanobiotix. Advisory Board; Nanobiotix. Travel Expenses; Nanobiotix, Pharmamar. P. Rutkowski: Honoraria; Novartis, BMS, MSD, Roche, Amgen, Eli Lilly, Pfizer, Blueprint Medicines. J.O. Thariat: Honoraria; Nanobiotix. S. Carrere: None. A. Ducassou: Honoraria; Nanobiotix. M. Sunyach: None. P. Ágoston: None. A. Hong: None. A. Mervoyer: None. M. Rastrelli: None. C. Le Pechoux: Honoraria; Nanobiotix, Amgen, Roche, PrimeOncology, Medscape Lilly, AstraZeneca. V. Moreno: None. R. Li: None. B. Tiangco: None. Z. Papai: None.

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A Phase 2 Study of 5-Day Preoperative Radiotherapy for Patients With High-Risk Primary Soft Tissue Sarcoma

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Purpose/Objective(s): Preoperative radiation therapy (RT) is an integral component of local control in soft tissue sarcoma (STS), but the conventional 5-week treatment course is burdensome for patients (pts). We conducted a single-institution phase 2 study of 5-day dose-equivalent preoperative RT for high-risk primary STS, which demonstrated acceptable rates of wound complications and 2-year toxicity. Here, we present results with longer follow-up, including additional pts from an expansion cohort.

Materials/Methods: The initial cohort accrued between April 2016 and May 2018 and included 52 pts with histologically confirmed extremity or trunk STS planning to undergo preoperative RT followed by surgery. The primary endpoint of the initial cohort was the rate of grade ≥2 radiation morbidity (fibrosis, lymphedema, or joint stiffness) at 2-years. An expansion cohort opened in October 2018 to compare wound complication rates between preoperative RT alone versus chemoRT and has enrolled an additional 47 pts. Patients received 30 Gy (RT alone) or 25 Gy (chemoRT) over 5 daily fractions to the primary tumor with standard margins. Here we report on pts with primary localized STS who completed preoperative RT and surgery in the initial and expansion cohorts (N = 79; chemoRT excluded). We assessed disease outcomes (local control, distant metastasis, and survival rates) and toxicity (grade ≥2 fibrosis, lymphedema, or joint stiffness) after minimum 2-year follow-up (N = 52). Fibrosis and joint stiffness were graded using RTOG/EORTC criteria, and lymphedema by Stern's scale. We also updated the major wound complication rate (defined per established criteria) after minimum 1-year follow up (N = 60).

Results: Of the 52 pts with minimum 2-year follow-up, predominant histologic subtypes included undifferentiated pleomorphic sarcoma, spindle cell sarcoma or sarcoma NOS (N = 24), myxofibrosarcoma (N = 8), and myxoid liposarcoma (N = 12). Median tumor size was 6.9 cm, and 15 pts had tumors ≥10 cm. At a median follow-up of 3 years, the local recurrence, distant metastasis and all-cause mortality rates were 6.5% (3 of 46 evaluable pts), 20.8% (10 of 48 evaluable pts), and 21.2% (11 of 52). Two of 3 pts (66%) with a local recurrence had undergone R1 resections, compared to 9 of 46 (19.5%) overall. The rate of overall grade ≥2 radiation morbidity in this same group was 13.0% (fibrosis: 5 pts, joint stiffness: 5 pts, lymphedema: 2 pts). Major wound complications were observed in 16 out of 60 (26.7%) evaluable pts.

Conclusion: Longer follow-up of a phase 2 study of 5-day pre-operative RT for pts with extremity/trunk STS demonstrates excellent local control. Rates of radiation fibrosis, joint stiffness and lymphedema, as well as wound complications, remain acceptable. We have also developed a web-based, interactive user interface for data visualization, which can help providers identify and understand relationships between baseline characteristics and clinical outcomes in our study.

Author Disclosure: R.R. Savjani: Research Grant; Varian Medical Systems. S.D. Nelson: None. S.M. Dry: None. M. Kamrava: American Board of Radiology, Brachytherapy Journal, American Brachytherapy Society Board of Directors. Co-Editor; Journal of Contemporary Brachytherapy. J. Hernandez: None. N. Chong: None. B. Chmielowski: None. A.S. Singh: None. J. Crompton: None. B. Crawford: None. S.V. Bukata: None. B. Kadera: None. N.M. Bernthal: None. J.B. Weidhaas: None. M.L. Steinberg: None. F.C. Eilber: None. A. Kalbasi: None.

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High Local Control Following Pre-Operative Radiotherapy for Adult Deep Soft Tissue Sarcoma of the Head and Neck

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