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2023 Multidisciplinary Thoracic Cancers Symposium November 30 - December 2, 2023

Plenary Session

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Stereotactic Radiation for Ultra-Central Non-Small Cell Lung Cancer: A Safety and Efficacy Trial (SUNSET)

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Purpose/Objective(s): The use of stereotactic body radiation (SBRT) for tumors in close proximity to the central mediastinal structures has been associated with a high risk of toxicity. This prospective study (NCT03306680) aimed to determine the maximally tolerated dose (MTD) of SBRT for ultra-central (UC) non-small cell lung carcinoma (NSCLC), using a time-to-event continual reassessment methodology (TITE-CRM).

Materials/Methods: Eligibility criteria included age ≥ 18 years, ECOG performance status 0-2, with stage T1-3N0M0(≤ 6 cm), NSCLC, and UC tumor location, defined as planning target volume (PTV) touching or overlapping the proximal bronchial tree (PBT), esophagus, pulmonary vein (PV), or pulmonary artery (PA). The MTD was defined as the dose of radiotherapy associated with a ≤ 30% rate of grade (G) 3-5 pre-specified treatment-related toxicity occurring within 2 years of treatment. The starting dose level was 60 Gy in 8 fractions (7.5 Gy/fraction) delivered daily, with de-escalation to 60 Gy in 10 or 15 fractions if toxicity rates exceeded 30% using TITE-CRM. Estimated sample size was 30 patients. The hotspot was limited to 120% within the PTV; tumors with endobronchial invasion were excluded. Adverse event rates were assessed using CTCAE version 4.0. Secondary endpoints included overall survival (OS), progression-free survival (PFS), local control (LC), regional control (RC), and distant control (DC), calculated using Kaplan-Meier estimates, and quality of life (QOL), assessed using the Functional Assessment of Cancer Therapy (FACT) Lung questionnaire. This primary analysis occurred two years after completion of accrual.

Results: Between March 2018 and April 2021, enrollment completed with 30 patients at five Canadian academic institutions. The median follow-up was 36.5 months (range: 8.9-50.8). The median age was 73 years (interquartile range [IQR]: 69-78), 17 (56.7%) were female, 23 (76.7%) were T1, 6 (20.0%) T2 and 1 (3.3%) T3. Tumor was located near PBT in 18 (60.0%), esophagus 5 (16.7%), PV 1 (3.3%) and PA 14 (46.7%). All patients were assigned a dose of 60 Gy in 8 fractions. Two patients (6.7%) experienced G3-5 adverse events related to treatment: one patient with G3 dyspnea and 1 G5 pneumonia (related to interstitial lung disease [ILD]); the latter had CT findings consistent with a background of ILD identified after SBRT. Three-year actuarial outcomes were as follows: OS was 72.5% (95% confidence interval [CI]: 52.3-85.3%), PFS 66.1% (95% CI: 46.1-80.2%), LC 89.6% (95% CI: 71.2-96.5%), RC 96.4% (95% CI: 77.2-99.5%) and DC 85.9% (95% CI: 66.7-94.5%). QOL scores declined numerically over time, but the decrease were not clinically or statistically significant.

Conclusion: 60 Gy in 8 fractions, planned and delivered with only a moderate hotspot, has a favorable adverse event rate, within the pre-specified acceptability criteria, and results in excellent tumor control.

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A Population-Based Analysis of the Management of Symptoms of Depression among Patients with Stage IV Non-Small Cell Lung Cancer in Ontario, Canada

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Purpose/Objective(s): Patients with lung cancer can experience significant psychological morbidities including depression. The purpose of the

study was to characterize the patterns and factors associated with interventions for symptoms of depression in Stage IV non-small cell lung cancer (NSCLC).

Materials/Methods: We conducted a population-based cohort study using health services administrative data in Ontario, Canada, of patients diagnosed with NSCLC from January 2007 to September 2018. Symptoms of moderate to severe depression was defined by reporting at least one Edmonton Symptom Assessment System (ESAS) score ≥2 following diagnosis. Patient factors included age, sex, comorbidity burden, residence, and income quintile. Interventions included psychiatry/psychology assessment, social work referral and anti-depressant therapy (for patients ≥65 years of age with drug coverage through the Ontario Drug Benefit program). Multivariable modified Poisson regression models were used to examine the association between patient factors and intervention use.

Results: A total of 13,159 patients with Stage IV NSCLC lung cancer was included in the study. Symptoms of moderate to severe depression was prevalent with 71.4% (n=9,397) of patients who reported ESAS ≥2 at least once. There was low utilization of psychiatry/psychology assessments (6.6%) and social work referrals (15.8%) in the cohort. For patients ≥65 years of age, 20.8% of patients were prescribed anti-depressant medications. Patients who reported moderate to severe depression were more likely to receive psychiatry assessment/ psychology referral (7.8% vs. 3.5%; standardized difference [SD] 19%), social work referral (17.4% vs. 11.9%; SD 16%) and anti-depressant prescriptions (23.8% vs. 13.8%; SD 26%) as compared to those with none or mild depression symptoms. In multivariable analyses, older patients were less likely to receive psychiatry/psychology assessment, social work referral and anti-depressant prescriptions. Females were more likely to obtain a psychiatry/psychology assessment or social work referral than males. In addition, patients from non-major urban or rural residences were less likely to receive psychiatry/psychology assessment or social work referral, however patients from rural residences were more likely to be prescribed anti-depressants.

Conclusion: There is a high prevalence of moderate to severe depression symptoms in Stage IV NSCLC. Although the proportion receiving public interventions is low, patients with moderate to severe depression symptoms were more likely to receive intervention. We identify patient populations who are less likely to receive interventions that will help inform resource planning.

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Prognostic Performance of a Genome-Wide Methylome Enrichment Platform in Early-Stage Non-Small Cell Lung Cancer (NSCLC)

G. Liu,[1] J. Zhang,[2] Y. Wang,[2] J. Burgener,[2] O. Hall,[2] S.Y. Shen,[2] M. Pienkowski,[1] S.H. Huang,[1] E. Sosa,[2] A. Polio,[2] S.B. Goldberg,[3] P. Mazzone,[4] S. Bratman,[2] A. Licon,[2] K. Brown,[2] B. Allen,[2] A.R. Hartman,[2] D.D. De Carvalho,[2] and B. Park[5]; [1]*Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada,* [2]*Adela, Inc., Foster City, CA,* [3]*Yale School of Medicine, Department of Medical Oncology, New Haven, CT,* [4]*Cleveland Clinic, Chagrin Falls, OH,* [5]*Vanderbilt-Ingram Cancer Center, Nashville, TN*

Purpose/Objective(s): Circulating tumor DNA (ctDNA) can be utilized to identify the presence of cancer as well as minimal residual disease (MRD). Quantification of ctDNA can be a useful cancer management tool to assess prognosis. Here we evaluate the feasibility of using a tumor-naïve genome-wide methylome enrichment platform to quantify ctDNA in plasma and predict recurrence in early-stage non-small cell lung cancer (NSCLC).

Materials/Methods: In a retrospective evaluation of banked, pre-treatment samples from newly diagnosed Stage I and II NSCLC patients (collected from 2009 to 2013, Princess Margaret Cancer Centre), samples were analyzed with a bisulfite-free, non-degradative genome-wide DNA methylation enrichment platform using 5-10 ng of cell-free DNA isolated from plasma. ctDNA was quantified from average normalized counts across informative regions. Events were defined as cancer recurrence or death due to any cause, whichever occurred earlier. A ctDNA quantity threshold was set where all samples from patients without an event fell below the threshold (i.e., 100% specificity). Time to recurrence or death was compared for samples with ctDNA quantities above the threshold to those below the threshold. Recurrence-free survival was estimated using Kaplan-Meier method, and the difference was assessed by the log-rank test. Multivariable Cox regression analysis was used to adjust for known prognostic covariates.

Results: Samples from 41 patients were included. The table describes clinico-demographic information. With a median follow-up time of 56.4 months, there were 27 events. Samples with ctDNA above the threshold showed significantly worse recurrence-free survival [hazard ratio (HR) 2.70 (95% CI 1.26, 5.78), log-rank P=0.008], even after accounting for histology (selected using univariate analysis) [HR 2.79 (95% CI 1.30, 6.02), P=0.009].

Conclusion: Our data shows that this blood-based genome-wide methylome enrichment platform can be used for ctDNA quantification and prognostication in early-stage NSCLC. Initial feasibility was evaluated here using treatment-naïve plasma samples. Applications for cancer management will be further evaluated in future studies utilizing post-treatment and longitudinal samples.

Abstract 3 − Table 1

Clinical Characteristics	Overall (N=41)
Age; Mean [SD], years	70.9 [11.3]
Female	22 (54%)
Male	19 (46%)
Stage IB	20 (49%)
Stage IB	7 (17%)
Stage IIA	10 (24%)
Stage IIB	4 (10%)
Adenocarcinoma	27 (66%)
Squamous cell carcinoma	14 (34%)

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Lung Cancer Survival Trends in the Veterans Health Administration

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Purpose/Objective(s): Lung cancer survival is improving in the United States. We investigated whether there was a similar trend within the Veterans Health Administration (VHA), the largest integrated healthcare system in the United States.

Materials/Methods: Data from the Veterans Affairs Central Cancer Registry (VACCR) were analyzed for temporal survival trends using Kaplan-Meier (K-M) estimates and linear regression.

Results: 54,922 Veterans were identified with lung cancer diagnosed from 2010-2017. Histologies were classified as non-small cell lung cancer (NSCLC) (64.2%), small cell lung cancer (SCLC) (12.9%), and 'other' (22.9%). The proportion with stage I increased from 18.1% to 30.4%, while stage IV decreased from 38.9% to 34.6% (both $p<0.001$). The three-year overall survival (OS) improved for stage I (58.6% to 68.4%, $p<0.001$), stage II (35.5% to 48.4%, $p<0.001$), stage III (18.7% to 29.4%, $p<0.001$), and stage IV (3.4% to 7.8%, $p<0.001$). For NSCLC, the median OS increased from 12 to 21 months ($p<0.001$), and 3-year OS increased from 24.1% to 38.3% ($p<0.001$). For SCLC, the median OS remained unchanged (eight to nine months, $p=0.10$), while the three-year OS increased from 9.1% to 12.3% ($p=0.014$). Compared to White Veterans, Black Veterans with NSCLC had similar OS ($p=0.81$), and those with SCLC had higher OS ($p=0.003$).

Conclusion: Lung cancer survival is improving within VHA. Compared to White Veterans, Black Veterans had similar or higher survival rates. The observed racial equity in outcomes within a geographically and socioeconomically diverse population warrants further investigation to better understand and replicate this achievement in other health care systems.

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Oral Scientific Sessions

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KontRASt-01 Update: Safety and Efficacy of JDQ443 in *KRAS G12C*-Mutated Solid Tumors Including Non-Small Cell Lung Cancer (NSCLC)

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Purpose/Objective(s): *KRAS G12C* oncogenic mutations occur in ~13% of NSCLCs and up to 4% of other solid tumors. JDQ443 is a selective, covalent, orally bioavailable $KRAS^{G12C}$ inhibitor that irreversibly traps $KRAS^{G12C}$ in the inactive, GDP-bound state. Clinical activity was seen in initial cohorts of patients (pts) treated with JDQ443 monotherapy, and 200 mg twice daily (BID) was selected as the recommended dose (RD) for expansion (Tan DS, et al. AACR 2022; Abstract CT033).

Materials/Methods: KontRASt-01 (NCT04699188) is a Phase Ib/II, open-label, multicenter, dose-escalation (DEs), and dose-expansion (DEx) trial of JDQ443 as a monotherapy or in combination with TNO155 (SHP2 inhibitor) and/or tislelizumab (anti−PD-1 monoclonal antibody). Primary objectives of DEs are to assess safety/tolerability and identify the RD and regimens for future studies. The primary objective of DEx is to assess efficacy. Key inclusion criteria: advanced, *KRAS G12C*-mutated solid tumors; previous standard-of-care treatment; age ≥ 18 years; and ECOG PS 0-1. Prior $KRAS^{G12C}$ inhibitor treatment is not permitted for the JDQ443 monotherapy arm and is allowed for the JDQ443 + TNO155 and JDQ443 + tislelizumab DEs arms.

Results: As of October 28, 2022, 84 pts were treated with JDQ443 monotherapy, orally, continuously, in DEs, DEx, and food effect (FE) cohorts at 200 mg once daily (QD; n = 10), 400 mg QD (n = 11), 200 mg BID (n = 56), and 300 mg BID (n = 7). Median age was 61 years (range 26-83); median prior lines of therapy was 3 (range 1-7); and indications included NSCLC (n = 38), colorectal cancer (n = 42), and others (n = 4). Median duration of exposure was 14.6 weeks (range 0.1-68.4) for all pts and 15.1 weeks (0.1-68.1) for pts treated at 200 mg BID. Among pts treated at 200 mg BID, 40 (71.4%) and 4 (7.1%) experienced treatment-related adverse events (TRAEs) of any grade (Gr) and of Gr 3, respectively. There were no Gr 4/5 TRAEs at any dose level. The most common TRAEs (any Gr, occurring in ≥ 10% of pts) at 200 mg BID were fatigue (17.9%), edema (14.3%), diarrhea (16.1%), nausea (16.1%), vomiting (10.7%), and peripheral neuropathy (10.7%). Gr 3 TRAEs were neutropenia in 2 pts, ALT and AST increase in 1 pt, and myalgia in 1 pt. One pt receiving 200 mg BID required a dose reduction due to a TRAE of Gr 2 peripheral neuropathy. Among response evaluable pts with NSCLC treated in DEs and FE cohorts, the confirmed overall response rate was 41.7% (10/24 pts) across dose levels and 54.5% (6/11 pts) at the RD of 200 mg BID. Combination JDQ443 + TNO155 and JDQ443 + tislelizumab arms are enrolling. Additional data will be available at the time of presentation.

Conclusion: JDQ443 demonstrates an acceptable safety and tolerability profile at 200 mg BID, with clinical activity in pts with NSCLC. Enrollment is ongoing to the JDQ443 monotherapy DEx and the JDQ443 + TNO155 and JDQ443 + tislelizumab combination arms.

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Dose-volume Predictors of Radiation Pneumonitis Following Thoracic Hypofractionated Radiotherapy

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Purpose/Objective(s): Hypofractionated radiation therapy (HFRT) is often used for patients with thoracic tumors, especially those in a central or ultra-central location. This is typically prescribed to 60 Gy in 15 fractions, though we previously demonstrated similar local control, overall survival, and toxicity with 72 Gy in 18 fractions. We sought to identify dosimetric risk factors associated with radiation pneumonitis in patients treated with HFRT delivered in 4 Gy per fraction. We hypothesized that a higher lung V20 (volume receiving 20 Gy), mean lung dose (MLD), and/or lung V5 (volume receiving 5 Gy) would be associated with an increased risk of grade ≥2 pneumonitis.

Materials/Methods: All patients were treated with thoracic HFRT to 60 Gy in 15 fractions or 72 Gy in 18 fractions at a single health care system from 2013-2020. Central tumors were defined as within 2 cm of the trachea, proximal tracheobronchial tree, esophagus, spinal cord, or heart, and ultra-central tumors were defined as within 1 cm of these structures. The primary endpoint was grade ≥2 pneumonitis. We adjusted for target size and dosimetric variables in univariable and multivariable logistic regression analyses. We calculated the dose at which the predicted probability of grade ≥2 pneumonitis would be <20%.

Results: A total of 107 patients were included and followed over a median of 24.3 months. Among these patients, 51.4% received 60 Gy in 15 fractions, 48.6% received 72 Gy in 18 fractions, 65.4% had central tumors, and 52.3% had ultra-central tumors. Grade ≥2 radiation pneumonitis occurred in 18 patients (16.8%), and there was no difference between the two dose-fractionation regimens (17.3% vs. 16.3%, p=0.88). Grade ≥3 radiation pneumonitis occurred in four patients (3.7%), among whom two (1.9%) were grade 5. When comparing patients who experienced a grade ≥2 radiation pneumonitis vs. those who did not, there was a statistically significant difference in lung V20 (mean 23.4% vs. 14.9%, OR 1.18 [95% CI 1.09-1.28], p<0.001), MLD (mean 13.0 Gy vs. 9.5 Gy, OR 1.35 [95% CI 1.15-1.56], p<0.001), and lung V5 (mean 49.6% vs. 40.6%, OR 1.04 [95% CI 1.01-1.08], p=0.01). The thresholds for 20% risk of grade ≥2 pneumonitis were lung V20 of 18.0%, MLD of 10.8 Gy, and V5 of 42.0%. On multivariable analysis, only lung V20 had a statistically significant association with grade ≥2 pneumonitis (adjusted OR 1.48 [95% CI 1.03-2.13], p=0.03). The two patients with grade 5 toxicities had lung V20 of 24.7% and 29.6%, MLD of 13.2 Gy and 16.5 Gy, and lung V5 of 53.0% and 63.3%.

Conclusion: When using 4 Gy per fraction to either 60 Gy or 72 Gy, maintaining lung V20<18.0% may be a reasonable goal to minimize the risk grade ≥2 radiation pneumonitis. MLD<10.8 Gy and V5<42.0% could be considered as lower-priority constraints as well. Further research will be needed to externally validate these dose constraints prior to implementation in clinical practice or clinical trial planning guidelines.

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Esophagitis Following Intensity-Modulated Radiotherapy for Lung Cancer

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Purpose/Objective(s): Despite highly conformal radiotherapy techniques, esophagitis remains a clinically relevant problem for lung cancer patients undergoing standard fractionation radiotherapy potentially resulting in treatment breaks and reduced overall survival. Clinical and dosimetrical risk factors and the importance of adherence to standard dose thresholds are investigated.

Materials/Methods: Seventy-two consecutive non-small cell or small cell lung cancer patients (stage I and II 22%, III 64%, IV 15%) underwent radiotherapy to a median prescribed dose of 60 Gy (range 45-66) in 1.5(bid) - 3 Gy-fractions using IMRT/VMAT and IGRT. Concurrent chemotherapy or immunotherapy was delivered in 47/72 (65%) patients. Esophagitis grades were recorded prospectively according to CTCAE v5 criteria. Incidence and risk factors for esophagitis grade 0 and 1 vs. grade ≥2 were analyzed, statistical significance was assessed using chi-square test. The effect of esophagitis on survival was investigated using Kaplan-Meier curves and log rank test.

Results: Median age was 68 years (range 45-90), 33 (46%) were female, 32 (44%) African American and 52 (72%) had tumors in the upper lobes. Median follow up for surviving patients was 16 months (sufficient to assess acute and subacute toxicities). 53 (74%) had grade 0 or 1, 19 (26%) grades ≥2 esophagitis. Median average esophagus dose was 14.6 Gy (range 2.9 - 33.8 Gy), maximum dose 60.1 Gy (range 16.7 - 67.9 Gy) and median V60Gy 0% (0-28.3%). Eighteen patients (25%) exceeded any standard esophagus constraint (average ≤34Gy, max dose ≤105%, V60Gy ≤17%, avoid full circumference) of which 10 developed grade ≥2 esophagitis corresponding to 53% of all symptomatic patients (p=0.001). Grade ≥2 esophagitis was significantly related with esophagus length irradiated to 30, 40 and 50 Gy (p=0.01-0.002), percentage of esophagus ≥30Gy (p=0.016), irradiation of full circumference with prescribed dose (p=0.014) and concurrent chemotherapy (p=0.0017). Younger patients were at higher risk as well (p=0.04). Estimated mean survival was not different for grade 0/1 vs. grade ≥2 esophagitis (29.7 months vs. 20.7 months, log rank p=0.77).

Conclusion: Grade ≥2 esophagitis occurs in every fourth patient despite using highly conformal radiotherapy techniques. While patients had a higher risk for grade ≥2 esophagitis when dose constraints were exceeded, 47% of patients with grade ≥2 esophagitis did not exceed established dose constraints indicating that for IMRT/VMAT current standard constraints are not well aligned with the esophagitis risk. Adding constraints in the intermediate dose range as identified in the present study (esophagus length and percentage irradiated to 30 Gy) might lead to better plan quality and lower toxicity risk.

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Efficacy and Safety of Immune Checkpoint Inhibitors (ICI) in Resectable Non-Small Cell Lung Cancer (NSCLC): A Systematic Review and Meta-Analysis

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Purpose/Objective(s): Recent efforts aimed to add ICI to chemotherapy in the neoadjuvant and adjuvant setting (Neo/Adj) to improve outcomes of patients with resectable NSCLC. The objective of this systematic review and meta-analysis is to evaluate the efficacy and safety of such strategy and identify subgroups of patients who may derive the most benefit.

Materials/Methods: Randomized control trials comparing Neo/Adj ICI plus chemotherapy vs chemotherapy alone in resectable NSCLC (pre-Sep 2022) were retrieved from PubMed, Embase, Cochrane Library and updated based on recent conferences. Primary outcomes were pathological complete response (pCR), event-free, disease-free, and progression-free survival (EFS, DFS, PFS). Secondary outcomes were major pathologic response (MPR), overall survival (OS), and safety. Subgroup analyses of EFS/ DFS/ PFS included histology, smoking status, and PDL-1 status. Pooled hazard ratios (HR), odds ratios (OR) and risk ratios (RR) were meta-analyzed using the generic variance, Peto and Mantel-Haenszel methods as appropriate. Random effect models were used to compute pooled estimates.

Results: 3926 patients across five neoadjuvant and two adjuvant trials were included. Neoadjuvant ICI improved pCR fivefold compared to chemotherapy alone (OR 5.35; 95% CI, 4.02 - 7.13). Both neo- and adjuvant use of ICI decreased recurrence risk by 34% (HR 0.66; 95% CI, 0.54 - 0.81). Two-year OS improved with adding either neo- or adjuvant ICI (RR 0.73; 95% CI, 0.58 - 0.92) with a trend towards better median OS (HR 0.76; 95% CI, 0.57 - 1.02). Neoadjuvant ICI improved MPR fourfold vs. chemotherapy (OR = 3.91; 95%, CI 2.90 - 5.28). In subgroup analyses, those with non-squamous NSCLC, ever smokers, and tumors with PD-L1>=1% seem to derive a greater benefit from ICI. Neo/Adj ICI increased immune-related adverse effects risk threefold (RR = 3.36; 95% CI, 2.11 - 5.36), with an increase in grade 3 treatment-related toxicity (RR = 1.28; 95% CI, 0.93 - 1.78).

Conclusion: Based on preliminary data, adding Neo/Adj ICI improves recurrence rate in resectable NSCLC with a trend towards improved OS. Safety signals were consistent with historical data. Further subgroup evaluations may help to identify suitable population for either approach.

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Clinical, Quality of Life and Cost Outcomes in Patients with Early Stage Non Small Cell Lung Cancer Undergoing Surgery or SBRT

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Purpose/Objective(s): To compare frailty, QOL and 90-day cost of treatment between patients who underwent surgery or SBRT for early stage NSCLC and identify objective parameters that could aide treatment selection and shared decision-making.

Materials/Methods: Data from treatment naïve adult patients newly diagnosed with early stage NSCLC was collected prospectively. Combined decision on treatment option was based on multidisciplinary clinical assessment and patient preference. Demographics, PFT, NSQIP risk scores were collected. Frailty index score ≥3 was considered frail. Cancer specific QOL questionnaires QLQ-C30/QLQ-LC13/mMRC were administered.

Results: Patients were more likely to undergo SBRT if frail (OR-4.92), required functional assistance (IADL, OR-5.01), had pre-clinical morbidity/disability (OR-3.48), worse mobility (TUG test, OR-4.04) or poor nutritional status (MNA, OR- 2.18). Multivariate modeling demonstrated that an increase in NSQIP estimated risk of death (OR=12.60), higher frailty index (OR - 4.80) and decreasing FEV1% increased the probability of receiving SBRT. More surgery patients had complications (41% vs 17%, p<0.05). OS estimates at six months, one and two-years for surgery was 99.1%, 97.3% and 90.7% vs 95.7%, 86.2 and 70.1% for SBRT (p<0.05), respectively. RFS at one and two-year for surgery was 95.1% and 81.5% vs 88.2% and 64.8% for SBRT (p<0.05). Among QOL measures in the surgical cohort, the change in physical functioning, fatigue and dyspnea scores declined over the two-year period from baseline. There was no change from baseline in QOL measures with SBRT. At two-years the change in QOL measure was similar between the cohorts, except change in role functioning was significantly lower in SBRT patients. Median 90-day treatment-related Medicare/Medicaid costs were lower in SBRT $11,188 vs

surgery $15,018 (p<0.05). In patients without major complications, treatment related costs were similar between SBRT and surgery ($11,188 vs $11,846, p<0.05).

Conclusion: Frailty assessment, when used as part of a multifactorial risk model inclusive of increased comorbidities, higher pack year history, poor pulmonary function, and increased NSQIP risk, helped to identify patients selected for SBRT. While QOL did not differ, OS and RFS declined significantly with SBRT at 2 years in this unmatched comparison. Future longitudinal registries with long-term follow-up are needed to provide better discriminatory ability regarding the treatment impact on QOL and to develop robust treatment selection criteria.

Abstract 104 — Table 1: Baseline characteristics

	Surgery(n=122)	SBRT(n=48)
Age, years, mean*	67.5	72.2
Male%	39.3	45.8
Pack-years, median*	40	51
Years of smoking, median*	40	46.5
Medical History, %		
Angina*	12.8	33.3
Coronary Artery Bypass Grafting*	12	35.6
Chronic Obstructive Pulmonary Disease*	79.6	93.6
Pneumonia*	9.9	25.5
History of Cancer*	22	41
Pulmonary Function, median		
FVC %*	90	75
FEV1 %*	82	60
FEV1/FVC*	0.7	0.63
DLCO %*	69	55
NSQIP estimated risk, median		
Any complication*	11.6	10.3
Death*	0.6	1.7

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Disparities in Delivery of Local-Consolidative Surgery for Patients with Single-Site Oligometastatic Non-Small Cell Lung Cancer

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Purpose/Objective(s): Local-consolidative surgery with resection of the primary tumor has been demonstrated to selectively play a role in the treatment of stage IV single-site oligometastatic, non-small cell lung cancer. However, it is not clear what factors influence the practice of local-consolidative surgery. Here, we explored how socioeconomic determinants of health associated with the delivery of this practice in a contemporary multi centric cohort from the United States.

Materials/Methods: In this study, we evaluated patients with clinical stage IVA (M1A and M1B, 8th Edition AJCC) NSCLC in the National Cancer Database (2018-2020), and stratified the cohort based on the receipt of multimodal treatment with local-consolidative resection of the primary tumor (LCS) vs. definitive systemic therapy (ST). Using multivariable logistic regression analysis, we studied the association between patient, socioeconomic, and treatment facility factors and the delivery of local-consolidative surgery.

Results: Among 20,264 patients with stage IVA non-small cell lung cancer, 2.8% (574) underwent multimodal therapy with local-consolidative surgery, and 97.2% (19,962) had definitive systemic therapy without surgery. Patients who were female (3.1% vs. 2.6% male, p=0.03), those <65 years (3.4% vs. 2.2% ≥65 years,p<0.001), non-Hispanic whites (3% vs. 2.3% other races, p=0.01), those treated in academic facilities (3.3% vs. 2.3% of those treated in community facilities, p<0.001), those with private insurance (3.8%vs. 2.0% with public insurance/uninsured, p<0.001), those above median income level (3.1% vs. 2.4% below median income level, p<0.001) and those living >10 miles from the treatment facility (3.2% vs.2.4% <10 miles from facility, p<0.001) were more likely to receive LCS. On multivariable logistic regression analysis, younger age (<65 years aOR 1.48, 95%CI 1.23-1.80,p<0.001), White race (aOR 1.27, 95%CI 1.02-1.57, p=0.03), treatment at an academic facility (aOR1.39, 95%CI 1.17-1.65, p<0.001), being above median income level (aOR 1.29, 95%CI 1.08-1.53,p=0.006) and residing >10 miles from the treatment facility (aOR 1.26, 95%CI 1.06-1.49, p=0.009) were independently associated with increased utilization of LCS.

Conclusion: LCS of the primary tumor remains rare, but will likely become more utilized with advances in systemic therapy. In this study, the elderly, racial minorities, those treated at community facilities, and those socioeconomically disadvantaged were less likely to receive local-consolidative surgery. A granular determination of reasons for these disparities warrants further investigation, ideally accompanied by targeted interventions.

Abstract 105 — Table 1

Variable	Adjusted Odds Ratio	95%CI
Female	1.17	0.99-1.39
Non-Hispanic Whites	1.27	1.02-1.57
<65 Years	1.48	1.23-1.80
Academic Facility	1.39	1.17-1.65
Private Insurance	1.76	0.89-3.45
>Median income	1.29	1.08-1.53
>10 Miles from facility	1.26	1.06-1.49
>Education indicator	1.03	0.85-1.24
CCI >1	0.88	0.69-1.13

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Dosimetric Factors Associated with Esophagitis Following Hypofractionated Radiotherapy to the Thorax

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Purpose/Objective(s): Hypofractionated radiation therapy (HFRT) is commonly prescribed, particularly those with central or ultra-central lung tumors. Our prior research showed comparable local control (LC), overall survival (OS), and toxicity with 72 Gy in 18 fractions compared to 60 Gy in 15 fractions. Our hypothesis was that an elevated mean esophagus dose (Dmean), maximum dose to the esophagus (Dmax), and other dosimetric parameters would be associated with grade ≥2 esophagitis in patients undergoing HFRT at 4 Gy per fraction.

Materials/Methods: We included all thoracic HFRT patients treated with 60 Gy in 15 fractions or 72 Gy in 18 fractions at a single healthcare system from 2013-2020. The primary endpoint was grade ≥2 esophagitis. Target size and dosimetric variables (including esophagus Dmean, Dmax, V40 [volume receiving 40 Gy],and V60 [volume receiving 60 Gy]) were assessed

on univariable and multivariable logistic regression analyses. We calculated predicted probabilities of grade ≥2 esophagitis to determine the doses that would keep this risk under 20%.

Results: We included 107 patients, among whom 55 (51.4%) received 60 Gy in 15 fractions and 52 (48.6%) received 72 Gy in 18 fractions. Tumors within 2 cm of the esophagus comprised 27.1% of total patients, and tumors within 1 cm of the esophagus comprised 10.3% of total patients. Median follow-up was 24.3 months. There were 13 cases (12.1%) of grade ≥2 esophagitis, with no statistically significant difference between 60 Gy and 72 Gy (9.4% vs. 14.8%, p=0.39). Three patients (2.8%) developed grade 3 esophagitis, with no cases of grade 4-5 esophagitis. When comparing patients who experienced a grade ≥2 esophagitis vs. those who did not, there was a statistically significant difference in esophagus Dmean (mean 13.8 Gy vs. 9.7 Gy, OR 1.11 [95% CI 1.01-1.23], p=0.02), esophagus Dmax (mean 45.8 Gy vs. 35.9 Gy, OR 1.05 [95% CI 1.00-1.09], p=0.03), and esophagus V40 (mean 5.5% vs. 2.3%, OR 1.10 [95% CI 1.01-1.21], p=0.04), but no statistically significant difference in esophagus V60 (mean 0.20% vs. 0.01%, OR 7.65 [95% CI 0.23-255.8], p=0.26). None of these associations were statistically significant on multivariable analysis. Patients with esophagus Dmean<17.5 Gy and Dmax<54.0 Gy were noted to have a risk of grade ≥2 esophagitis under 20%, while the esophagus V40 and V60 volumes were too low to determine a clinically useful threshold.

Conclusion: When prescribing 4 Gy per day to 60-72 Gy for thoracic tumors, we propose constraining esophagus Dmean<17.5 Gy and Dmax<54.0 Gy whenever feasible. External validation is needed to determine appropriateness of applying these planning guidelines in clinical practice or clinical trials.

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Poster Q&A Sessions

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The Keynote B36 (EF-36) Pilot Study of Tumor Treating Fields (TTFields) Therapy with pembrolizumab as First-Line Treatment of PD-L1-Positive, Advanced or Metastatic Non-Small Cell Lung Cancer

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Purpose/Objective(s): TTFields are electric fields that disrupt cancer cell division and have been shown to cause immunogenic cell death and stimulate an antitumor immune response in preclinical non-small cell lung cancer (NSCLC) models. TTFields therapy is a noninvasive treatment currently approved for glioblastoma and mesothelioma. In the pivotal LUNAR study, TTFields therapy demonstrated a survival benefit when applied to the thorax in patients with metastatic NSCLC following progression on/after platinum-based therapy, concomitant with an immune checkpoint inhibitor (ICI) or docetaxel (HR: 0.75 [95% CI 0.56−0.98]; p=0.04) with a pre-specified clinically meaningful and statistically significant benefit in ICI patients. Herein, we describe the pilot Keynote B36 study (EF-36; NCT04892472) evaluating first-line TTFields therapy concomitant with pembrolizumab for PD-L1 positive advanced or metastatic NSCLC confirmed by tumor proportion score (TPS) ≥ 1% at local study site.

Materials/Methods: Approximately 100 patients with PD-L1-positive, treatment-naïve, advanced or metastatic NSCLC (ineligible for EGFR- or ALK-directed therapy) will be enrolled and randomized 1:1 (stratified by PD-L1 status [TPS ≥50%/1−49%] and histology) to TTFields therapy (150 kHz; NovoTTF-200T system) concomitant with pembrolizumab (200 mg IV every three weeks [Q3W]) or pembrolizumab (200 mg IV Q3W) alone. Key inclusion criteria are age ≥22 years, ECOG PS 0/1, and evaluable disease in the thorax per RECIST 1.1. With the exception of palliative radiotherapy, patients who have received prior treatment in the metastatic setting are ineligible. Study treatments will continue for 24 months (TTFields therapy) and 35 cycles (pembrolizumab), or until disease progression, intolerable toxicity, or investigator/patient withdrawal for any reason. Follow-up evaluations will occur every nine weeks for the first year, then every 12 weeks thereafter. Primary endpoint is progression-free survival (PFS). Secondary endpoints are overall survival, objective response rate, duration of response, disease control rate at 18 weeks, and safety. PFS and response will be investigator-assessed per RECIST 1.1. Expected PFS for the pembrolizumab (alone) arm was determined using data from the phase 3 KEYNOTE-598 study (8.4 months). The study is powered at 80% (1-sided alpha of 0.2) to detect a hazard ratio of <0.668 for TTFields therapy/pembrolizumab vs pembrolizumab alone, corresponding to an increase in median PFS from 8.4 to 12.6 months. An interim analysis for futility will be performed after ≥14 PFS events. Enrollment is planned at 30 sites in the US.

Results: TBD

Conclusion: TBD

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2001

A Prospective, Multi-Institutional Digital Health Pilot Study to Detect Pneumonitis Early in Patients with Stage III NSCLC on durvalumab Monitored Remotely: Findings from the ON TRAX Study

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Purpose/Objective(s): Standard of care (SoC) for eligible patients with unresectable Stage III non-small cell lung cancer (NSCLC) is the PACIFIC regimen, chemoradiotherapy (CRT) followed by durvalumab, with pneumonitis being the most common adverse event leading to treatment discontinuation. ON TRAX was a multicenter, prospective pilot study that evaluated the ability of a multiparametric remote monitoring system to detect early signs of pneumonitis in patients receiving durvalumab.

Materials/Methods: The pilot aimed to enroll 75 patients (from 25 sites) with unresectable stage III NSCLC after CRT, but prior to receiving SoC

durvalumab, with no major comorbidities and not on oxygen. Patients were monitored remotely while on durvalumab for up to one year with a platform of mobile devices (FDA-cleared wearable recording continuous SpO2, respiratory rate, pulse, temperature and motion; spirometer for daily lung function; tablet for patient reported outcomes) and digital applications. The primary objective of the study was to identify pneumonitis by grade, with an exploratory objective to develop a longitudinal algorithm that predicts pneumonitis early. After all the data was collected, individual daily pneumonitis risk scores between 0-1 were computed retrospectively using a pre-monitoring baseline score based on established risk factors plus a weighted sum of univariate vital sign and spirometry variables with thresholds optimized based on clinician-confirmed pneumonitis cases. A rolling pneumonitis risk score was calculated by taking the average of daily scores over the prior five days. We used a k-fold (k=3) approach for the training data set and held an additional 20% of the total data points for validation.

Results: The pilot was terminated prematurely due to low enrollment during COVID-19 pandemic and low patient retention for the length of the study. Of the 40 enrolled patients (median age 65 years, 60% male, 60% stage IIIA), nine (23%) completed the study and 31 discontinued early (48% due to study closure, 23% withdrawal of consent, 5% device-related AEs), but remained on SoC durvalumab. Median (IQR) length of monitoring was 81 (44-206) days with a total of 76,960 hours of data. Only four patients (10%) experienced pneumonitis while on the study, with three recorded as grade 2 and 1 as grade 3. The best predictive performance of the longitudinal algorithm was observed with the rolling pneumonitis risk score. Setting a threshold of >0.68 for the score yielded 75% sensitivity, 65% specificity and an odds ratio of 5.5 [95% CI: 0.54-58.8] for correctly predicting pneumonitis within two weeks prior to diagnosis.

Conclusion: Even with low incidence of on-study pneumonitis, the longitudinal algorithm developed using remote monitoring demonstrated potential in predicting pneumonitis in patients receiving durvalumab post-CRT when their rolling pneumonitis risk score exceeded the threshold. Future research with a larger sample size and longer follow-up is needed for the validation and refinement of the algorithm.

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2002

Retrospective Study of Pancreatic Lesions and Deaths from Pancreatic Cancer in a Large Cohort of Low-Dose CT Screening for Lung Cancer

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Purpose/Objective(s): Lung cancer screening reduces cancer mortality, but effective pancreatic cancer screening remains elusive. The main objective of this study is to describe pancreatic events in a large cohort of participants enrolled in a low-dose CT (LDCT) lung screening program. We aimed to examine the association between identified pancreatic lesions and the participants' outcomes and aimed to conduct a comprehensive analysis of the records of participants who died due to pancreatic cancer.

Materials/Methods: We utilized data from ELCAP (Early Lung and Cardiac Action Program), a large prospectively collected institutional database of LDCT lung screenings. Firstly, we reviewed the documented pancreatic lesions, their frequency, as well as the demographics of participants presenting these lesions and their outcome from seven New York institutions. Secondly, we analyzed scans of participants who had died of pancreatic cancer, using data from a larger cohort of participating institutions via the United States National Death Index.

Results: Pancreatic lesions were documented in 89 (0.9%) of the 9467 participants. Among these 89 participants, median age 64, 92% were smokers and 41% had a history of alcohol consumption. The most frequent lesions were calcifications (57 cases, 64%), followed by pancreatic atrophy/fatty infiltration (16 cases, 18%). Other lesions comprised of four cysts, three low attenuation cases, two pancreatic duct dilatation cases, one lipoma, and one enlarged pancreas. Five (5.6%) of the 89 were diagnosed and treated for lung cancer. Among these 89 participants, one has died from pancreatic cancer. The pancreas was described as enlarged, and a follow-up contrast-enhanced CT scan revealed a lesion in the pancreatic tail and hepatic lesions suggestive of metastases. Biopsy confirmed metastatic pancreatic adenocarcinoma. Chemotherapy was initiated. The patient passed away eight months after their last screening CT. Another analysis focused on the documented deaths and causes of death. Eighty deaths due to pancreatic cancer (ICD-9 code: C259) were ascribed. Median time to death after the last screening: 5.6 years. Among 80 patients, three had pancreatic lesions described on their last screening CT: one with a cystic structure in the tail of the pancreas, second with an enlarged pancreas, and third with dilatation of the main pancreatic duct. Thirteen of the 80 patients died within 24 months after their last scan. Additional investigations were proposed in four cases: two cases for suspicious lung lesions of metastases, one case for the presence of ascites, and one was the case described above.

Conclusion: Reports of pancreatic lesions are uncommon among participants enrolled in LDCT lung cancer screening programs. The majority of reported pancreatic lesions are benign.

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2003

Tumor Treating Fields (TTFields) Therapy with Standard of Care in Metastatic Non-small Cell Lung Cancer Following Progression on or after Platinum Therapy: Global, Randomized, Pivotal Phase 3 LUNAR Study

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Purpose/Objective(s): TTFields are electric fields that disrupt cancer cell viability, with downstream effects demonstrated in preclinical models including abnormal mitosis and cell stress, leading to immunogenic cell death and an enhanced antitumor immune response. TTFields therapy delivered noninvasively by a portable medical device is approved for glioblastoma and mesothelioma. The phase 3/pivotal LUNAR study (NCT02973789) assessed TTFields therapy with investigator's choice of immune checkpoint inhibitor (ICI) or docetaxel (DTX), the standard of care (SOC) at time of study design, for metastatic non-small cell lung cancer (NSCLC) that had progressed on or after platinum-based therapy.

Materials/Methods: Adults with metastatic NSCLC progressing on/after platinum-based therapy, and ECOG PS ≤2, were randomized 1:1 to TTFields/SOC or SOC. Primary endpoint was overall survival (OS). Key secondary endpoints were OS in ICI and DTX subgroups. Other secondary endpoints included progression-free survival (PFS) and adverse events (AEs).

Results: 276 patients (TTFields+SOC, n=137; SOC alone, n=139) were included. Median (m) age was 64 years (range, 22−86), 65% were male, 56% had non-squamous NSCLC, 96% had ECOG PS 0−1, 11% had >1 prior line of systemic therapy, and 31% had prior ICI. Characteristics were balanced between arms. OS was significantly extended with TTFields+SOC vs SOC: mOS (95% CI) 13.2 (10.3−15.5) months (mo) vs 9.9 (8.1−11.5) mo; HR 0.74 (95% CI 0.56−0.98); *P*=0.035. 1-year survival (95% CI) was 53% (44−61) and 42% (34−50), respectively and mPFS (95% CI) was 4.8 (4.1−5.7) mo vs 4.1 (3.1−4.6) mo (HR 0.85; 95% CI 0.67−1.11; *P*=0.23), respectively. In ICI-treated patients (n=134), TTFields significantly improved OS vs ICI alone: mOS (95% CI) 18.5 (10.6−30.3) vs 10.8 (8.2−18.4) mo; HR 0.63 (95% CI 0.41−0.96); *P*=0.03. In the DTX subgroup (n=142), mOS of patients treated with TTFields therapy was 11.1 (95% CI 8.2−14.1) mo vs 8.7 (95% CI 6.3−11.3) mo for patients receiving DTX alone; HR 0.81 (95% CI 0.55−1.19); *P*=0.28. Adverse events (AEs) were similar for patients receiving TTFields+SOC (97%) vs SOC alone (91%). 71% of patients reported a device-related AE; most were grade 1/2 dermatitis (39%) or pruritus (12%); 8 patients (6%) reported a grade 3 AE. No grade 4 AEs or deaths were attributable to TTFields.

Conclusion: TTFields therapy added to SOC extended OS vs. SOC alone, without exacerbating systemic toxicities, in patients with mNSCLC following progression on or after platinum therapy. These findings warrant the use of TTFields therapy to manage previously treated mNSCLC.

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2004

Targeted Therapy for Lung Cancer and Pancreatic Toxicity: Retrospective Study and Recommendations

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Purpose/Objective(s): Discoveries in non-small-cell lung cancer (NSCLC) led to the approval of multitude of tyrosine kinase inhibitors (TKI). Elevation of pancreatic enzymes (EPE), lipase and amylase, is frequently seen after TKI introduction. It is not always clear whether EPE in this setting has clinical relevance, and recommendations on pancreatic enzymes assessment are not standardized. Our hypothesis was that EPE associated with TKI did not have clinical implication most of the time. The aim of this study was to establish the risk of clinical pancreatitis associated with TKIs, and if routine assessment of pancreatic enzymes was needed.

Materials/Methods: In a monocentric retrospective study, we examined medical records of adult patients with metastatic NSCLC and genetic alterations in ALK, ROS, BRAF, RET, or NTRK, treated with TKI at Gustave Roussy, Villejuif (France) between 2011-2023. Patients having pancreatic enzymes assessed at least twice after treatment introduction were included. Clinical symptoms; blood levels of amylase, lipase, calcium and triglyceride levels; radiological findings and confirmed pancreatitis diagnosis were reported at baseline and at the moment of toxicity. Paired T-test and Paired Wilcoxon test were performed for comparative analyses.

Results: We reviewed medical records of 231 patients with NSCLC treated with TKI. Out of the total patient population, 75 had at least two pancreatic enzymes assessment. EPE was found in 34 patients (45% of tested cases). One case of clinical pancreatitis was confirmed in a patient treated with dabrafenib/trametinib, with favorable evolution after treatment suspension, hydration and analgesia. Treatment could be resumed with no new complication. EPE was attributed to TKI in 29/34 cases, 1/34 to primary pancreatic tumor and 4/34 unknown cause. EPE was found in 9 patients before initiation of TKI. Radiological assessment did not show signs of pancreatitis in any of the patients with EPE. Crizotinib was the drug most frequently linked to EPE (38%), followed by lorlatinib (26%), ceritinib (12%), entrectinib (8%), dabrafenib/trametinib (6%), repotrectinib (6%) and brigatinib (3%). Median time to EPE occurred after 42 days, with a range between four days and five years. Mean amylase at the time of toxicity was 141 U/l (Upper Limit Normal (ULN) =100 U/l), with a mean raise of 50 U/l, while mean lipase was 98U/l (ULN =67 U/l), with a mean raise of 79U/l. No significant differences in calcium and triglycerides were found in the TKI-treated entire population nor in the crizotinib subgroup. There was a limited but significant increase in mean triglyceride levels in patients treated with lorlatinib, raising from 1.7 mmol/l to 2.4 mmol/l (p = 0.027).

Conclusion: Despite frequent EPE after TKI introduction, clinical pancreatitis are rare. Based on these results, we conclude that no routine assessment of pancreatic enzyme is required when introducing TKI treatment. To our knowledge, this is the first retrospective study about EPE linked to TKI in NSLC.

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2005

Implementation of an Early-Stage Lung Cancer Survivorship Clinic in a Comprehensive Cancer Center

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Purpose/Objective(s): Early-stage lung cancer survivors are a growing population. A comprehensive plan to address needs relevant to longer survival (e.g., psychological distress, persistent symptoms, physical function) and clinic capacity is necessary. How to deliver comprehensive survivorship care that meets national standards and results in improved patient outcomes is a challenge. Survivorship clinics staffed by advanced practice providers (APP) are an option to address these needs.

Materials/Methods: In June 2019, Atrium Health Wake Forest Baptist Comprehensive Cancer Center (AHWFB-CCC) opened a dedicated survivorship clinic. Stakeholders from the lung cancer disease-oriented team developed a standard referral pathway for patients to survivorship. A standard workflow was developed in the electronic medical record. Eligible lung cancer survivors were referred to the Lung Cancer Survivorship Clinic for a survivorship orientation visit (SOV) with a lung cancer specific APP. Prior to the SOV, a welcome video, disease-specific questionnaire, and electronic patient reported outcome (ePRO) tools (i.e., PROMIS-29 and Distress Thermometer) were sent to the patients' electronic chart. At the SOV, the ePRO responses and survivorship care plan were reviewed. Patients were offered a post visit survey. A comparison of PROMIS-29 Scores to the United States (US) lung cancer survivor population was performed using a T-test. PROMIS-29 T-score responses based on treatment modality were also compared using T-test. **Results:** From January 2020 to March 2023, 315 lung cancer patients completed a SOV. Most patients were able to complete the pre-visit questions via the electronic chart. AHWFB-CCC survivors reported improved PROMIS-29 T-Scores compared to the average United States (US) early-stage lung cancer survivor, with meaningfully better scores ($\geq$ 3 pts) in four of the seven health-related domains measured. PROMIS-29 T-Scores did not differ by treatment modality (all p values >0.05). Most patients found the SOV helpful and expressed better understanding of their cancer treatment and side effects after the SOV.

Conclusion: Our model of an optimized electronic medical record pathway paired with an APP led survivorship visit is feasible and can address current challenges in providing survivorship care to early-stage lung cancer survivors. Survivors had similar ePROs regardless of treatment modality, indicating their survivorship care could be consolidated. Future evaluation is needed to establish if this care model improves outcomes over subsequent visits, minimizes the effect of health disparities, or enhances care capacity.

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2006

Real-World Outcomes of Stage III NSCLC Treated with Chemoradiation +/- durvalumab

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Purpose/Objective(s): The standard of care for patients with unresectable stage III NSCLC is chemoradiation (CRT) with adjuvant durvalumab based on the PACIFIC trial. We sought to assess outcomes and their associated factors for patients treated with the PACIFIC regimen.

Materials/Methods: We performed a retrospective review of Stage III NSCLC patients ≥18 years old treated with CRT 1/1/2010-3/1/2022. Demographics, treatments, outcomes, and failure patterns were collected. Progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier analysis and log-rank tests. The effect of prognostic variables on PFS and OS were assessed using the Cox proportional-hazards model.

Results: Of 281 Stage III NSCLC patients, 180 were treated with CRT. Forty-nine patients received adjuvant durvalumab with median PFS 25.5 months (95% CI 11.6-NA) and median OS 44.8 months (95% CI 25.3-NA). Comparatively, 55 patients received CRT without adjuvant therapy and had median PFS of 11.9 months (95% CI 8.57-40.0) and median OS of 57.0 months (95% CI 25.1-NA). Patients treated with adjuvant durvalumab had no difference in OS (p=0.79) and numerically improved PFS (p=0.11). Among the 49 patients who received adjuvant durvalumab, 19 (38.8%) had Stage IIIA disease, 24 (49.0%) Stage IIIB, and six (12.2%) Stage IIIC. Forty-six were current/former smokers with a median pack-year history of 35. Patients received a median of 16 durvalumab cycles (IQR 5-26). 36 had available PD-L1 staining data, 22 (61.1%) of whom had ≥1% expression. There was no difference in PFS or OS based on PD-L1 expression. There was no difference in PFS or OS by dose of radiation (32 patients received 60 Gy, 11 patients received 66 Gy; PFS HR 0.81 (95% CI 0.30-2.21) OS HR 0.78 (95% CI 0.25-2.41). Patients initiated adjuvant durvalumab a median of 1.47 months (IQR 0.80-9.87) after finishing radiotherapy. Lastly, 26/49 patients stopped durvalumab treatment early, the most common reasons for which were pneumonitis (9/26, 34.6%), locoregional progression (5/26, 19.2%), distant metastatic progression (4/26, 15.4%), and fatigue (2/26, 7.7%). They underwent a median of five cycles of durvalumab with increased likelihood of earlier progression (HR 12.91, 95% CI 4.23-39.45) and death (HR 10.79, 95% CI 3.13-38.43).

Conclusion: In this single institution retrospective study, Stage III NSCLC showed similar PFS and OS outcomes upon receiving adjuvant durvalumab per the PACIFIC regimen. PD-L1 staining was not associated with outcomes, and patients commonly stopped adjuvant therapy for pneumonitis, progression, and fatigue. We found that earlier initiation of durvalumab therapy was not correlated with improved outcomes and instead saw a significant trend towards earlier progression and death on univariate analysis, likely reflecting advanced disease and clinician concern. Continued work in Stage III NSCLC in the setting of neoadjuvant chemoimmunotherapy is needed.

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2007

Impact of Effective Dose to Immune Cells (EDIC) in Early Stage NSCLC Treated with Lung SBRT

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Purpose/Objective(s): Effective dose to immune cells (EDIC) models the effects of radiation therapy on the immune system. EDIC has been previously shown to be a strong independent prognosticator of overall survival, progression free survival, and locoregional control in patients with locoregionally advanced non-small cell lung cancer (NSCLC). In this study, we examine the prognostic impact of EDIC in patients with early-stage NSCLC treated with lung stereotactic body radiation therapy (SBRT).

Materials/Methods: This single-institution, multi-center retrospective study included patients with cT1-T2 N0 M0 NSCLC treated definitively with SBRT between 2009-2018. Patients with a history of prior thoracic radiation therapy were excluded. Heart and lung contours were standardized to the RTOG thoracic OAR atlas. EDIC was calculated using mean heart dose, mean lung dose, and integrated total dose volume as previously described. Patients were stratified into low EDIC and high EDIC groups using median EDIC as the cut point. Overall survival (OS), progression free survival (PFS), distant metastasis-free survival (DMFS), and locoregional failure free survival (LRFFS) were measured using the date of first radiation treatment as the index start time. Associations between EDIC and survival measures were evaluated using the Kaplan-Meier method. Gross tumor volume (GTV) was used to correct for the effect of tumor size on survival outcomes.

Results: 282 eligible patients were identified (152 male, 130 female) with a median age of 73 (range 46-95). Median length of follow up was 24 months. Patients were most commonly prescribed a dose of 50Gy in 5 fractions (n=127, 45%), 48Gy in 4 fractions (n=81, 29%), 54Gy in 3 fractions (n=53, 19%), or 60Gy in 3 or 8 fractions (n=17, 6%). 210 patients had cT1 disease and 72 patients had cT2 disease. Most common histologic subtypes were adenocarcinoma (n=138, 49%) and squamous cell carcinoma (n=91, 32%). Median EDIC for all patients was 0.737 (standard deviation 0.43, interquartile range 0.53). Relative to the low EDIC group, high EDIC patients had significantly inferior five-year PFS (70.2% vs 50.4%, p=0.0025), DMFS (83.6% vs 71.0%, p=0.048), and LRFFS (95.6% vs 78.1%, p=0.0006). Five-year OS was not significantly different between groups based on median EDIC cut point (41.0% vs 31.0%, p=0.16). A trend towards improved five-year OS was seen when using an optimized EDIC cutpoint of 0.71 (42.3% vs. 30.0%, p=0.085). Significant differences in PFS and LRFFS were maintained after correction for differences in tumor sizes between the groups.

Conclusion: This study demonstrates the impact of EDIC on clinical outcomes in patients with early-stage NSCLC treated with SBRT. Further investigation on methods to reduce dose to the immune compartment during SBRT optimization is warranted. This may also have implications for SBRT planning in the context of immunotherapy, given ongoing trials evaluating the combination of these modalities.

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2008

Quantification of Radiotherapy-Induced Cardiac and Aortic Toxicity Using Magnetic Resonance Imaging in Lung cancer

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Purpose/Objective(s): To investigate the potential of novel Magnetic Resonance Imaging (MRI) techniques in early detection of focal radiotherapy (RT)-induced cardiac and aortic toxicity in patients with lung cancer.

Materials/Methods: Nine patients with lung cancer who were scheduled to receive RT (mean dose 57.3 Gy, 2 Gy per fraction) were recruited for this longitudinal IRB-approved study. Each patient underwent MRI scans at three time points: baseline before RT, three months, and six months following RT completion. Each scan included cine, T1/T2, late gadolinium enhancement (LGE), and 4D-flow MRI. Mechanical and biological characteristics of the heart and aorta were assessed globally (i.e., over the entire left ventricle (LV) or the entire aorta) and regionally (i.e., according to the American Heart Association (AHA) model).

Results: Dose-dependent changes were observed in regional metrics. RT dose was correlated with increased LGE and T1/T2 signals at six months (T1 signal also correlated at three months) ($P<0.0458$), particularly in regions exposed to >50 Gy of radiation ($P<0.0331$). No dose-dependent responses were found in longitudinal, circumferential, or radial strain changes at three or six months ($P>0.1$). All regional metrics exhibited changes at three months post-RT but only LGE and longitudinal strain changes persisted for at least six months ($P<0.0469$), while others returned to normal values. Significant mechanical changes were observed primarily in the septal region of the left ventricle (LV) ($P<0.0391$), while biological changes (LGE/T1/T2) were noted in high-dose and/or septal areas ($P<0.0391$). Correlations were observed among regional cardiac metrics (including multiple correlations between strain and T1/T2) and between regional radial/circumferential strain at the LV septum and ascending aortic dose ($P<0.0362$). Global metrics (e.g., LV ejection fraction, wall shear stress, global strain, global T1/T2) showed no significant changes except for increased LGE at six months and reduced ascending aortic circumferential strain at three months post-radiotherapy ($P<0.0356$).

Conclusion: RT is a localized treatment, resulting in mechanical and biological changes in regional MRI-based metrics primarily in areas where high doses were delivered. Significant LGE changes consistent with fibrosis persisted at six months, while other regional parameters resolved (or lost statistical significance) with longer observation. Biological changes exhibited a stronger correlation with dose, especially at areas receiving >50 Gy of radiation, emphasizing the significance of employing LGE in conjunction with T1/T2 signal for cardiac evaluation following RT. The novel observation of a correlation between aortic dose and changes in radial/circumferential strain at the septum of the LV suggests the importance of assessing LV-aortic coupling in evaluating functional cardiovascular toxicity after RT.

Author Disclosure: **A. Omidi**: None. **E. Weiss**: royalties; UpToDate. **M. Rosu**: None. **G. Thomas**: None. **J. Wilson**: Stock; Enzolytics.

2009

Mucosal Dose Constraints for Endoluminal High Dose Rate Brachytherapy for Esophageal Cancer

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Purpose/Objective(s): Endoluminal brachytherapy for esophageal cancers is an option for treatment of persistent or recurrent esophageal cancer. RTOG 9207 utilized esophageal brachytherapy as a boost technique with 15 Gy in 3 fractions after chemotherapy and radiation. Preliminary analysis showed 17% fistula formation and since then the technique has been underutilized. It is hypothesized that the toxicity is attributable to mucosal dose. We evaluated all patients treated at our institution to evaluate mucosal dose and toxicity to predict dose constraints that can be utilized for future planning.

Materials/Methods: All patients treated with endoluminal esophageal brachytherapy 1/2017-12/2022 were included. All patients underwent placement of brachytherapy catheters under endoscopic guidance to allow

evaluation of the tumor response and mucosal toxicity prior to each fraction. All planning was done with CT based planning. Target volume included primary tumor with tissue 2 cm proximal and distal to gross tumor volume. Mucosal contour was generated to include 1-2 mm on the luminal surface. A treatment plan was generated to provide 5 Gy per fraction with the intent V90>90%, D80>85%, generally limiting the mucosal surface dose to 8-10 Gy on the initial patients. Toxicity data was collected for fistula formation and correlated with dosimetric parameters.

Results: Twenty patients were included in this study. They received a total of 76 fractions. 3/20 (15%) patients received 5 fractions, 4/20 (25%) received 4 fractions, 9/20 (45%) received 3 fractions and 4/20 (25%) received 2 fractions of 5 Gy each. Median V90 was 86.43% (range 92-60%). Median D80 was 4.9 Gy (range 3.01-5.24). Two patients developed fistulas. Median mucosal dose to 0.5 cc was 19.64 Gy, 1 cc 16.19 Gy, 2 cc 12.33 Gy in patients with fistula formation, In patients with no fistula - 0.5 cc was 17.04 Gy (Range 20.96-11.65), 1 cc was 14.25 Gy (range 9.68-17.7), 2 cc was 11.69 Gy(7.47-13.59).

Conclusion: Risk of fistula formation is high with Esophageal brachytherapy when mucosa dose to 0.5 cc>19 Gy, 1cc>16 Gy and 2 cc>12 Gy. We recommend contouring the mucosa 1-2 mm of the luminal surface and monitoring the dose. After data analysis, we recommend using 0.5 cc<12-14 Gy, 1 cc < 12-14 Gy and 2 cc< 10- 11 Gy as mucosal dose constraints during radiation planning for esophageal brachytherapy to limit toxicity.

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2010

Withdrawn

2011

Impact of Comorbidity Index on Clinical Outcome after Stereotactic Body Radiation Therapy in High-Risk Early-Stage Non-Small Cell Lung Cancer

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Purpose/Objective(s): In patients who are medically operable, surgical resection has been the standard of care for early-stage non-small cell lung cancer (NSCLC). Recent evidence marks stereotactic body radiotherapy (SBRT) as a suitable alternative. Nonetheless, SBRT is frequently planned for patients who are medically inoperable and have multiple comorbidities. The current study aims to assess the effect of comorbidity on survival following SBRT for high-risk early-stage NSCLC patients.

Materials/Methods: We retrospectively reviewed 63 patients with early-stage NSCLC, ≥4 cm (T2-T3, N0), treated with SBRT, between September 2013 and May 2022 at a single institution. SBRT is defined as five fractions or less with minimum dose per fraction 9Gy. We used ECOG scale to quantify performance status, and the Charlson comorbidity index (CCI) was used to quantify the comorbidities burden and its effect on overall survival. Primary outcomes were local recurrence, regional cancer recurrence, distant recurrence, and overall survival. Analyses included Cox regression, Kaplan-Meier survival, and log-rank tests.

Results: A total of 63 patients (37 women and 26 men) with NSCLC stage T2-T3 were identified after excluding patients with a history of prior malignancy, previous radiation treatment, or lesions smaller than 4 cm. 53 patients had stage T2, and 10 had stage T3 NSCLC. Median size was 4.10 cm (4.00, 6.60), and median volume was 57.8 cc (23.9, 251). All patients received SBRT, six had adjuvant chemotherapy. Thirty-seven patients 60% had mediastinal evaluation. The median follow-up was 43.8 months, and the median age at diagnosis was 79 years (range 60−99). At three-year, OS, LC, RR and DM was 47.2% [95% CI 33.9-65.6], 91% [95% CI 82.6-1], 68.9% [95% CI 55.5-85.5] and 77.8% [95% CI 63.3-95.6] respectively. On both univariate and multivariate analysis, CCI was significantly correlated with worse OS, HR 1.23 (1.04-1.44, p = 0.014) and 1.24 (1.05-1.46, p = 0.011).

Conclusion: In patients with high-risk early-stage non-small cell lung cancer, comorbidity has a significant impact on survival after SBRT. Prospective studies are needed to validate CCI as prognostic tool It is recommended that a validated comorbidity index be used in prognostic analyses.

Author Disclosure: **S.A. AlKhatib**: None. **A.M. Feldman**: None. **K. Adil**: None. **B. Movsas**: None.

2012

A Phase II Trial of JDQ443 in *KRAS G12C*-Mutated NSCLC with PD-L1 Expression <1% or PD-L1 Expression ≥1% and an *STK11* Co-Mutation

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Purpose/Objective(s): Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is the most frequently mutated oncogene in non-small cell lung cancer (NSCLC). *KRAS G12C*, the most frequent *KRAS* variant, is found in ∼13% of patients (pts) with NSCLC. KRAS is a GTPase that regulates cell signaling pathways necessary for proliferation, differentiation, and survival. *KRAS* mutation reduces the intrinsic GTPase activity of the enzyme, allowing for the accumulation of active, GTP-bound KRAS and hyperactivation of downstream signaling, driving tumorigenesis. JDQ443 is a potent, selective $KRAS^{G12C}$ inhibitor that irreversibly traps $KRAS^{G12C}$ in its inactive, GDP bound state and blocks downstream signaling. In preliminary data from the Phase Ib part of the KontRASt-01 study (NCT04699188), JDQ443 showed promising antitumor activity and an acceptable safety profile in previously treated pts with *KRAS G12C*-mutated advanced NSCLC. Pts with *KRAS G12C*-mutated NSCLC currently receive the same first-line (1L) treatment as those without driver mutations, consisting of immunotherapy alone or combined with chemotherapy; however, ∼30% of pts with NSCLC present with programmed death-ligand 1 (PD-L1) expression <1%, and ∼10-20% of pts harbor an *STK11* mutation, both indicators of poor response to immunotherapy. Therefore, alternative 1L treatment options are needed for these pts. Of note, PD-L1 expression and *STK11* mutation do not affect responsiveness to $KRAS^{G12C}$ inhibitors, raising interest in the evaluation of these targeted therapies as 1L alternatives to immunotherapy for pts with *KRAS G12C*-mutated NSCLC.

Materials/Methods: KontRASt-06 (NCT05445843) is an open-label, Phase II, single-arm, multicenter study evaluating JDQ443 monotherapy (200 mg JDQ443 twice daily in 21-day cycles) as a 1L treatment for two cohorts of adult pts with locally advanced or metastatic, *KRAS G12C*-mutated NSCLC. Cohort A (n = 90) includes pts whose tumors have PD-L1 expression <1%, regardless of *STK11* mutation status, while Cohort B (n = 30) includes pts whose tumors have PD-L1 expression ≥1% and an *STK11* co-mutation. Local testing for PD-L1 status and *KRAS* and *STK11* mutations is accepted; *KRAS* and *STK11* mutations may be assessed in blood samples. A tissue sample is required for retrospective biomarker

status confirmation and exploratory study. The study is currently enrolling pts into both cohorts. The primary endpoint is the overall response rate (ORR) per RECIST version 1.1, assessed by a blinded independent review committee, in Cohort A. Key secondary endpoints are ORR in Cohort B and duration of response in both cohorts. Other secondary endpoints include progression-free survival, overall survival, safety, pharmacokinetics, and pt-reported outcomes. A comprehensive biomarker strategy aims to investigate predictors of treatment response and resistance in the study population.

Results: TBD

Conclusion: TBD

Author Disclosure: **C. Lindsay**: Grant/research funding; Revolution Medicines. Compensation/Payment; Amgen. Trial lead; Novartis. **R. Veluswamy**: Grant/research funding; AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Onconova Therapeutics. Honoraria; AstraZeneca, BeiGene, Boehringer Ingelheim, G1 Therapeutics, Merus, Novocure, Regeneron. Travel expenses; Boehringer Ingelheim, Regeneron. TBC; BerGenBio, Novartis. **G. Castro Junior**: Honoraria; Amgen, AstraZeneca, Bristol Myers Squibb, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda. Travel expenses; Amgen, AstraZeneca, Merck Sharp & Dohme, Roche. TBC; Lilly, Bayer, Daiichi Sankyo. **D.Y. Tan**: Grant/research funding; Novartis, AstraZeneca, GlaxoSmithKline. Honoraria; Bristol Myers Squibb, Novartis, Pfizer, Roche, Takeda. Travel expenses; Pfizer, Roche, Boerhringer Ingelheim. TBC; C4 Therapeutics, Loxo, Merck. **R. Caparica**: Stock; Novartis. **S. Glaser**: Stock; Novartis AG, Alcon AG. **S. Malhotra**: Stock; Novartis. Stock options; Novartis. **E. Felip**: Travel expenses; AstraZeneca, Janssen. Compensation/Payment; Amgen, AstraZeneca, Bayer, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, F. Hoffman LaRoche, GlaxoSmithKline, Janssen, Eli Lilly, Merck Serono, Merck Sharpe & Dohme, Novartis, Peptomyc, Pfizer, Sanofi, Takeda, Turning Point Therapeutics, Abbvie. TBC; Medical Trends, Medscape, Pe. **E. Chan**: Stock; Novartis, Gilead.

2013

KontRASt-02: A Phase III Trial Investigating the Efficacy and Safety of the KRAS^{G12C} Inhibitor JDQ443 vs. Docetaxel in Patients with Previously Treated, Locally Advanced or Metastatic, *KRAS G12C*-Mutated NSCLC

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Purpose/Objective(s): Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is the most frequent mutated oncogene in non-small cell lung cancer (NSCLC). *KRAS G12C* is the most common *KRAS* variant, present in ~13% of patients (pts) with non-squamous NSCLC. *KRAS G12C* mutations cause the accumulation of active, GTP-bound KRAS, which leads to activation of downstream pathways involved in cell proliferation and invasiveness. JDQ443 is a potent, structurally novel, selective KRAS^{G12C} inhibitor that irreversibly traps KRAS^{G12C} in its inactive, GDP-bound form. Data from the JDQ443 monotherapy arm of the first-in-human KontRASt-01 study demonstrated encouraging antitumor activity and an acceptable safety profile of JDQ443 in pts with previously treated, *KRAS G12C*-mutated, advanced NSCLC. For pts with advanced NSCLC who progress following first-line immunotherapy or doublet platinum-based chemotherapy, single-agent docetaxel remains a standard option, although it presents modest activity and is generally poorly tolerated. In this context, alternative treatment options are needed to improve pt outcomes.

Materials/Methods: KontRASt-02 (NCT05132075) is a global, Phase III, open-label, randomized, multicenter study evaluating JDQ443 as a monotherapy in comparison to docetaxel in pts with *KRAS G12C*-mutated, advanced NSCLC previously treated with PD-(L)1 inhibitors and platinum-based chemotherapy (either in combination or as sequential treatments). Approximately 360 pts stratified by ECOG performance status (0 vs. 1 and 2) and prior therapy (platinum-based chemotherapy and immunotherapy combined vs sequential) will be randomized 1:1 to receive 200 mg oral JDQ443 twice daily continuously or 75 mg/m^2 intravenous docetaxel once every 21 days. The primary endpoint of this study is progression-free survival (PFS) per Blinded Independent Review Committee (BIRC) according to RECIST version 1.1. The key secondary endpoint is overall survival (OS); other secondary endpoints include objective response rate, disease control rate, time to response, duration of response, PFS on subsequent therapy, safety of JDQ443 monotherapy, pt-reported outcomes, pharmacokinetics, time to deterioration of ECOG performance status, and safety in pts who crossover from docetaxel to JDQ443. Exploratory objectives include biomarker analyses aimed at investigating predictors of responsiveness to JDQ443. Pts randomized to docetaxel will be allowed to crossover to JDQ443 following confirmed disease progression per BIRC. To allow more pts to be treated with JDQ443, crossover will also be offered to all pts on docetaxel if the primary endpoint (PFS) is met. Treatment beyond progression will be allowed for pts receiving JDQ443 according to investigator judgment. The KontRASt-02 study is currently enrolling pts.

Results: TBD

Conclusion: TBD

Author Disclosure: **F. Cappuzzo**: Honoraria; Amgen, AstraZeneca/MedImmune, Bayer, Bristol Myers Squibb, Lilly, MSD Oncology, Novocure, Pfizer, PharmaMar, Roche/Genentech, Sanofi, Takeda. Travel expenses; OSE Immunotherapeutics. **G. Castro Junior**: Honoraria; Amgen, AstraZeneca, Bristol Myers Squibb, Janssen, Merck Serono, Merck Sharp & Dohme, Novartis, Roche, Takeda, Libbs. Travel expenses; Amgen, AstraZeneca, Merck Sharp & Dohme, Roche. TBC; Lilly, Bayer, Daiichi-Sankyo. **J. Kang**: Grant/research funding; AstraZeneca, Ono Pharmaceutical, Yuhan, Daiichi Sankyo/UCB Japan. Honoraria; AstraZeneca, Boehringer Ingelheim, Lilly O., Ono Pharmaceutical, Genexine. TBC; MSD Oncology, Pfizer, Roche. **Y. Wu**: Grant/research funding; Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, Roche. Honoraria; AstraZeneca, BeiGene Beijing, Boehringer Ingelheim, Bristol Myers Squibb, Hengrui Pharmaceutical, Lilly, MSD Oncology, Pfizer, Roche. TBC; Takeda. **O.T. Brustugun**: None. **P.K. Cheema**: Honoraria; Amgen, AstraZeneca, GlaxoSmithKline, Janssen Oncology, Merck. TBC; Bayer, Bristol Myers Squibb, Novartis, Pfizer, Roche. **T.K. Owonikoko**: Grant/research funding; NIH, Merck, Ymabs, Inc, Amgen, Inc, NIH, AstraZeneca, Calithera Biosciences, Amgen, Inc., Novartis, Ymabs, Inc., Boehringer-Ingelheim, Cyclacel, Emory University, NIH, Winship Cancer Institute, NCI CTEP. Compensation/Payment; Eli Lilly, Springer, Inc., Genentech, Janssen, AstraZeneca, Amgen, Inc., Takeda, Lilly, Exe. **A. Longin**: Stock; Novartis. **J. Duan**: Stock; Novartis, Novartis International. **R. Caparica**: Stock; Novartis. **H.H. Loong**: Grant/research funding; MSD Oncology. Travel expenses; Bayer, MSD Oncology, Pfizer. TBC; Boehringer Ingelheim, Celgene, Eisai, GlaxoSmithKline, Guardant Health, Illumina, Lilly, Novartis, Roche/Genentech, Takeda, Ignyta. **E. Chan**: Stock; Novartis, Gilead.

2014

Risk Factors for Cardiac-Related Outcomes in Stage III Non-Small Cell Lung Cancer Patients

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Purpose/Objective(s): Patients that undergo radiation therapy (RT) for locally advanced non-small cell lung cancer (NSCLC) have different pre-treatment risk factors and treatment-related risk factors that may ultimately affect their long-term cardiovascular health. We examined whether detrimental cardiac-related outcomes, disease progression, and death are associated with aforementioned risk factors.

Materials/Methods: We performed a retrospective review of patients ≥18 years old with Stage III NSCLC that received RT 01/01/2010-03/01/2022. Demographics, pre-treatment and treatment-related risk factors, and cardiac-related outcomes (major adverse cardiac event (MACE - defined as cardiac death, unstable angina, MI, HF hospitalization or coronary revascularization), new diagnosis of hypertension or arrhythmia) were collected. Logistic regression models were used to create univariable and multivariable analyses (MVA) between risk factors and 1) cardiac-related outcomes, 2) progression-free survival (PFS), and 3) overall survival (OS).

Results: 221 patients who had Stage III NSCLC were identified, with a median age of 74 years, 52% male, 48% female, 89.1% current/former smokers with 30 median pack-years. 115 (52.0%) had stage IIIA disease, 98 (44.3%) had stage IIIB disease, and 8 (3.6%) had stage IIIC disease. All patients received RT, 50 (22.6%) received surgery, 216 (97.7%) received chemotherapy. No studied risk factors were significant for MACE or new diagnosis of hypertension. Receiving surgery as part of treatment was found to be significant for a new diagnosis of arrhythmia on MVA (OR 4.00, 95%CI 1.38-11.88, p=0.011). No studied risk factors were significant for PFS. The mean radiation dose on the heart was found to be significant for OS (mean heart dose for alive patients 933 cGy vs 1198 cGy for patients who experienced death, OR 1.0, 95%CI 1.0-1.0, p=0.024). Smoking pack-years trended to significance for OS (OR 1.02, 95%CI 1.0-1.04, p=0.062).

Conclusion: In this single institution retrospective study, we find that Stage III NSCLC treated with RT who also received surgery as part of treatment were associated with significantly higher risk of the new diagnosis of arrhythmia following treatment, and mean radiation dose on the heart is significantly associated with overall survival. In the emerging era of neoadjuvant chemo(immune)therapy, further work to understand the mechanisms behind how different NSCLC treatment modalities affect the heart is needed.

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2015

SiCARIO: A Phase I/II Study of Split-Course Adaptive Radioimmunotherapy for the Treatment of Oligometastatic Non-Small Cell Lung Cancer (NSCLC) Using Adaptive Radiotherapy

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Purpose/Objective(s): The current standard of care (SOC) for oligometastatic NSCLC involves treatment with cytotoxic chemotherapy alone, chemotherapy combined with immune checkpoint blockade (ICB), or ICB alone based on tumor PD-L1 expression level. While improvements associated with addition of ICB have been observed in this cohort, local and/or distant failure remains a near certainty. New strategies are needed to enhance the efficacy of these agents to provide more durable responses and in select patients, potentially curative approaches. Increasing pre-clinical data supports synergy between radiotherapy (RT) and immune-based therapies, however, radiation treatment paradigms have not been updated to better harness the potential biologic interactions between RT and the immune system. This study seeks to determine if a high dose per fraction, split course, anatomically and biologically adapted RT timed concurrently with immunotherapy containing systemic regimens can improve outcomes. Emerging clinical evidence supports concurrent treatment with high-dose per fraction RT as an optimal approach to induce antitumor immunity in combination with ICB. Use of a split course approach may improve the therapeutic window of RT in this setting, and act to sequentially re-prime the immune system to evolving antigenic signatures of the tumor and micro-environment.

Materials/Methods: This is a Phase I/II, single institution, open label clinical trial in patients with de novo stage IV NSCLC with up to ten sites of extracranial metastases. Patients with brain metastases which can be addressed with surgery and/or stereotactic radiosurgery are eligible. Patients will receive RT to all sites of extracranial disease and thoracic primary in 8 Gy fractions every three weeks to a total dose of 40 Gy in 5 fractions concurrent with standard of care (SOC) (chemo)immunotherapy. RT plans will be adapted between fractions as needed using a novel, CT-linac-based adaptive RT platform from a technology company. Planned enrollment is 25 patients to observe an improvement in best overall response rate to 75% compared to historical controls. The primary objectives are to assess the safety, tolerability, and overall response rate (ORR) of the SiCARIO regimen combined with SOC systemic therapy. Secondary objectives include PFS, OS and new metastasis free survival. Exploratory objectives include serum biomarkers of response (ctDNA and immune profiling), and imaging biomarkers including 18F-FDG and 18F-FSPG PET response. This study will also serve as a practical evaluation of a CT-linac-based adaptive platform for development of efficient clinical workflows integrating both anatomic and functional imaging data to deliver complex, multi-site RT plans. Enrollment is currently ongoing with potential for future expansion pending initial outcomes.

Results: TBD/NA (Trial-in-Progress)

Conclusion: TBD/NA (Trial-in-Progress)

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