

Late-Breaking Abstracts from ASTRO's 63rd Annual Meeting (October 24-27, 2021)

LBA-1

MC1675, a Phase III Evaluation of De-Escalated Adjuvant Radiation Therapy (DART) vs. Standard Adjuvant Treatment for Human Papillomavirus Associated Oropharyngeal Squamous Cell Carcinoma

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Purpose/Objective(s): We previously reported the results of a phase II clinical trial evaluating 30-36 Gy of adjuvant radiation therapy (RT) for selected patients with HPV+ OPSCC. Herein we report the two-year results of a phase III trial comparing this 30-36 Gy regimen with standard of care (SOC) adjuvant RT.

Materials/Methods: All patients (pts) received transoral robotic surgery (TORS) and neck dissection for a margin negative resection. Pts with pT4 disease or who required >2 attempts to clear margins were excluded. Pts with intermediate risk factors received 30 Gy/1.5 Gy b.i.d. + docetaxel 15 mg/m² days 1 and 8, while pts with extranodal extension (ENE) simultaneously received 36 Gy/1.8 Gy b.i.d. to ENE+ nodal levels. Pts were randomized (2:1) to DART or SOC (60 Gy ± weekly cisplatin 40 mg/m²). Stratification was by risk group (intermediate risk vs ENE+) and smoking status (< vs ≥10 pack-yr). The primary endpoint was grade ≥3 AE rate ≥3 mos after RT with the study powered to have 90% power to detect a grade ≥3 AE rate reduction from 25% to 7%. Secondary endpoints were OS, LRC, PFS, and QOL. Pts received a swallow evaluation (MBSImP) before, 1 mo, and 1 yr post-RT. Pts also had QOL assessed with the FACT-HN, EORTC-HN35, and University of Michigan Xerostomia QOL Scale (XeQOLS) pre-RT and 1, 3, 12, and 24 mos post-RT.

Results: Accrual was from 10/16 – 8/20 (n = 194, DART: 130, SOC: 64, ENE+: 115 (59%), Non-smokers: 139 (72%), median age 59.4 yrs (37.9-81.6), male 89%. Median follow-up as of 7/21 was 25.3 mo. 1.6% DART and 27.4% SOC pts (p<0.0001) required a feeding tube. Grade ≥3 AEs at 3 months were 1.6% DART vs 7.1% SOC (p=0.058). Swallowing function change from baseline to 1 month was superior in the DART arm (DART vs SOC, median) MBSImP: -0.3 vs -2.6 (p=0.0155) as was baseline to 3 month QOL FACT-HN: 5.1 vs -3.2 (p=0.0007); EORTC-HN Pain: -8.6 vs 2.5 (p=0.0009); XeQOLS: 2.9 vs 11.7 (p=0.0001). 2 yr statistics between DART and SOC arms were similar except for PFS on the

DART/ENE+ arm (Table). PFS on the DART/ENE+ arm was driven by the pN2 cohort (AJCC 8, >4 LN). For ENE+/pN0-1 pts, (DART vs SOC) 2 yr PFS was 89.6% vs 95.8%; LRC 95.8% vs 100.0%; DMFS 96.4% vs 95.8%. For ENE+/pN2 (DART vs SOC) PFS was 42.9% vs 100%; LRC 77.0% vs 100%; DMFS 59.4% vs 100%.

Conclusion: DART demonstrated less toxicity, improved swallowing function and QOL when compared to SOC. DART also had excellent LRC, PFS, and OS rates, particularly in the ENE negative cohort. Caution is advised for de-escalating ENE+ pts with pN2 disease.

Abstract LBA-1 – Table 1

	2 Year Statistics (95% CI)					
	Entire study		ENE-		ENE+	
	DART	SOC	DART	SOC	DART	SOC
OS	96.1% (92.3-100.0)	97.0% (91.3-100.0)	100.0% (100.0-100.0)	90.9% (75.4-100.0)	93.4% (87.3-100.0)	100.0% (100.0-100.0)
LRC	95.5% (91.6-99.5)	97.9% (93.8-100)	100.0% (100.0-100.0)	93.3% (81.5-100.0)	92.2% (85.7-99.1)	100.0% (100.0-100.0)
PFS	86.5% (80.2-93.3)	95.1% (88.8-100.0)	97.6% (93.0-100.0)	93.3% (81.5-100.0)	78.9% (69.5-89.6)	96.2% (89.0-100.0)

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LBA-2

A Randomized Trial of Radiotherapy vs. Trans-Oral Surgery for Treatment De-Escalation in HPV-Associated Oropharyngeal Squamous Cell Carcinoma (ORATOR2)

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Purpose/Objective(s): Widespread oral human papillomavirus (HPV) infections have led to a rapid increase in the incidence of oropharyngeal squamous cell carcinoma (OPSCC). HPV-related OPSCCs have a better prognosis than conventional alcohol- and smoking-related OPSCCs, suggesting a role for treatment de-escalation. The goal of this phase II randomized trial was to assess survival, oncologic, and toxicity outcomes with two de-escalation approaches: primary reduced-dose radiotherapy (RT) vs. primary transoral surgery plus neck dissection (TOS + ND) with reduced-dose adjuvant therapy.

Materials/Methods: We enrolled patients with T1-T2N0-2 (AJCC 8th edition) p16-positive OPSCC. After stratifying by smoking status, we randomized patients (1:1) to either the primary RT arm, which consisted of 60 Gy of RT and concurrent weekly cisplatin chemotherapy in node-positive patients vs. the TOS + ND arm, consisting of surgery and neck dissection, with adjuvant reduced-dose RT depending on pathologic findings. The primary endpoint was overall survival (OS), and secondary endpoints included progression-free survival (PFS), quality of life (QOL, using the MDADI and other metrics), and toxicity. The trial was closed to accrual in November 2020 due to excessive toxicity in the TOS + ND arm, consisting of two treatment-related deaths from known complications of TOS (one bleed and one cervical osteomyelitis following post-operative RT). After closure to accrual, all previously enrolled patients remained on follow-up. All analyses were pre-specified and intention-to-treat, unless otherwise specified. Due to these unexpected toxicity findings, the trial is being reported while survival outcomes remain immature, and therefore p-values are not reported for OS and PFS comparisons.

Results: Between February 2018 and November 2020, 61 patients were randomized (n=30 in the RT arm and n=31 in the TOS + ND arm). Median age was 61.9 years, most patients (51%) were never-smokers, and the large majority of patients (n=51; 86%) were male. The arms were well-balanced. Median follow-up was 17 months (IQR: 15-20 months). Two-year estimates of OS were 100% in the RT arm (95% confidence interval [CI]: 100%-100%) and 89.1% (95% CI: 69.6%-96.4%) in the TOS + ND arm. Two-year PFS estimates were 100% in the RT arm (95% CI: 100%-100%) and 83.5% (95% CI: 60.8%-93.7%) in the TOS + ND arm. Grade 2-5 toxicities occurred in 67% of patients in the RT arm and 71% in the TOS + ND arm, with significantly more anorexia and dysgeusia in the RT arm. Mean (±SD) MDADI total scores at 1-year were similar between arms (85.7 ± 15.6 and 84.7 ± 14.5, respectively). One patient in each arm required a percutaneous feeding tube, and none required feeding tubes at 1-year.

Conclusion: The primary RT approach achieved excellent oncologic outcomes in treatment de-escalation, with a moderate toxicity profile, and should be tested in phase III trials. The primary TOS approach was associated with an upfront risk of treatment-related mortality and suboptimal PFS. (NCT03210103)

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LBA-3

Consolidative Use of Radiotherapy to Block (CURB) Oligoprogression – Interim Analysis of the First Randomized Study of Stereotactic Body Radiotherapy in Patients With Oligoproliferative Metastatic Cancers of the Lung and Breast

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Purpose/Objective(s): We hypothesize that there is an oligoproliferative state in metastatic cancer, in which disease control can be improved with local therapy to progressive lesions only. This study therefore evaluated the impact of stereotactic body radiotherapy (SBRT) to sites of oligoproliferation in patients with metastatic non-small-cell lung cancer (NSCLC) and breast cancer with 1-5 progressive lesions.

Materials/Methods: We enrolled patients with metastatic NSCLC or breast cancer who received ≥ 1 line of systemic therapy and had oligoproliferative lesions amenable to SBRT. There was no upper limit of non-progressive lesions. Oligoproliferation was defined as Response Evaluation or Positron Emission Tomography Response Criteria in Solid Tumors documented progression ≤ 5 individual lesions. Stratification factors included number of progressive sites (1 vs. 2-5), prior systemic therapy (immunotherapy vs. other), primary tumor (NSCLC vs. breast), and tumor marker status (driver mutation and hormone receptor status). Patients were randomized 1:1 between SBRT to all progressive sites plus palliative standard of care (SOC) vs. palliative SOC only. Systemic therapy was per physician's discretion. The primary endpoint was progression-free survival (PFS). We used a randomized phase II design with a one-sided alpha of 0.05 and a power of 0.80, yielding a target accrual of 160 patients. PFS was compared using one-sided stratified log-rank test. One interim analysis was planned.

Results: From January 2019 to May 2021, 102 patients were randomized - 58 NSCLC (30 in the SBRT arm) and 44 breast (22 in each arm). Median age was 67. Most patients (75%) had > 1 site of oligoprogression and 47% had > 5 total metastatic lesions. Fifty-five (54%) patients received immunotherapy. The majority of NSCLC (86%) did not harbor an actionable driver mutation and 32% of breast cancer were triple negative. Baseline factors were balanced between arms.

At a median follow-up of 51 weeks, 71 patients progressed and 30 died. Median PFS was 22 weeks in the SBRT arm vs. 10 weeks in the palliative SOC arm ($p=0.005$). This was driven entirely by the PFS benefit from SBRT in the NSCLC patients (44 weeks with SBRT vs. 9 weeks with SOC; $p=0.004$). No difference in median PFS was seen in the breast cohort (18 weeks with SBRT vs. 17 weeks with SOC; $p=0.5$). In multivariable Cox model inclusive of stratification factors, age, sex, lines of systemic therapy, and change of systemic therapy, the PFS benefit of SBRT remained substantial in the NSCLC cohort (Hazard Ratio: 0.38; 95% CI: 0.18-77; $p=0.007$). Grade ≥ 2 adverse events occurred in 8 patients in the SBRT arm, including 1 grade 3 pneumonitis.

Conclusion: In this pre-planned interim analysis of the first and largest randomized trial of radiotherapy for oligoprogressive metastatic NSCLC and breast cancer, we demonstrated the benefit of SBRT to sites of oligoprogression on overall PFS, meeting the primary endpoint. The mechanism of the differential benefits between NSCLC and breast cohorts merits further evaluation.

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