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Late-Breaking Abstracts: ASTRO's 64th Annual Meeting (October 23-26, 2022)

Oral Scientific Sessions
LBA 01

NRG/RTOG 1112: Randomized Phase III Study of Sorafenib vs. Stereotactic Body Radiation Therapy (SBRT) Followed by Sorafenib in Hepatocellular Carcinoma (HCC) (NCT01730937)

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Purpose/Objective(s): The role of SBRT in the treatment of HCC is not well established. The hypothesis of this study was that overall survival (OS) would improve with SBRT followed by sorafenib (SBRT/S) vs. sorafenib alone (S), in patients with advanced HCC.

Materials/Methods: Eligible patients had new or recurrent HCC, unsuitable for resection, transplant, ablation or TACE, with Zubrod performance status (PS) 0-2, Child-Pugh A, intermediate (B) or advanced (C) Barcelona Clinic Liver Cancer Stage (BCLC), ≤ 5 HCCs, sum of hepatic HCCs ≤ 20 cm, and sum of extrahepatic metastases ≤ 3 cm. Patients were randomized 1:1 to S 400 mg BID vs. SBRT (27.5-50Gy in 5 fractions, with dose individualized based on mean liver dose and other dose constraints) followed by S 200 mg BID then increased to 400 mg BID after 28 days if appropriate. Primary endpoint was OS. Reported secondary endpoints were progression-free survival (PFS), time to progression (TTP), and adverse events (AEs - CTCAEv4). Planned sample size was 292 patients (238 OS events, HR=0.72, 80% power, 1-sided alpha=0.05). Accrual closed early, primarily due to a change in HCC standard of care systemic therapy. Statistics were amended to report data as of 7/1/2022, projecting 155 OS events providing 65% power for the original hypothesis, with the same alpha. OS and PFS were estimated by Kaplan-Meier and arms compared using log-rank test. Cox proportional hazards models were used to analyze treatment effect. TTP was estimated with cumulative incidence and arms compared using Gray's test. Secondary endpoints were tested with 2-sided alpha=0.05.

Results: Of 193 patients accrued from April 2013 to March 2021 from 23 sites, 177 eligible patients were randomized to S (n=92) vs. SBRT/S (n=85). Median age was 66 years (27-84); 41% had Hepatitis C and 19% had Hepatitis B or B/C. The majority were stage BCLC C (82%), with macrovascular invasion (74%). 4% had metastases. Median follow-up for all and alive patients was 13.2 and 33.7 months, respectively. With 153 OS events, median OS was improved from 12.3 months (90% CI 10.6, 14.3) with S to 15.8 months (90% CI 11.4-19.2) with SBRT/S (HR=0.77, 1-sided p=0.0554). After adjusting for PS, M stage, Child Pugh A5 vs. 6, and degree of vascular HCC, OS was statistically significantly improved for SBRT/S (HR=0.72, 95% CI 0.52-0.99, 2-sided Cox p=0.042). Median PFS was improved from 5.5 months (95% CI 3.4-6.3) with S to 9.2 months (95% CI 7.5-11.9) with SBRT/S (HR=0.55, 95% CI 0.40-0.75, 2-sided p=0.0001). TTP was also improved with SBRT/S (HR=0.69, 95% CI 0.48-0.998, 2-sided Gray's p=0.034). Treatment-related grade 3+ AEs were not significantly different (S - 42%, SBRT/S - 47%; p=0.52). There was one grade 5 treatment-related AE, in the S arm.

Conclusion: Adding SBRT improved OS, PFS, and TTP in patients with advanced HCC, compared to Sorafenib alone, with no significant increase in AEs.

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LBA 02

Radiotherapy with Durvalumab vs. Cetuximab in Patients with Locoregionally Advanced Head and Neck Cancer and a Contraindication to Cisplatin: Phase II Results of NRG-HN004

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Purpose/Objective(s): The optimal treatment for patients with locoregionally advanced head and neck squamous cell carcinoma (HNSCC) and contraindication to cisplatin is uncertain. This trial (NCT03258554) tested the primary hypothesis that radiation therapy (RT) with concurrent and adjuvant durvalumab, a PD-L1 inhibitor, improves progression-free survival (PFS) compared to standard RT with cetuximab.

Materials/Methods: This phase II/III randomized trial enrolled patients ≥ 18 years of age who had previously untreated AJCC 8th stage III-IVB SCC of the larynx, hypopharynx, oral cavity, p16- oropharynx/unknown primary (OPC/UP) or stage III and selected stage I-II p16+ OPC/UP, with a contraindication to cisplatin: ECOG performance status (PS) 2; renal or hearing impairment; peripheral neuropathy; age ≥ 70 with moderate/severe comorbidity; age < 70 with severe comorbidity. Favorable-risk p16+ HNSCC, PS >2, inadequate end-organ function, or active autoimmune disease were exclusion criteria. Patients were randomized 2:1 to RT (70 Gy, 35 fractions, 7 weeks) plus either: (arm A) durvalumab 1500 mg IV q4 weeks starting 2 weeks before RT (7 cycles) or (arm B) cetuximab 400 mg/m^2 IV 1 week prior to RT then 250 mg/m^2 weekly (8 cycles). The primary phase II endpoint was PFS with planned sample size of 234 randomized patients (69 PFS events, hazard ratio 0.65, 80% power, 1-sided alpha 0.20). The difference in PFS between arms was tested using a log-rank test.

Results: This study enrolled 190 patients (186 randomized; 123 arm A; 63 arm B) from Mar 2019-Jul 2021. Following planned interim futility analysis, the trial was temporarily closed to accrual, pending analysis based on total required phase II PFS events (met in Jun 2022). Median age was 72 years (59% ≥ 70). 95% had ≥ 3 comorbidities (median 5); 58% had T3-4; 49% had N2-3; 47% had p16+ OPC/UP. 87% in arm A and 89% in arm B completed RT. 89%/63% completed concurrent/adjuvant durvalumab and 81% completed ≥ 7 cycles of cetuximab. At median follow-up of 1.2 years, PFS was not improved and locoregional failure (LRF) was higher with durvalumab (Table). Grade ≥ 3 adverse events were 69%/79% for arm A/B. Grade ≥ 3 dysphagia, mucositis, and dermatitis rates were 22%/30%, 11%/20%, and 5%/13% for arm A/B, respectively.

Conclusion: Novel eligibility criteria and feasibility of accrual were established. However, RT with durvalumab did not show a signal toward improved PFS and led to significantly worse LRF, compared to RT with cetuximab in HNSCC pts with a contraindication to cisplatin. The trial will not move to phase III.

Abstract LBA 02 − Table 1

Table	2-year rates, % (95% CI)			
	RT + durvalumab	RT + cetuximab	HR (95% CI)	p-value
PFS	51 (41, 61)	66 (53, 80)	1.47 (0.86, 2.52)	0.92[a]
OS	70 (60, 80)	78 (66, 91)	1.21 (0.63, 2.31)	0.72[a]
LRF	32 (23, 42)	15 (7, 25)	2.17 (1.00, 4.69)	0.04[b]
Distant metastasis	9 (4, 15)	11 (4, 22)	0.76 (0.27, 2.15)	0.61[b]

[a] 1-sided
[b] 2-sided

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LBA 03

Durvalumab in Combination with Chemoradiotherapy (CRT) in Locally Advanced Cervical Cancer (LACC): Radiotherapy (RT) Delivery and Subgroup Analyses from CALLA

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Purpose/Objective(s): Concurrent platinum-based CRT has been standard of care in LACC for 20+ years. Simultaneously, RT techniques/technology have advanced, providing opportunity for improved treatment outcomes. In LACC, global standardization is critical to enhance RT quality and brachytherapy (BT) utilization. CALLA was the first global, placebo-controlled, Phase 3 study evaluating durvalumab (D), in combination with and following CRT, in LACC . We examine RT technological approaches, quality assurance measures, and related RT-based findings from CALLA.

Materials/Methods: Newly diagnosed, untreated patients (pts) with high-risk LACC (FIGO 2009 IB2−IIB node positive, IIIA−IVA any node status) were randomized 1:1 to D (1500 mg IV) or placebo (P) Q4W (total ≤24 doses), in combination with and following CRT. CRT comprised concurrent weekly IV platinum agent with external beam radiotherapy (EBRT) and BT. Detailed EBRT/BT protocol guidelines were included to ensure regional alignment. Prior to site qualification, a feasibility questionnaire and credentialing process confirmed compliance. A global RT subcommittee reviewed RT quality/compliance and created a scoring system to identify plan variations and potential clinical significance. RT quality was evaluated for each pt, including detailed review of contouring, EBRT plan dose/metrics, BT utilization/quality, RT completion, and treatment plan dose/quality variations.

Results: A total of 770 women (105 sites,15 countries; 44% Hispanic, 39% Asian) were randomized. The primary endpoint of PFS was not met (hazard ratio [95% CI] for D+CRT vs P+CRT: 0.84 [0.65−1.08]; *P*=0.174). PFS

at 12 and 24 months for D+CRT vs P+CRT were 76.0% vs 73.3% and 65.9% vs 62.1%, respectively. EBRT and BT were completed per protocol in 96.4% and 94.3% of pts for D+CRT and 98.4% and 95.3% for P+CRT. RT was delivered in ≤59 days in 72.2% and 72.5% for D+CRT and P+CRT, respectively. Intensity-modulated RT was used for 86.8% (D+CRT) and 88.1% (P+CRT) of pts. A majority of pts received volume-directed BT (59.7% D+CRT, 63.3% P+CRT), and 87.4% and 88.1% of BT was high-dose rate. In both arms, median RT dose delivered was 5400 cGy and median equivalent dose was 8387.0 cGy (median BT dose/fraction 700 cGy, 4 fractions) (RT doses omit Japan). Clinically significant unacceptable variations in RT delivery were low; <25% of unacceptable variations were clinically significant. PFS by RT subgroups were generally aligned with the ITT population.
Conclusion: CALLA integrated an exceptional quality assurance/control strategy to ensure global protocol compliance, showing high-quality RT delivery is achievable with high compliance. Although D+CRT did not significantly improve PFS vs P+CRT, CALLA illustrates the importance of strong multidisciplinary collaboration for optimal CRT delivery in high-risk LACC. Funding: AstraZeneca

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LBA 04

Prophylactic Radiation Therapy vs. Standard-of-Care for Patients with High-Risk, Asymptomatic Bone Metastases: A Multicenter, Randomized Phase II Trial

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Purpose/Objective(s): External beam radiotherapy (RT) is standard-of-care (SOC) for pain relief of symptomatic bone metastases. We aimed to test whether radiation for asymptomatic bone metastases prevents skeletal-related events (SRE).
Materials/Methods: We conducted a multicenter, randomized phase 2 trial (NCT03523351) of prophylactic RT to high-risk, asymptomatic bone metastases vs SOC. Patients were eligible if they were at least 18 years old with a metastatic solid tumor malignancy and more than 5 metastatic lesions, including at least one asymptomatic high-risk bone lesion, defined as: bulky disease (≥2cm in longest diameter), junctional spine or posterior spinal element disease, disease involving hip or sacroiliac joint, or disease in long bone involving 1/3-2/3 cortical thickness. Patients were stratified by histology and planned SOC (systemic therapy or observation) and randomly assigned in a 1:1 ratio to RT to all enrolled high-risk bone metastases or SOC alone. The primary outcome of SRE (defined as fracture, cord compression, or intervention with surgery or radiation) was analyzed from randomization to death or 12 months. A sample size of 66 was deemed necessary to achieve 80% power to detect a difference of 30% (experimental arm) versus 60% (SOC arm) using a two-sample, one-sided proportion test with alpha<0.05. We used the log-rank test for time-to-event analyses and Wilcoxon rank sum test to compare hospitalizations, brief pain inventory and quality of life (using EQ-5D-5L) between arms.
Results: Between May 8, 2018 and August 9, 2021, 78 patients with 122 bone metastases were enrolled and randomized to prophylactic RT (n=39) or SOC (n=39). The most common primary cancer types were lung (27%), breast (24%), and prostate (22%). Seventy-one patients (91%) were evaluable for the primary endpoint. At one year, SRE occurred in 1 of 62 lesions (1.6%) in the RT arm and 14 of 49 lesions (29%) in the SOC arm (p<0.001). There was a significant difference in time-to-SRE by type of high-risk feature (p=0.016), with most events occurring in junctional spine and bulky disease. There were significantly fewer patients hospitalized for SRE in the RT arm compared to the SOC arm (4 vs 0, p=0.045). At a median follow-up of 2.4 years, overall survival was significantly longer in the RT arm (HR 0.50, 95% CI 0.28, 0.91; p=0.02). Median OS among 11 patients with an SRE was 1.1 years compared to 1.5 years among 67 patients without an SRE. Pain was reduced at 3 months in the RT arm (p<0.05) compared to the SOC arm. EQ-5D-5L was similar between the groups at all time points.
Conclusion: Radiation delivered prophylactically to asymptomatic, high-risk bone metastases reduced skeletal-related events, meeting the primary endpoint of the study. Importantly, we observed an improvement in overall survival, with potential mechanisms of palliation or debulking warranting further investigation in a phase 3 trial.

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LBA 05

Addition of Metastasis-Directed Therapy to Intermittent Hormone Therapy for Oligometastatic Prostate Cancer (EXTEND): A Multicenter, Randomized Phase II Trial

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Purpose/Objective(s): There has been increased utilization of metastasis directed therapy (MDT) for oligometastatic prostate cancer. Despite data demonstrating the benefit of upfront hormone therapy (HT) and synergy between radiation and HT, there exists no randomized trials testing their combination. As it is accepted by most clinicians and men with prostate cancer that time off HT holds intrinsic value, we evaluated whether the addition of metastasis directed therapy (MDT) to intermittent HT in men with oligometastatic prostate cancer facilities time off HT by improving PFS and eugonad PFS.

Materials/Methods: EXTEND (NCT03599765) is a phase II randomized basket trial for multiple solid tumors testing whether the addition of MDT improves PFS. The primary endpoint was pre-specified to be independently assessed and reported for the prostate intermittent HT basket at 41 events. Men with ≤5 metastases were randomized after ≥2 months of HT to continuing HT with or without MDT. HT consisted of a luteinizing hormone-releasing hormone agonist/antagonist with or without a 2nd generation androgen-receptor targeting agent (SART). The primary endpoint was progression, defined as death or radiographic, clinical, or biochemical progression. A planned HT break occurred 6 months after enrollment, after which HT was withheld until progression. The study was designed to have 80% power to detect an improvement in median PFS from 18 to 36 months, with a type I error of 0.1. Exploratory analysis included flow cytometry and TCR sequencing from peripheral blood at baseline and 3 months follow up.

Results: Between Sept 2018 to Nov 2020, 87 men were randomized, 43 combined therapy and 44 to HT-only. Arms were well balanced. At a median follow-up of 22.1 months (range 13.0 to 39.3 months), 41 events were observed. PFS was improved by the receipt of MDT (median not reached vs 15.8 months for HT-only, P<0.001; HR=0.25 [95% CI, 0.12 to 0.55]). Among secondary endpoints, time from eugonad testosterone levels (>150 ng/dL) to progression was improved by MDT (median not reached vs 6.1 months, P=0.03), as was time to appearance of new lesions (2-year rate 33% vs 41%, P=0.04). Three grade 3 toxicities were observed in each arm. Subgroup analysis identified PFS improvement with MDT in patients who received (HR=0.24 [95% CI, 0.08 to 0.71]) or did not receive a SART (HR=0.36 [95% CI, 0.15 to 0.83]). Flow cytometry and TCR sequencing demonstrated increases in markers of T cell activation, proliferation, and clonal expansion limited to the combined therapy arm.

Conclusion: EXTEND represents the first randomized study to evaluate MDT with HT in oligometastatic prostate cancer and demonstrated improvement in PFS and eugonad PFS. Combination of MDT with intermittent HT may allow for both excellent disease control while facilitating prolonged eugonad testosterone intervals.

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LBA 06

Celiac Plexus Radio-Surgery for Pain Management in Advanced Cancer: An International Phase II Trial

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Purpose/Objective(s): Upper abdominal / lower back pain characterizes pancreatic and other upper gastrointestinal malignancies; its satisfactory treatment is an unmet clinical need. We hypothesized that ablative radiation delivered to the celiac plexus would decrease pain. Following promising results from a small pilot study (PMID 35257800), we sought to validate the results in a multi-institutional setting.

Materials/Methods: An international single arm Phase II study. Inclusion criteria included average pain level of ≥ 5/11, ECOG 0-2, life expectancy ≥ 8 weeks and either pancreatic cancer or anatomical involvement of the celiac blood vessels. The intervention was a single fraction of 25Gy delivered to the celiac plexus, (surrogate marker the anterior & lateral aspects of aorta at T12-L2 levels). The primary endpoint was 'complete or partial pain response' based upon the BPI average pain 11-point scale: a decrease between the score immediately before treatment and 3 weeks' post-treatment ≥ 2. Secondary endpoints included change in total daily opioid usage (morphine equivalent dose) and use of breakthrough analgesics. Evaluable patients were protocol defined; criteria included eligible irradiated subjects, who had stable pre-treatment pain levels, and were alive 3 weeks' post-treatment. The sample size was 90 evaluable patients, giving 90% power to show that the response rate was at least 40%.

Results: The trial accrued between 2018 and 2022 across 7 medical centres and 5 countries. Of 149 patients enrolled, 125 received treatment, of whom 90 were classified evaluable. Median age was 65.5 years (range 28-88), 65% were female, 92% had pancreatic cancer, and 86% had metastatic disease. Median ECOG was 1, median no. systemic treatment lines was 1 (range 0-5), and median baseline opioid use 31 mg/d. Of the 90 evaluable patients at 3 weeks, 48 (53.3%, 95% CI 42.5-63.9) had at least a partial pain response. Average pain decreased by a mean of 2.5 points at 3 weeks (86 reported) and 3.2 points at 6 weeks (67 reported), both p<0.001. Opioid usage decreased by 0.6 mg/d at 3 weeks (NS) and 16.9 mg/d at 6 weeks (p=0.005). There was a meaningful decrease in breakthrough analgesic use at both

week 3, mean change -1.9 times / day (95% CI: -3.6, -0.1, p = 0.03) and week 6, mean change 3.7 times / day (95% CI: -6.3, -1.1; p = 0.01). Pain interference scores improved significantly across all domains at both 3 and 6 weeks, aside from walking at 3 weeks. Treatment was well tolerated; amongst 125 treated patients there were 6 SAEs considered 'possibly related' to treatment, all of which are commonly associated with advanced cancer. Median time to SAE was 49 days post treatment.

Conclusion: Celiac plexus SBRT decreases pain, opioid use and pain interference scores with minimal side effects, providing a new possible treatment option for pancreatic cancer pain & other tumors invading the celiac axis. Supported by Gateway for Cancer Research and the Israel Cancer Association.

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LBA 07

Final Analysis of Consolidative Use of Radiotherapy to Block (CURB) Oligoprogression Trial - A Randomized Study of Stereotactic Body Radiotherapy for Oligoprogressive Metastatic Lung and Breast Cancers

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Purpose/Objective(s): To assess if stereotactic body radiotherapy (SBRT) for oligoprogressive metastatic lung or breast cancer prolongs progression-free survival (PFS), overall survival (OS), and alters circulating tumor (ct) DNA profile.

Materials/Methods: We enrolled patients with metastatic non-small-cell lung cancer (NSCLC) or breast cancer with ≤5 oligoprogressive lesions after ≥1 line of systemic therapy. Stratification factors included number of oligoprogressive lesions, prior immunotherapy, primary site, and receptor/mutation status. Patients were randomized 1:1 to standard of care (SOC) with or without SBRT to all progressive sites. The primary endpoint was PFS. Secondary endpoints included OS, toxicity, and quality-of-life (QoL). Blood was collected at baseline and at 8 weeks for ctDNA analysis. A hybridization capture and deep sequencing assay was used to identify genomic alterations and calculate estimated variant allele frequencies (VAFs) of tumor-derived mutations. Patients were followed for 12 months for PFS and until death or last contact for OS. One-sided stratified log-rank test was used to assess survival outcomes.

Results: From January 2019 to July 2021, 106 patients were randomized - 59 with NSCLC and 47 with breast cancer. Most (75%) had >1 site of oligoprogression and 47% had >5 total lesions. The majority of NSCLCs (86%) had no actionable driver mutation and 66% of breast cancers were triple-negative. Median PFS was 3.2 months in SOC arm vs. 7.2 months in SBRT arm (p=0.002). Stratified analysis showed that NSCLC patients derived substantial PFS benefit from SBRT (2.2 months in SOC vs. 10 months in SBRT arm; p=0.002), whereas breast cancer patients did not (4.2 vs. 4.4 months, p=0.2). No difference in OS between arms has yet been seen in either cohort. Grade ≥2 toxicities occurred in 8 patients after SBRT. There was no difference in QoL between treatment arms. The study was closed to accrual after a preplanned interim analysis crossed a prespecified efficacy threshold. Analysis of 52 pairs of baseline and 8-week blood samples with detectable ctDNA showed significant reduction of median VAFs over time comparing SBRT to SOC in the NSCLC cohort (p=0.03), but not the breast cancer cohort (p=0.56). Increasing median VAFs at 8 weeks was predictive of subsequent disease progression (Hazard Ratio: 1.17, 95% CI: 1.02-1.36, p=0.03), independent of treatment arm or primary site.

Conclusion: In this first and largest randomized trial of radiotherapy for oligoprogressive metastatic cancer, we observed a more than 4-fold PFS benefit in patients with oligoprogressive metastatic NSCLC receiving SBRT, with corresponding decrease in ctDNA VAFs. There was no PFS benefit or change in ctDNA after SBRT for breast cancer, suggesting a more diffusely systemic pathophysiology. The benefit of SBRT in oligoprogressive metastatic NSCLC will require validation in a larger study and the distinction in oligoprogressive biology between these diseases warrants further evaluation.

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LBA 08

LUSTRE: A Phase III Randomized Trial of Stereotactic Body Radiotherapy (SBRT) vs. Conventionally Hypofractionated Radiotherapy (CRT) for Medically Inoperable Stage I Non-Small Cell Lung Cancer (NSCLC)

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Purpose/Objective(s): SBRT has been adopted as standard of care for Stage I medically inoperable NSCLC, yet there is inconclusive data from randomized controlled trials (RCT) regarding efficacy. There remains concern regarding long term disease control and toxicity, particularly in centrally located tumors. The purpose of this trial was to compare SBRT to hypofractionated CRT in central and peripheral NSCLC.

Materials/Methods: A phase III RCT was conducted in 16 Canadian centers. Patients deemed medically inoperable with either histologically confirmed stage I (≤5cm) NSCLC or a suspicious growing FDG-PET avid lesion were randomized 2:1 to receive either SBRT of 48 Gy/4 fractions (peripheral NSCLC) or 60 Gy/8 fractions (central NSCLC - within 1 cm of mediastinum or 2 cm of the proximal bronchial tree), versus CRT of 60 Gy/15 fractions. Stratification was by tumor size (≤3cm vs >3-5 cm), location: central vs peripheral, and clinical center. All radiation plans were subject to real-time/final review. The primary outcome was local control (LC), defined by the absence of primary tumor or marginal failure. Secondary outcomes included disease-free survival (DFS), overall survival (OS), toxicity, and radiation treatment related death (RTRD). Outcomes were centrally adjudicated, blinded by arm. The primary objective was to detect a LC improvement of SBRT at 3 years from 75% to 87.5% (Hazard Ratio (HR)=0.46) assuming a two-sided α=0.05 and power of 85%, with a planned sample size of 324 patients.

Results: From May 2014 to January 2020, 233 (154 SBRT, 79 CRT) patients were accrued. Recruitment to the trial closed early due to slow accrual. The mean age of patients was 75 years; 27% had tumors that were centrally located; 49% had biopsy-proven NSCLC; 71% had ≤3cm lesions; and mean tumor diameter was 2.5 cm. With a median follow-up of 36 months, 34 (18 SBRT, 16 CRT) local failures were observed. The 3-year LC rate was 87.6% for SBRT and 81.2% for CRT (HR=0.61, 95% confidence interval (CI):0.31-1.20, p=0.15). The observed treatment effects for DFS were HR=0.83 (95% CI:0.54-1.28, p=0.40), and HR=1.18 (95% CI:0.80-1.76, p=0.40) for OS. Only one patient in each arm experienced grade 3 acute toxicity (no grade 4/5 toxicities were observed). Late grade 3/4 toxicities occurred in 7 patients: SBRT - central 3/45 (6.6%), peripheral 2/109 (1.8%), CRT - central 1/19 (5.2%), peripheral 1/60 (1.6%). One patient who received 60 Gy/8 fractions for a central NSCLC experienced a possible RTRD (hemoptysis).

Conclusion: This is the largest reported RCT of lung SBRT compared to a contemporary CRT control arm, with mature follow-up and the inclusion of patients with central tumors. There was an observed improvement of LC with SBRT compared to CRT, however, the trial was underpowered to confirm this. No evidence of differences were observed in DFS and OS. Very few patients experienced severe late toxicities, including those with central tumors. This study confirms the efficacy and safety of SBRT for both central and peripheral Stage I NSCLC (NCT01968941).

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LBA 09

Stereotactic MR-Guided On-Table Adaptive Radiation Therapy (SMART) for Patients with Borderline or Locally Advanced Pancreatic Cancer: Primary Endpoint Outcomes of a Prospective Phase II Multi-Center International Trial

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Purpose/Objective(s): Retrospective studies demonstrate that ablative stereotactic MR-guided on-table adaptive radiation therapy (SMART) achieves favorable local control (LC) and overall survival (OS) with limited grade 3+ toxicity compared to historical non-ablative outcomes for locally advanced and borderline resectable pancreatic cancer (LAPC/BRPC). We conducted an international multi-center single-arm phase 2 trial of ablative 5-fraction SMART for LAPC/BRPC.

Materials/Methods: Subjects were required to have biopsy-confirmed adenocarcinoma, receive ≥3 months of chemotherapy, have no distant metastasis and CA19-9 ≤500 U/mL. SMART was delivered on a 0.35T MR-^{60}Co or MR-linac system prescribed to 50 Gy in 5 fractions (biologically effective dose$_{10}$ [BED$_{10}$]=100 Gy) using continuous intrafraction cine-MRI, soft tissue tracking, and automatic beam gating. The original plan was recomputed onto the daily anatomy and if that plan would not have met constraints, on-table adaptive replanning using an isotoxicity approach was performed. The primary objective was to demonstrate <15.8% acute grade 3+ gastrointestinal (GI) toxicity definitely related to SMART measured through 90 days and evaluated according to Common Terminology Criteria for Adverse Events v5.0 (CTCAE). All patients have completed 90-day follow-up. Secondary objectives included OS, distant progression free survival (DPFS), and patient-reported quality of life.

Results: 136 patients across 13 sites were enrolled between 2019-2021. Mean age was 65.7 years. Head of pancreas lesions were most common (66.9%; n=91). 43.4% (n=59) had BRPC, 56.6% (n=77) LAPC. Mean induction chemotherapy duration was 155.7 days, typically with FOLFIRINOX 65.4% (n=89) or gemcitabine doublet 16.9% (n=23). Mean CA19-9 after induction chemotherapy was 71.7 U/mL. On-table adaptive replanning was used for 93.1% of fractions. SMART was delivered in consecutive days (56.6%) or every other day (43.4%). Median follow-up was 16.4 months and 8.8 months from diagnosis and SMART, respectively. 31.6% (n=43) had surgery after SMART. The incidence of acute grade 3+ GI toxicity definitely and probably related to SMART were 0% and 2.2% (n=3), respectively. 1-year LC and DPFS from SMART were 82.9% and 50.6%, respectively. 1-year OS was 93.9% from diagnosis and 65.0% from SMART.

Conclusion: This is the first prospective, multi-institutional study of ablative SMART with prescribed BED_{10} of 100 Gy delivered in 5 fractions for BRPC/LAPC. The primary objective was met, signaling that further prospective evaluation of ablative SMART for BRPC/LAPC is warranted with a focus on long-term LC and OS compared to chemotherapy alone.

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LBA 10

GETUG-AFU 22 Phase II Randomized Trial Evaluating Outcomes of Post-Operative Immediate Salvage Radiation Therapy with or without ADT for Patients with Persistently Elevated PSA Level

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Purpose/Objective(s): Radical prostatectomy (RP) is one of the recommended option for localized prostate cancer (PCa) treatment but no clear recommendations guide post-operative treatment patients with persistently elevated prostate-specific antigen (PSA) after RP. The aim of this trial was to compare immediate salvage radiation therapy (iSRT) with or without short-term androgen deprivation therapy (ADT) in these patients.

Materials/Methods: RP patients with nonmetastatic PCa on conventional preoperative imaging, and with a post-RP PSA level between 0.2 and 2 ng/mL were randomized (1:1) to iSRT alone (iSRT arm) or 6 months of ADT (degarelix) with iSRT (iSRT+ADT arm). ISRT consisted of pelvic irradiation (46 Gy in 23 Fr) with a boost on the prostate bed (66 Gy in 33 Fr). The primary endpoint was event-free survival (EFS). Biochemical progression-free survival (bPFS), metastates-free survival (MFS), overall survival (OS), quality of life, and toxicities were evaluated as secondary endpoints.

Results: From Jan-2013 to Sept-2015, 125 pts were included (iSRT arm: 64 pts; iSRT+ADT arm: 61). Median follow up was 75.0 months (95% CI: 74.1-76.6). The baseline characteristics were well-balanced between the two arms. Median PSA was 0.6 ng/mL (0.12-3.65) at randomization. All patients received the planned iSRT and 98.4% in the arm iSRT+ADT received ADT as planned. The efficacy results were analyzed at 5 years. EFS was 62.3% (95% CI: 48.9-73.2) in iSRT arm and 63.5% (95% CI: 49.9-74.2) in iSRT+ADT arm (HR=0.83; 95%CI: 0.47-1.47; p=0.528). bPFS was 62.3% (95% CI: 48.9-73.2) in iSRT arm and 66% (95% CI: 52.3-76.6) in iSRT +ADT arm (HR=0.76; 95%CI: 0.44-1.31; p=0.322). MFS was in favor of the iSRT+ADT arm with HR=0.51 (95% CI: 0.26-0.99; p=0.048). OS data were not mature at the time of analysis. Multivariate analysis demonstrated that PSA level <0.6 ng/ml at randomization and tumor ≤pT3a were associated with increased bPFS (HR=1.84; 95%CI: 1.02-3.33; p=0.05 and HR=2.96; 95%CI: 1.66-5.25; p=0.0002, respectively). PSA level <0.6 ng/ml at randomization was associated with improved MFS (HR=2.82; 95%CI: 1.14-6.95; p=0.019). No grade 4 toxicities were observed. Overall, no difference in acute toxicity were observed between the 2 arms and more late toxicities (≥6 months after iSRT) were observed in the iSRT+ADT than the iSRT arm (53.1% vs 70.5%; p=0.046). At 12 months ADT-related symptoms were more important in the iSRT+ADT arm (QLQ-PR25; p=0.04). At 24 months, no difference in QLQ-C30 or QLQ-PR25 analysis was reported. After an initial 25-fold decrease in blood testosterone level, all patients recovered to normal level 12 months after starting ADT.

Conclusion: Despite the lack of differences in terms of EFS between the two arms, this study demonstrated that iSRT+ADT improved MFS without impaired quality-of-life for patients with persistently elevated PSA after RP.

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Patterns of Failure after Stereotactic Radiosurgery vs. Whole Brain Radiotherapy for Resected Brain Metastases: Central Imaging Review of the N107C/CEC.3 (Alliance) Phase III Clinical Trial

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Purpose/Objective(s): Whole brain radiotherapy (WBRT) has historically been the main instrument to decrease intracranial progression after resection of brain metastases. The previously reported NCCTG N107C/CEC.3 (Alliance) randomized phase III clinical trial of WBRT vs. stereotactic radiosurgery (SRS) demonstrated that overall survival did not significantly differ between arms, while SRS was associated with less cognitive decline than WBRT. However, the initial analysis also showed that local tumor bed control (LC) was significantly worse with SRS than WBRT, with an unexpectedly low 12-month LC rate of 60.5% in patients receiving post-operative SRS. To further investigate LC, a central imaging review was performed.

Materials/Methods: In N107C/CEC.3, 194 patients were randomized to SRS (n=98) or WBRT (n=96). SRS dose was dependent on resection cavity volume and ranged from 12 Gy to 20 Gy all in a single fraction, and WBRT dose was 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. For this analysis, patients with local failure (LF) or leptomeningeal failure that had imaging available were centrally reviewed by two radiation oncologists to verify pattern of failure. Patient and treatment characteristics were assessed for association with updated outcomes after central review using Cox proportional hazards, Pearson's chi-square, or Kruskal-Wallis tests.

Results: Seventy-three patients with LF or leptomeningeal failure determined by their local site were centrally reviewed. After adding patients with no LF or leptomeningeal failure, 185 (95% of total enrolled) patients were included in this analysis as 9 patients with LF did not have imaging available for central review. Of 59 patients initially determined to have LF, 20 were determined on central review to be free of LF. Accordingly, after central review post-operative SRS was no longer associated with significantly lower rates of LC than WBRT (79.2% vs. 86.5% 12-month LC, respectively, p=0.099). After central review, the interrelated variables of tumor diameter, target volume, and prescription dose were associated with risk of LF. Patients with resection cavities > 3 cm had higher rates of LF than those with smaller cavities (23.5% vs. 12.6% 12-month LF rate, respectively; p=0.010). Larger target volume was associated with increased risk of LF (HR: 1.05, 95% CI: 1.01 − 1.09, p=0.008), while higher prescription dose was associated with lower risk of LF (HR: 0.81, 95% CI: 0.67 − 0.96, p=0.018).

Conclusion: In contrast to the initial report, after central review SRS was not associated with significantly higher rates of LF than WBRT. Patients with larger surgical cavities had higher rates of LF, though it is unclear whether this is related to cavity size, biology, or radiation dose. Randomized data comparing single to multifraction SRS in larger surgical cavities is awaited.

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