Abstract 3327; Table 2 Hematologic and non-hematologic toxicity

	NCI-CTC grade (n = 20)											
	0		1		2		3		4		5	
Toxicity	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematologic												
Leukocytopenia	0	0	8	40	10	50	2	10	0	0	0	0
Neutropenia	11	55	6	30	2	10	1	5	0	0	0	0
Anemia	5	25	15	75	1	5	0	0	0	0	0	0
Thrombocytopenia	19	95	0	0	1	5	0	0	0	0	0	0
Decreased lymphocyte count	0	0	3	15	5	25	11	55	1	5	0	0
Decreased monocyte count	18	90	2	10	0	0	0	0	0	0	0	0
Non-hematologic												
Esophagitis	9	45	6	30	5	25	0	0	0	0	0	0
Nausea	18	90	2	10	0	0	0	0	0	0	0	0
GI hemorrhage	18	90	1	5	0	0	0	0	0	0	1	5
Fatigue	17	85	2	10	1	5	0	0	0	0	0	0
AST increase	19	95	1	5	0	0	0	0	0	0	0	0
ALT increase	19	95	1	5	0	0	0	0	0	0	0	0
Pneumonitis	16	80	4	20	0	0	0	0	0	0	0	0
Dermatitis	19	95	1	5	0	0	0	0	0	0	0	0

combined with pembrolizumab for the treatment of local advanced, resectable esophageal squamous cell cancer (ESCC).

Materials/Methods: Participants will receive carboplatin (AUC = 2) and paclitaxel (50mg/m^2) or nab-paclitaxel (60mg/m^2) on day 1,8,15,22,29, and pembrolizumab (2mg/kg) IV on days 1 and 22. A total of 41.4 Gy was given in 23 fractions. Surgery will be performed within 6 weeks after completion of preoperative therapy.

Results: Twenty patients were enrolled from June 2019 to December 2019. The median age was 61.2 years (range, 39 to 66 years). All of them had treatment-related adverse events (AEs) (all grade 1 or 2). The common grade 3 hematologic toxicities were decreased lymphocyte count (55%), followed by leukopenia (10%). One patient developed grade 4 decreased lymphocyte count (5%). And one patient (5%) discontinued NCRT for one week due to grade 3 hematologic toxicities. No treatment-related grade 3-4 non-hematologic AEs were observed, excepting for one patient dying from treatment-related GI hemorrhage, which occurred in two weeks after complete of neoadjuvant treatment. The common non-hematologic toxicities were esophagitis, followed by fatigue and pneumonitis. Until last follow-up, fourteen patients had received radical surgery, among them nine had pathological complete response (pCR: 60%). One patient developed liver metastasis after completion of neoadjuvant treatment (PD, 5%), one patient died from GI hemorrhage after neoadjuvant treatment and the remaining four patients still awaits radical surgery as scheduled.

Conclusion: This trial shows that NCRT plus pembrolizumab improves pathological response rate among patients with locally advanced ESCC, with acceptable and manageable adverse events.

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3328

DNA Damage Response Protein Mutations Associated with Response to Radiotherapy in Gastrointestinal Malignancies

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Purpose/Objective(s): The prevalence of DNA damage response (DDR) protein mutations among gastrointestinal (GI) malignancies is not well characterized. As next-generation sequencing (NGS) has become more commercially available, there is an opportunity to better establish the role of mutations in DDR proteins and their response to radiotherapy. Understanding somatic genetic aberrations that can influence radiation response can help guide patient-specific radiotherapy (RT). In this current study, commercially available DNA sequencing was conducted on patients with GI cancers to identify significant genetic mutations in the DDR pathway and to quantify their associations with local control.

Materials/Methods: A total of 65 solid tumor biopsy specimens from pathologically confirmed GI cancers underwent molecular profiling with NGS. All patients were treated with external beam radiation therapy to primary lesions or to distant metastases. Clinical outcomes were measured from time of RT to time of progression or last follow-up and included RT to primary lesions and distant metastases. In addition to looking at each gene individually, unsupervised hierarchical clustering with K = 2 clusters was used to identify tumor mutational profiles. DDR pathway genes included MGMT, MLH1, MSH2/6, PTEN, P53, ATM and BRCA 1/2. Univariate Cox proportional hazards models were fit for 16 genes for the outcome of local control (LC) after RT as well as for the two resulting clusters. A multiple testing correction was applied to the gene-specific results to control the false discovery rate (FDR).

Results: Patients were treated with RT to the primary or metastatic site for colorectal (CRC, n = 25), gastroesophageal (GE, n = 5), liver and bile duct (LBD, n = 8), pancreatic (PC, n = 22) and other (OC, n = 5) GI cancers. Ninety two percent of patients had at least one mutation in the DDR pathway with mutations in TOPO1/2 (65%), PTEN (54%) and MGMT (52%) occurring most frequently. Overall, no individual gene was significantly associated with LC after the multiple testing correction, with MLH1 and MSH6 having the strongest association (HR = 0.33, p = 0.03, FDR = 0.25). Two identified clusters based on MLH1/MSH6 mutations had improved LC compared to those without (HR = 0.33, p = 0.03).

Conclusion: Mutations in DNA damage response proteins are common in gastrointestinal malignancies. In our analysis, tumors with mutations in the DNA repair genes MLH1 and MSH6 had better local control compared to those without these mutations. DNA damage and repair proteins represent a promising target for novel drug therapies in conjunction with radiotherapy.

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Phase I/II Study Of Radiation Enhancing Hafnium Oxide Nanoparticles NBTXR3 Activated by SBRT in HCC and Liver Metastases Patients

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Purpose/Objective(s): Stereotactic body radiotherapy (SBRT) is a well-tolerated and valuable alternative for patients with unresectable hepatocellular carcinoma (HCC) or liver metastases (mets) who are not eligible for standard treatment such as surgery, local ablation or chemoembolization. Yet, the energy dose delivered to the tumor is limited due to potential toxicity to healthy tissues and the need to preserve liver function. Thus, achieving local control in liver cancers remains a challenge. The first-in-class radioenhancer NBTXR3 (hafnium oxide nanoparticles), administered by intratumoral (IT) injection once prior to RT treatment, augments the energy dose deposit within tumor cells when activated by RT.

The result is increased tumor cell death compared to RT alone without increasing radiation exposure to surrounding tissues. Patients with HCC or mets may benefit from this new approach. Here we report on a phase I/II study evaluating NBTXR3 activated by SBRT in these patients.

Materials/Methods: In the phase I part of the study [NCT02721056], five NBTXR3 dose levels equivalent to 10, 15, 22, 33, and 42% of baseline tumor volume are tested following a traditional 3+3 design. NBTXR3 is administered by IT injection followed by SBRT (45 Gy / 3 fractions / 5-7 days or 50 Gy / 5 fractions / 15 days). Primary endpoints include determination of the recommended phase 2 dose (RP2D) based on the incidence of the early DLTs. Secondary endpoints include the safety profile, liver disease scores evolution, and early efficacy by target lesions response rate (mRECIST/RECIST 1.1).

Results: To date, 22 patients have been treated and the 4 first dose levels are completed with 6 patients at 10% (2 SBRT doses tested due to organ constraints), 4 patients each at 15% and 22% (due to fiducial displacement and incomplete injected dose) and 3 patients at 33%. The last dose level (42%) is ongoing with 5 patients treated so far. No early DLT has been observed at any dose level. Five AEs (3 G1-2; 2 G3) related to the injection and 4 AEs related to NBTXR3 (3 G1-2; 1 G3), including 1 SAE (bile duct stenosis, also related to RT) were observed. No grade 4-5 AEs were observed. CT-scan showed no leakage of NBTXR3 into surrounding healthy tissues and SBRT safety profile was as expected. No clinically meaningful changes in CPS and APRI were observed post-treatment. In patients evaluable for efficacy, best observed target lesion responses were 5 complete response and 3 partial response in HCC patients (n = 8) and, 5 partial response and 1 stable disease in liver mets patients (n = 6).

Conclusion: NBTXR3 intratumoral injection is feasible and NBTXR3 demonstrates a very good safety and tolerability profile thus far. Recruitment is nearly completed at the 42% dose level. Early efficacy results highlight the potential for NBTXR3 to improve the clinical outcomes of patients with unresectable primary or metastatic liver cancer.

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3330

Simultaneous Integrated Boost For Mediastinal Lymph Node Recurrence After Radical Surgery Of Esophageal Cancer: A Phase I Dose-Escalating Study

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Purpose/Objective(s): We conducted a phase I dose-escalating trial to investigate the optimal dose of salvage chemoradiotherapy (CRT) for the treatment of mediastinal lymph node recurrence after esophagectomy in esophageal squamous cell cancer (ESCC).

Materials/Methods: Patients with histopathologically proven diagnosis of ESCC after esophagectomy presented with clinical diagnosis of ≤5 mediastinal lymph node recurrence were eligible. Participants would receive three levels of radiotherapy dose for the recurrences: LEVEL 1: dose given at PTV-G will be 58.8Gy/28 fractions; 2.1Gy/per fraction; LEVEL 2: dose given at PTV-G will be 64.4Gy/28 fractions; 2.3Gy/per fraction; LEVEL 3: dose given at PTV-G will be 70Gy/28 fractions; 2.5Gy/per fraction with concurrent chemotherapy (S-1 or cisplatin-based doublet therapy). All patients would receive prophylactic irradiation of mediastinal lymphatic drainage area at the dose of 50.4Gy/28 fractions; 1.8Gy/per fraction.

Results: Between June 2019 and September 2019, a total of 10 patients, aged 46-77 (median 62.5), were enrolled (table 1). The median duration from surgery to initial recurrence was 8.5 months (range: 3-43 months).

Abstract 3330; Table **Baseline characteristic of included 10 patients**

Characteristics	Numbers of patients	%
Age [years; median (range)]	62.5 (46-77)	
Gender		
Male	9	90
Female	1	10
ECOG score		
0	9	90
1	1	10
Tumor location (AJCC 8th)		
Upper thoracic	3	30
Middle thoracic	4	40
Lower thoracic	3	30
pT stage		
pT1	1	10
pT2	3	30
pT3	6	60
pN stage		
pN0	6	60
pN1	3	30
pN2	1	10
pStage (AJCC 8th)		
IB	1	10
IIA	4	40
IIB	1	10
IIIA	1	10
IIIB	3	30
Volume of recurrence		
Median (cm^3, range)	5.0(0.77-17.36) cm^3	
Duration from surgery to recurrence, months	8.5 (3-43) months	
Dose-escalating regimen		
58.8Gy/28Fx 64.4Gy/28Fx	4 3	40 30
70Gy/28Fx	3	30

The most common recurrent site according to JES was 106recR, accounting for 35%. Dose-limiting toxicity was not observed. The most common hematologic toxicities were leukocytopenia and anemia. The most common non-hematologic toxicity was esophagitis (grade 1: 80%). The ORR according to RECIST was 70% (CR: 5 patients; PR: 2 patients); three patients had SD after salvage CRT. Until the last follow-up of January 2020, one patient in level 1 dose developed multiple lung metastases after 6 months of salvage CRT, and another patient in level 1 dose developed an out-of-field recurrence in the left cervical lymph node area.

Conclusion: The regimen of salvage CRT with simultaneous integrated boost for mediastinal lymph node recurrence in ESCC patients after esophagectomy is feasible and well tolerable. This salvage radiotherapy regimen (at dose Level III, 70Gy) is currently being tested in a Phase II setting.

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The Safety of MRI Simulation-guided Boost in Short-course Preoperative Radiotherapy for Unresectable Rectal Cancer (SUNRISE): a planned interim analysis of a randomized Phase II Trial

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Purpose/Objective(s): The R0 resection rate remains unsatisfactory even after preoperative neoadjuvant chemoradiotherapy, hence improvements in