

Late Breaking Abstracts

LBA1

Two Years of Anti-Androgen Treatment Increases Other-Cause Mortality in Men Receiving Early Salvage Radiotherapy: A Secondary Analysis of the NRG Oncology/RTOG 9601 Randomized Phase III Trial

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Purpose/Objective(s): Salvage radiation therapy (SRT) is recommended for men with biochemically recurrent prostate cancer post-radical prostatectomy. RTOG 9601 was a randomized phase 3 clinical trial that demonstrated an overall survival (OS) benefit from the addition of long-term anti-androgen therapy to SRT. However, hormone therapy has well documented side effects and has been shown to increase cardiac event rates, and there remains no evidence of an OS benefit from hormone therapy for men treated with early SRT. Herein, we aim to determine if pre-SRT PSA can serve as both a prognostic and predictive biomarker of benefit or harm from hormone therapy.

Materials/Methods: A secondary analysis of the NRG Oncology/RTOG 9601 double-blind, placebo-controlled randomized trial was conducted (NCT00002874). Patients were treated between 1998-2003 at over 100 centers across North America. Men with adverse pathology (positive surgical margin or pathologic T3 disease) and a PSA of 0.2-4.0 ng/mL were enrolled. Patients were stratified by entry PSA (0.2-1.5 vs >1.5-4.0 ng/mL). Men were randomized to either SRT plus a nonsteroidal anti-androgen (bicalutamide 150mg/day) or placebo for two years. The primary endpoint was OS. Secondary endpoints relevant to the present analysis include distant metastasis (DM) and other-cause mortality (OCM). Subgroup analyses were performed using the pre-specified PSA stratification variable (1.5 ng/mL) including tests for interaction. Competing risk analyses were performed for DM and OCM.

Results: Of 760 patients, 85% (n=642/760) were in the pre-SRT PSA of ≤ 1.5 ng/mL stratum. There was no significant OS benefit with bicalutamide in men with PSA ≤ 1.5 ng/mL (HR 0.87 [95%CI 0.66-1.16]), whereas in men with PSA > 1.5 ng/mL (n=118) OS was significantly improved (HR 0.45 [0.25-0.81]). Interaction test of PSA and hormone therapy benefit for OS was significant (p=0.02). Within the PSA ≤ 1.5 ng/mL subgroup,

men with pre-SRT PSA ≤ 0.6 ng/mL (n=389) had increased OCM (sHR:1.94, [1.17-3.20]) from bicalutamide which was greatest in men with PSA 0.2-0.3 (n=148; sHR:4.14 [1.57-10.89]). There was also increased grade 3-5 cardiac events in those treated on the bicalutamide arm (p=0.04). The present subgroup analysis met 8 of 10 criteria for the reliability and credibility of this subgroup analysis.

Conclusion: Pre-SRT PSA is both a prognostic and true predictive biomarker for benefit of hormone therapy with SRT. Long-term anti-androgen therapy did not improve OS in patients receiving early SRT, and may increase OCM. Ongoing trials are enrolling to identify which patients receiving early SRT will benefit from hormone therapy (NRG GU006, NCT03371719).

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LBA2

Results of a Phase II Randomized Trial of Proton Beam Therapy vs Intensity Modulated Radiation Therapy in Esophageal Cancer

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Purpose/Objective(s): Proton Beam Therapy (PBT) is dosimetrically superior to Intensity Modulated Radiation Therapy (IMRT) in sparing critical organs in esophageal cancer (EC) patients (pts) treated with chemoradiation therapy (CRT). The extent to which better dosimetry translates into clinical benefit is not well established. We conducted a randomized trial to compare PBT to IMRT in terms of total toxicity burden (TTB) and progression free survival (PFS) time.

Materials/Methods: For this single institutional randomized phase IIB clinical trial (NCT01512589), EC pts were randomized to PBT or IMRT using the Pocock-Simon method to balance adaptively on induction chemotherapy, potential resectability, stage, histology and age ≥ 65 . Both step-and-shoot or volumetric arc therapy were allowed for IMRT, and passive scattering or scanning beam for PBT. The trial used a Bayesian group sequential trial design, based on TTB and PFS. TTB is defined as a severity-weighted sum over 11 specific severe adverse events (AE) that can occur from start of CRT up to 12 months, including postoperative complications (POC) for pts who undergo surgery. Each AE grade was assigned a weight quantifying its severity on a scale of 0-100. Planned interim analysis occurred at 33%, 50% and 67% of the information for PFS and toxicity follow-up time. Planned maximum accrual was 180. Estimated mean TTB is reported with 95% highest posterior density intervals.

Results: The trial began in April 2012 and closed in March 2019 prior to activation of the phase III NRG-GI006 trial (NCT03801876). The DSMB approved the closure and analysis of the phase IIB trial. At that point, 145 pts were randomized, 72 to IMRT and 73 to PBT, with 105 pts evaluable (61 IMRT and 44 PBT). For the 29 unevaluable pts on the PBT arm, 22 (76%) were treated off protocol due to insurance denial. For the 11 unevaluable pts on the IMRT arm, 8 (72%) withdrew consent due to wanting PBT only. The two evaluable cohorts were balanced, with the exception of a non-significantly higher median age (68 vs 66) and greater unresectability (16% vs 10%) for the PBT group. Just under 50% had surgery after CRT in both arms, and 90% PBT pts were treated with passive scattering. The posterior probability that mean TTB is higher for IMRT vs. PBT is 0.9994, which exceeds the design's interim stopping boundary at 67% follow-up of 0.9942. IMRT had posterior mean TTB 2.3 times higher [40.2 (26.5-55.2) vs. 17.2 (10.5-24.4)], and mean POC severity score that was 7 times higher [19.2 (7.6-32.7) vs. 2.4 (0.34-5.02)] than PBT. With median follow-up time of 52.9 weeks (interquartile range 25.6-167.6 weeks), PFS was comparable among CRT cohorts.

Conclusion: Dosimetric superiority of PBT translates to clinically significant reductions in severe adverse events following CRT. Further validation of this finding is being tested with NRG-GI006 which additionally compares overall survival between IMRT and PBT.

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LBA3

Primary Outcomes of a Phase II Randomized Trial of Observation Versus Stereotactic Ablative RadiatIon for Oligometastatic Prostate Cancer (ORIOLE)



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Purpose/Objective(s): Mounting evidence supports complete metastatic ablation for oligometastatic cancer but the relevance of this approach to oligometastatic prostate cancer (OMPC) remain an area of active study. Importantly, biomarkers to determine patients who benefit most from complete ablation are unknown. We hypothesize that stereotactic ablative radiation (SABR) will improve oncologic outcomes in men with OMPC.

Materials/Methods: In this phase II randomized trial, men with recurrent hormone-sensitive OMPC (1-3 radiation fields) were stratified by primary management (radiotherapy vs surgery), PSA doubling time, and prior androgen deprivation therapy and randomized 2:1 to SABR or observation (OBS). The primary endpoint was progression at 6 months by PSA ($\geq 25\%$ increase and \geq nadir + 2 ng/mL), conventional imaging (RECIST 1.1 criteria or new lesion on bone scan), or symptomatic decline. Tissue, liquid and imaging correlative studies were obtained and analyzed as biomarkers.

Results: From 5/2016-3/2018, 54 patients were randomized. Progression at 6 months was observed in 19% of patients in the SABR arm and 61% of patients in the OBS arm (ITT, $p=0.005$). Median progression-free survival (PFS) was not reached for men treated with SABR and 5.8 months for men who underwent OBS (HR 0.30, $p=0.0023$). Of 35 patients in the SABR arm who received PSMA-based PET/CT imaging at baseline and 6 months, those with total consolidation of radiotracer-avid disease were less likely to develop new lesions at 6 months (16% vs 63%, $p=0.006$) and had significantly longer median PFS (unreached vs 11.8 months, $p=0.003$) and distant metastasis-free survival (DMFS) (29 vs 6.0 months, $p=0.0008$). No grade III or higher toxicity was observed. Deep sequencing of T-cell receptor DNA identified significantly more clonotypic expansions ($p=0.03$) between baseline and day 90 with SABR than with observation, greater peripheral baseline clonality was correlated with progression at 180 days in the SABR arm only, and clusters of similar expanded T-cell receptors were identified in 3 patients after SABR. Analysis of circulating tumor DNA (ctDNA) is in progress.

Conclusion: SABR for OMPC affords significant benefits in freedom from progression at 6 months and PFS. In fact, the PFS for patients treated with SABR still has not been reached and is well over one year. Total consolidation of disease identified by PSMA-PET with SABR provides a substantial advantage in DMFS (4.8 times greater) when compared to subtotal consolidation. SABR also induces a systemic adaptive immune response and baseline clonality was associated with predictive response to SABR. These results underline the importance of prospective randomized investigation of the oligometastatic state with concurrent collection of imaging and biological correlates.

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LBA4

Longer Term Results from a Phase I/II Study of EP-guided Noninvasive Cardiac Radioablation for Treatment of Ventricular Tachycardia (ENCORE-VT)



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Purpose/Objective(s): A prospective phase I/II trial of noninvasive cardiac radioablation in high risk patients with treatment-refractory episodes of ventricular arrhythmias demonstrated acceptable primary endpoint 90-day and 6-month safety profile with 11% serious adverse event (SAE) rate, 94% reduction in ventricular tachycardia (VT) episodes, and 89% 6-month overall survival (OS). Longer-term safety and efficacy of this technique is reported.

Materials/Methods: Arrhythmogenic scar regions were targeted by combining noninvasive anatomic and electric cardiac imaging with a standard stereotactic body radiation therapy workflow followed by delivery of a single fraction of 25 Gy to the target. SAEs were defined as CTCAE v4.0 grade 3-5 events that were possibly, probably, or definitely related to treatment. Efficacy was tracked using indwelling implantable cardioverter defibrillators or 24-hour PVC burden (as measured by Holter monitor) comparing the 6 months before treatment to 6-month intervals after treatment.

Results: 19 patients underwent treatment. Median follow-up of living patients is 24.1 months (range, 12.8-28.8). One and 2-year OS was 72% and 58%. Eight deaths have been recorded to date: 1 unrelated (pancreatitis), 3 unlikely (accident, amiodarone toxicity, VT recurrence), and 4 possible (2 heart failure, 2 VT recurrence). Additional probably or definitely related late (>6 month) SAEs included a grade 3 pericardial effusion at 2.2 years and a grade 4 gastropericardial fistula at 2.4 years requiring surgical repair.

The group experienced a median of 119 vs. 3 vs. 2 VT episodes in the 6 months before treatment vs. 0-6 months vs. 6-12 months after treatment. 17/18 evaluable patients had a reduction in VT (mean 94% reduction in total VT burden compared to baseline) in the first 6 months. 16/18 patients had a persistent reduction in VT during the next 6 months (mean 84% reduction in total VT burden compared to baseline).

Conclusion: Noninvasive electrophysiology-guided cardiac radioablation in high risk refractory ventricular arrhythmia is associated with markedly reduced burden that largely persisted through the first year. Two SAEs probably or definitely related to treatment were observed > 2 years after treatment. Vigilant long-term follow-up will define the full safety profile of this novel therapy.

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LBA5

Detectable HPV ctDNA in Post-Operative Oropharyngeal Squamous Cell Carcinoma Patients is Associated With Progression



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Purpose/Objective(s): Circulating tumor DNA (ctDNA) as a cancer biomarker may assist in detection, risk stratification, treatment assessment, and surveillance. There are limited data on the rates of detectability and ctDNA kinetics in the post-operative (post-op) setting for patients with Human Papilloma Virus (HPV)-associated oropharyngeal squamous cell carcinoma (HPV-OPSCC). We aimed to investigate ctDNA detectability rates by post-op risk category and association with prognosis in this population.

Materials/Methods: Prospectively collected serum samples from 29 treatment-naïve HPV-OPSCC patients were first tested for assay validation. 7 HPV negative OPSCC patients were included as a control. A cohort of 46 post-op HPV-OPSCC patients were identified with serum collection post-op but before adjuvant therapy. Serum was analyzed in a blinded fashion for E6/E7 HPV ctDNA for these 82 samples using a previously described ddPCR multiplex assay (HPV 16, 18, 31, 33). HPV ctDNA detectability was compared statistically across groups. Estimates of progression-free (PFS) and overall survival (OS) were made using the Kaplan-Meier (KM) method. Associations of patient and tumor characteristics with recurrence were assessed using a univariate Cox proportional hazards regression model.

Results: Prior to treatment, ctDNA was detectable in 27 of 29 patients for a sensitivity of 93%. None of the 7 HPV-negative patients had detectable ctDNA for a specificity of 100%. Post-op serum was collected at a median of 25 days (range 11-46) after surgery. Post-op ctDNA was detectable in 43% (20/46) of patients: 47% (18/38) of patients with high-risk features (ENE or R1) compared to 25% (2/8) of patients with intermediate-risk features (p=0.25). All detectable were HPV type 16. Median follow-up for the post-op HPV-OPSCC cohort (n=45) was 20 months (1 patient not completing adjuvant therapy by time of analysis was excluded). Eleven patients (24%) recurred: locoregional (n=5) or distant (n=6); 64% (7/11) of patients who recurred had detectable ctDNA compared to 35% (10/34) in patients who did not recur (p=0.1). Detectable ctDNA was significantly associated with 24-month PFS (45% vs. 84%, p=.04) and OS (80% vs. 100%, p=.02). Univariately, T4 tumors (HR: 14.3, p<0.01), >4 lymph nodes (HR: 5.5, p<0.01), and detectable ctDNA (HR 3.31, p=0.05) were positively associated with disease recurrence.

Conclusion: HPV ctDNA is a highly sensitive and specific means of determining HPV-status prior to treatment and remains detectable for many patients post-op. Detectable ctDNA was significantly associated with worsened PFS and OS. Risk stratification using a complement of ctDNA and historical risk factors may be instrumental in improved patient selection for treatment intensity decision making for patients with HPV-OPSCC and warrants further study.

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LBA6

Patterns of Disease Progression with Durvalumab in Stage III Non-small Cell Lung Cancer (PACIFIC)



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Purpose/Objective(s): In the ph 3 PACIFIC study of unresectable, Stage III NSCLC pts without progression after chemoradiotherapy (CRT), durvalumab (durva) demonstrated significant improvements versus placebo (pbo) in the primary endpoints progression-free survival and overall survival, with manageable safety and no detrimental effect on pt-reported outcomes. We performed exploratory analyses to characterize patterns of disease progression, including the sites of first progression.

Materials/Methods: Pts with WHO PS 0/1 (any tumor PD-L1 status) who received ≥ 2 cycles of platinum-based CRT were randomized (2:1), 1–42 days following CRT, to receive durva or pbo up to 12 months, stratified by age, sex, and smoking history. Disease progression was assessed by blinded independent central review (RECIST v1.1). Scans were re-evaluated for unequivocal new lesions by a new, independent reviewer. New lesions identified within the chest wall, including the diaphragm, were categorized as intra-thoracic (local), with all other lesions categorized as extra-thoracic (distant). The proportions of pts with progression (or death), region of first progression, location and number of organs with new lesions, and number of new lesions at progression were descriptively summarized. Time to progression by region was estimated by Kaplan-Meier method with between-treatment HRs calculated by stratified Log rank test.

Results: 713 pts were randomized (durva, n=476; pbo, n=237). As of March 22, 2018, 45.4% and 64.6% in the durva and pbo groups, respectively, had disease progression or death. Local only (intra-thoracic) progression occurred in 36.6% and 48.1%, respectively; distant only (extra-thoracic) progression in 6.9% and 13.1%; and simultaneous local and distant progression in 1.9% and 3.4%. New extra-thoracic lesions at first progression occurred in 8.8% and 16.5% in the durva and pbo groups, respectively. Most new distant lesions occurred in a single organ (8.4% and 15.6% of all patients). The most common site at progression was the brain, among 61.9% and 66.7% of pts with extra-thoracic lesions, of whom pts in the durva and pbo groups presented with 1 (46.2% and 34.6%), 2 (30.8% and 34.6%), 3–5 (23.1% and 19.2%), or > 5 brain lesions (0 and 11.5%). Median time to first progression in each region was improved with durva versus pbo (local only: 25.2 vs. 9.2 months [HR, 0.55; 95% CI, 0.43–0.70]; distant only: not reached [NR] vs. NR [HR, 0.41; 95% CI, 0.27–0.63]; and both: NR vs. NR [HR, 0.48; 95% CI, 0.28–0.82]).

Conclusion: Most pts experienced their first progression inside the thorax regardless of treatment arm; however, fewer pts receiving durva experienced local and/or distant progression. In addition, the time to first progression was improved with durva versus pbo regardless of location. Most new distant lesions were detected in a single organ, with >90% of pts having ≤ 5 lesions, which suggests that local ablative therapy may extend survival.

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LBA7

RhoA/ROCK Pathway Inhibitor Ameliorates Radiation-induced Erectile Dysfunction in Rats



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Purpose/Objective(s): Localized prostate cancer (PCa) has a high cure rate of 95.5%. PCa patients receive radiation therapy (RT) as a standard of care treatment. However, the major concern is the treatment-related side effects compromising the quality of life (QoL) in PCa patients. Radiation-induced Erectile Dysfunction (RiED) is a common and irreversible late side effect of RT, that develops in more than half of PCa patients. There is no FDA approved drug to treat RiED. Phosphodiesterase type 5 inhibitors (PDE5i) are the most common pharmacological agents being used to treat RiED. However, a significant number of patients (> 40%) fail to respond to treatment with PDE5i, suggesting an urgent need for in-depth investigations into the mechanisms of RiED and the development of effective therapeutic options to combat RiED. We have for the first time identified that the RhoA/ROCK pathway is involved in RiED. We found that prostatic RT increased RhoA/ROCK signaling in the cavernous nerve (CN) and penile tissues potentiates RiED in rats. We investigated by inhibiting the RhoA/ROCK pathway with a specific inhibitor called Fasudil to improve RiED in our established rat model.

Materials/Methods: Male Sprague-Dawley rats were exposed to a single dose of 25Gy prostate-confined RT. 10mg/kg Hydroxy Fasudil hydrochloride was injected intraperitoneally 2 days prior RT and continued daily until 4 weeks. Erectile function was evaluated by intracavernous pressure (ICP) and Mean Arterial pressure (MAP) measurements conducted at 14 weeks post-RT. Cavernous nerve injury was evaluated using transmission electron microscopy (TEM). Masson trichrome staining was performed to elucidate the level of fibrosis in penile tissues.

Results: We have found that the ICP/MAP ratio in RT treated rats were significantly reduced ($p < 0.0001$) versus non-RT rats (control). Fasudil treatment significant ($p < 0.001$) improved the ICP/MAP ratio, area under the curve, and maximum ICP values. Interestingly, Fasudil treated cohort exhibited increased CN myelination with decrease g-ratio ($p < 0.01$) and decreased axonal atrophy of the CN fibers as observed by TEM analysis. Further, Fasudil treatment showed decreased penile tissue fibrosis after 14 weeks compared to the RT treated rats. There were no Fasudil treatment related side effects observed in rats.

Conclusion: Our results provide the first preclinical evidence about the effects of RhoA/ROCK pathway inhibition by Fasudil treatment as a novel therapeutic option to treat RiED in rats. Fasudil could be used in PCa patients undergoing RT in the future to improve their QoL.

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LBA8

New Kid on the Block- Mini Beam Radiation Treatment- Final Report of a Randomized Phase III Study of Treating Canine Denovo Brain Tumors



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Purpose/Objective(s): The challenge in treating malignant brain neoplasms lies in eradicating tumor while minimizing treatment-related

damage to normal adjacent brain. These tumors are currently treated with conventional radiation therapy techniques, which control the tumor but are associated with considerable side effects. Synchrotron generated microbeam radiation therapy (SMBRT) has shown promising results in preserving brain architecture while killing tumor cells, however physical characteristics of SMBRT limit its use. We have successfully implemented a new clinical device, which produces fine beams of radiation called mini-beams (MBRT) of 1000 microns size using 6 MV photons. The objective of this study is to test if MBRT can emulate the SMBRT biological effects using spontaneous brain tumors in dogs.

Materials/Methods: Pet dogs with de-novo brain tumors were accrued for treatment across the country. Dogs were randomized between standard Stereotactic (9 Gy x 3 fractions) radiation treatment (SRS) Vs single fraction MBRT (26 Gy to mean dose). Dogs were followed for clinical assessment and MRI. Whenever dogs were euthanized, a veterinary pathologist assessed the radiation changes and tumor response.

Results: Between 2013 and 2017, we accrued 16 dogs (8 on SRS and 8 on MBRT arm). There were definite treatment-related changes seen in both arms of treatment, however vascular changes were more pronounced in SRS group and were also seen outside 50% isodoses. Similarly, treatment-related toxicity in the form of seizure was also noted in SRS treated dogs. The SRS treated dogs images and where available post mortem report showed residual tumor in all of them except one who had a good response. Two dogs are still on follow up.

Among dogs treated with MBRT, treatment changes were confined to within 50% isodose lines. In contrast, the mini beam treated dogs have almost complete response as noted on the follow up MRI. Four of 7 dogs have pathological complete response and one dog is still on follow up.

Conclusion: Preliminary results show MBRT resulted in impressive tumor control and fewer long term pathologically correlated toxicities. This might pave way for a new modality of radiation treatment which would require a phase I human studies.

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LBA9

Association of the Affordable Care Act (ACA) and Risk of Suicide in Cancer Patients



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Purpose/Objective(s): Cancer patients have a four times higher risk of suicide relative to other adults. As suicide risk factors include poor mental health and financial difficulty, efforts directed at these factors, including policy interventions, may reduce suicide among cancer patients. The Affordable Care Act (ACA) has been associated with decreased spending for low income individuals and improved mental health. However, little is known regarding the association of the ACA and suicide among cancer patients. The objective of this study was to quantify ACA-associated changes in the incidence of suicide by utilizing a quasi-experimental design.

Materials/Methods: Data for cancer patients ages 55-74 years diagnosed in 2011-2016 were obtained from the SEER database (update with 2016 was released to the public in April 2019). To reduce confounding from temporal trends in suicide, groups affected by the ACA, those ages 55-64 years, and not affected by the ACA, those ages 65-74 years, were compared. Younger patients also affected by the ACA were excluded to maintain greater similarity between the comparison groups. Cumulative incidence of suicide was calculated using competing risks survival analysis. Fine and Gray proportional hazards models for competing risks data were utilized to estimate the change in suicide risk from pre- (2011-13) to post-ACA (2014-16) between age groups. Models were adjusted for covariates (sex, race, marital status, metropolitan residence, county-level income and education, insurance status, stage at diagnosis, and cancer site). Subgroup analyses stratified by county income quartile and state Medicaid expansion status were also performed. All p-values were 2-sided, and p<0.05 was considered statistically significant.

Results: A total of 614 suicides among 890,320 cases were identified. Two-year suicide rates (per 100,000 individuals) pre- and post-ACA were 64.7 and 33.4 (HR = 0.66; 95% CI = 0.50, 0.86; p=0.003) for ages 55-64 years and 55.6 and 55.3 (HR = 0.94; 95% CI = 0.75, 1.16; p=0.55) for ages 65-74 years. Relative to changes in 65-74 year old patients, there was a reduction in the risk of suicide after the ACA for 55-64 year old patients (HR = 0.67; 95% CI = 0.47, 0.95; p=0.026), particularly for individuals in low income counties (HR = 0.45; 95% CI = 0.23, 0.88; p=0.020). There was no difference in ACA-associated changes in suicide risk by state Medicaid expansion status (p=0.20).

Conclusion: There was a decrease in suicide risk for ACA-eligible cancer patients but no change in suicide risk for ACA-ineligible cancer patients. Thus, the ACA may be associated with decreasing suicides among cancer patients, particularly for low income individuals, though additional impacts of Medicaid expansion are unclear.

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LBA10

NRG-HN002: A Randomized Phase II Trial for Patients With p16-Positive, Non-Smoking-Associated, Locoregionally Advanced Oropharyngeal Cancer



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Purpose/Objective(s): NRG-HN002 was designed to select the arm(s) achieving acceptable progression-free survival (PFS) without unacceptable swallowing-related quality of life [MD Anderson Dysphagia Inventory (MDADI)] in patients with p16+, non-smoking-associated, locoregionally advanced oropharyngeal cancer.

Materials/Methods: Eligible patients had stage T1-2N1-N2bM0 or T3N0-N2bM0 (AJCC 7th edition) oropharyngeal squamous cell carcinoma and ≤10 pack-year smoking history. p16 immunohistochemistry was centrally confirmed. Patients were stratified by unilateral vs bilateral radiation and randomized (1:1) to either 60 Gy of intensity modulated radiation therapy over 6 weeks + Cisplatin (IMRT+C) at 40 mg/m² weekly vs 60 Gy of modestly accelerated IMRT alone over 5 weeks. For the expected 2-year PFS of 91%, assuming a binomial distribution, 140 randomized eligible patients per arm were required for 80% power and 10% 1-sided type I error rate. For swallowing acceptability, the required mean 1-year MDADI composite score was ≥ 60.

Results: NRG-HN002 accrued 10/2014-2/2017. Of 316 patients enrolled, 306 were randomized and eligible. Among randomized eligible patients, 84.0% were male, 52.6% had tonsil primary, 62.4% had T2-3 disease, 75.5% had N2 disease, and 80.1% had bilateral IMRT. 97.7% completed

60 Gy IMRT. Of 157 patients receiving Cisplatin, 80.9% had ≥ 5 cycles and 72.6% had ≥ 200 mg/m². There were 15.1% grade 4 and 64.5% grade 3 acute (≤ 180 days after the end of treatment) toxicities on the IMRT+C arm as compared to 2.0% grade 4 and 50.3% grade 3 on the IMRT arm. There were 1.3% grade 4 and 20.0% grade 3 late toxicities on the IMRT+C arm as compared to 1.4% grade 4 and 16.7% grade 3 on the IMRT arm. There was no grade 5 toxicity reported. Nine patients withdrew consent and 5 did not have 2-year assessments, leaving 292 patients analyzable for PFS. At 2.6 years of median follow-up, the 2-year PFS estimate for the IMRT+C arm was 90.5% (95% CI 84.5-94.7%) with $p=0.0350$ thus rejecting the null hypothesis of 2-year PFS $\leq 85\%$. For IMRT, the 2-year PFS was 87.6% (95% CI 81.1-92.5%) with $p=0.2284$ thus failing to reject the null hypothesis. At 1 year, useable and timely MDADI completion rates were 77.1% and 71.1% in the IMRT+C and IMRT arms, respectively. Both arms passed the MDADI threshold, with 1-year means of 85.30 (95% CI 82.53-88.07) and 81.76 (95% CI 78.98-84.54) in the IMRT+C and IMRT arms, respectively. Estimated 2-year OS rates were 96.7% (95% CI 93.9-99.5%) for IMRT+C and 97.3% (95% CI 94.6-99.9%) for IMRT.

Conclusion: The IMRT+C arm met the acceptability criteria for both 2-year PFS and 1-year MDADI. The IMRT alone arm did not meet the PFS

acceptability criterion. Higher rates of grade ≥ 3 acute toxicity were reported for IMRT+C. Rates of late grade ≥ 3 toxicity and estimated 2-year OS rates were similar.

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