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2018 ASTRO Annual Meeting Late-breaking Abstract Selection

LBA1

Randomized Trial Evaluating Radiation following Surgical Excision for "Good Risk" DCIS: 12-Year Report from NRG/RTOG 9804

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Purpose/Objective(s): NRG/RTOG 9804 is the only prospective randomized trial to assess the impact of whole breast radiation (WBRT) versus observation (OBS) in women with "good risk" DCIS, following breast conservation surgery. The primary objective is local recurrence (LR) in the treated breast. Long-term results of this trial are presented here.

Materials/Methods: "Good risk" DCIS was defined for this trial as clinically occult DCIS, found by mammogram or incidental finding at surgery, with size ≤2.5 cm, final margins ≥3 mm, with low or intermediate nuclear grade. Consented patients were randomly assigned to WBRT with standard doses or OBS; boosts were not allowed. The use of Tamoxifen (Tam) for 5 years was optional. Cumulative incidence was used to estimate LR, Gray's test to compare treatments, and Fine-Gray regression for hazard ratios (HRs). Intended accrual was 1790, to detect LR HR = 0.58.

Results: 636 women were randomized from 1999 - 2006 and initial results were reported in 2013. For this long-term update, in addition to the analyses for the 585 eligible patients with follow-up, sensitivity analyses were also done including all patients with follow-up (n = 629). As analyses were essentially the same, the reported results are based on all patients with follow-up. Median age was 58 years and 76% were post-menopausal. Mean pathologic tumor size was 0.60 cm, 61% ≤ 0.5 cm, and 65% had a margin width ≥1.0 cm or a completely negative re-excision specimen. Highest nuclear grade was 1 in 44% and 2 in 56%. Intention to use Tam was indicated for 69% of patients, equally between treatment arms; however actually receiving Tam was different at 58% WBRT vs. 65% OBS (p = 0.05). With a median follow-up time of 12.4 years, the 12-year cumulative incidence of LR was 2.8% (95% CI: 1.1, 5.6) with WBRT and 11.4% (7.7, 15.8) with OBS (p = 0.0001; HR = 0.26, 95% CI: 0.13, 0.54). The 12-year cumulative incidence of invasive (INV) LR was 1.5% (0.4, 4.0) with WBRT and 5.8% (3.2, 9.5) with OBS (p = 0.016; HR = 0.34, 95% CI: 0.14, 0.85). On multivariable analysis, only WBRT (HR = 0.25, 95% CI: 0.12, 0.53; p = 0.0003) and the use of Tamoxifen (HR = 0.50, 95% CI: 0.27, 0.91; p = 0.024) were associated with reduced LR. Age (< 50 vs. ≥ 50) and pathologic tumor size were not significant for all LR, nor INV LR. As expected, no significant differences were observed in survival, disease-free survival or mastectomy use.

Conclusion: Whole breast radiation significantly reduced LR and INV LR in this "good risk" DCIS population. The larger than expected WBRT effect has yielded meaningful results despite not meeting targeted accrual. These results should not be presented to the patient as an absolute indication for WBRT in the defined "good risk" group, but rather should inform a meaningful patient-physician discussion that includes risks, benefits and the patient's own degree of comfort, which can vary greatly, with the differences in LR with and without radiation.

LBA2

FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results (CRUKE/04/015)

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Purpose/Objective(s): The UK FAST trial tested 5 fractions (Fr) of 5.7 Gy and 6.0 Gy against 25 Fr of 2.0 Gy in women prescribed whole breast radiotherapy (no boost) after local excision of early breast cancer. Analysis of primary endpoint (normal tissue effects [by photograph]) showed that the 28.5 Gy/5 Fr regimen appeared similar to control. Further follow-up now enables analysis of 10-year outcomes.

Materials/Methods: The FAST trial (ISRCTN62488883) randomised women aged ≥50 years with invasive breast carcinoma (pT1-2 pN0) to 3 whole breast radiotherapy schedules: 50 Gy in 25 Fr over 5 weeks (control), 30 Gy or 28.5 Gy in 5 Fr over 5 weeks (1:1:1). Exclusion criteria were planned lymphatic/breast boost radiotherapy or (neo)adjuvant cytotoxic therapy. Normal tissue effects (NTE) were assessed annually to 10 years by clinicians and photographs at 2 and 5 years compared with a pre-radiotherapy baseline. Breast tumour recurrence was a secondary endpoint.

Results: 915 women were recruited from 18 UK centres (2004-2007). Composite endpoint of any clinician-assessed breast NTE showed significantly higher levels at 5 and 10 years for 30 Gy compared with 50 Gy (Table). Prevalence of marked NTEs at 5 and 10 years were very low. Compared with 50Gy excess of moderate/marked effects for 30Gy were: 5 years +10.5%, 95%CI 4.9 to 16.1%; 10 years +9.4%, 95%CI 1.1 to 17.6% and for 28.5 Gy, were +2.4%, 95%CI -2.5 to 7.3% at 5 years and +5.5%, 95%CI -2.3 to 13.3% at 10 years. At 9.9 years median follow up, 10 local recurrences (50 Gy: 3, 30 Gy: 3, 28.5 Gy: 4) and 96 deaths (50 Gy: 33, 30 Gy: 33, 28.5 Gy: 30) have been reported.

Conclusion: Marked NTEs were rare for all schedules. Late moderate/marked NTE after 28.5Gy/5 Fr/5 weeks were similar to 50Gy/25 Fr/5 weeks, but higher after 30Gy/5 Fr/5 weeks. Local recurrence rates were very low at 10 years for all schedules. Further research of a 5-Fr regimen is

Table 1 Clinician assessments of NTE at 5 and 10 years

Worst grade of any NTE in the breast[1]	50Gy/25Fr (5 weeks) n (%)	30Gy/5Fr (5 weeks) n (%)	28.5Gy/5Fr (5 weeks) n (%)
At 5 years:	**N = 254**	**N = 267**	**N = 253**
None	160 (63.0)	152 (56.9)	155 (61.3)
Mild	75 (29.5)	67 (25.1)	73 (28.8)
Moderate	15 (5.9)	40 (15.0)	24 (9.5)
Marked	4 (1.6)	8 (3.0)	1 (0.4)
P-value[2]	-	*0.008*	*0.475*
At 10 years:	**N = 132**	**N = 130**	**N = 130**
None	90 (68.2)	66 (50.8)	72 (55.4)
Mild	30 (22.7)	40 (30.8)	39 (30.0)
Moderate	11 (8.3)	18 (13.8)	17 (13.1)
Marked	1 (0.8)	6 (4.6)	2 (1.5)
P-value[2]	-	*0.003*	*0.034*

[1] Shrinkage, induration, telangiectasia, edema;
[2] χ^2 trend test (none, mild, moderate/marked); comparison with 50Gy/25Fr

warranted; the UK FAST-Forward trial is testing 5 Fr delivered in 1 week. 15 or 16-Fr schedules of adjuvant radiotherapy for early breast cancer have now been shown to be effective and safe but a once-weekly 5-Fr schedule may be considered for patients in whom a daily visit for 3 or 5 weeks is not acceptable however careful consideration of the dose per Fr is required.

LBA3

Local Consolidative Therapy (LCT) Improves Overall Survival (OS) Compared to Maintenance Therapy/Observation in Oligometastatic Non-Small Cell Lung Cancer (NSCLC): Final Results of a Multicenter, Randomized, Controlled Phase 2 Trial

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Purpose/Objective(s): We previously observed that LCT improves progression free survival (PFS) in patients with oligometastatic NSCLC after front-line systemic therapy without progression (Gomez et al, Lancet Oncol 2016). Here we report the final analysis of this trial, including the mature secondary endpoint of OS.

Materials/Methods: Patients were enrolled from 3 institutions (MD Anderson Cancer Center, London Health Sciences Center, University of Colorado) and met the following eligibility criteria for randomization: 1) stage IV NSCLC, 2) $\leq$3 metastatic lesions, 3) ECOG performance status of 2 or less, and 4) no progression after standard front-line systemic therapy. Front-line therapy was four or more cycles of platinum doublet therapy or 3 or more months of EGFR or ALK inhibitors for patients with EGFR mutations/ALK rearrangements, respectively. Patients were then randomized in a 1:1 fashion to receive either standard maintenance therapy/observation (MT/O arm) versus LCT, defined as radiation or surgery to all remaining active sites of disease followed by MT/O (LCT arm). The primary endpoint was PFS, with secondary endpoints including OS, toxicity, and time to appearance of a new lesion. Kaplan-Meier estimates of survival endpoints were obtained, with differences assessed utilizing the log-rank test. Statistical tests were two-sided, and p-values$<$0.10 were deemed to be significant. At a 10% type I error and a 90% power to detect an improvement in PFS from 4 months (MT/O) to 7 months (LCT), the trial was designed to enroll 94 patients.

Results: The trial was closed by the MD Anderson DSMB after the accrual of 49 patients, due to a benefit detected in PFS; these results have been previously reported at a median follow-up of 12.4 months. For this analysis. median follow-up time for censored patients at the last known date alive is 38.8 months (range 28.3-61.4 months). The PFS benefit was durable, with a median of 14.2 months in the LCT arm (95% CI 7.4,2 4.3) vs. 4.4 months in the MT/O arm (95% CI 2.2, 8.3; p=0.014). The extended follow up also demonstrated a benefit in OS for patients in the LCT arm, with a median OS of 41.2 months (95% CI 18.9, NA) vs. 17.0 months in the MT/O arm (95% CI 10.1, 39.8; p=0.017). No additional Grade 3 or higher toxicities were observed in either arm. Time to new lesion failure trended towards significance with a median of 14.2 months in the LCT arm (95% CI 5.7, 26.2) vs. 6.0 months in the MT/O arm (95% CI 4.4, 8.3; p=0.11).

Conclusion: To our knowledge, this study represents the first randomized data showing an OS benefit for local ablative therapy in patients with oligometastatic NSCLC that do not progress after front-line systemic therapy. Ongoing phase II/III trials will assess the effect of LCT in larger populations and with the incorporation of novel therapeutic agents (immunotherapy, targeted therapy).

LBA4

NRG-RTOG 1016: Phase III Trial Comparing Radiation/Cetuximab to Radiation/Cisplatin in HPV-related Cancer of the Oropharynx

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Purpose/Objective(s): To determine whether radiation with cetuximab has non-inferior overall survival compared to radiation with cisplatin in patients with locoregionally advanced human papillomavirus (HPV)–related oropharynx cancer.

Materials/Methods: Eligible patients were randomized (1:1) to 70 Gy in 6 weeks accelerated (6 fractions/week) with 2 cycles of cisplatin 100mg/m2 every 3 weeks, versus the same radiation with weekly cetuximab. All patients had central laboratory confirmation of HPV status by p16 immunohistochemistry and were stratified by T-stage, N-stage, Zubrod performance status, and smoking history. At final analysis, non-inferiority would be concluded if the overall survival hazard ratio (cetuximab/cisplatin) upper confidence bound was $\leq$1.45.

Results: From 6/11 to 7/14, 849 patients were randomized, of whom 805 were analyzed. 90% were male with median age of 58. The overall survival hazard ratio was 1.45 (95%CI 1.03-2.05). Estimated 5-year survival rates were 84.6% (80.6-88.6) with cisplatin versus 77.9% (73.4-82.5) with cetuximab. Progression-free survival was significantly worse with cetuximab compared to cisplatin [hazard ratio 1.72 (1.29-2.29); one-sided log-rank p=0.0001] with 5-year estimates of 78.4% (73.8-83.0) with cisplatin and 67.3% (62.4-72.2) with cetuximab. Estimated 5-year local-regional failure/distant metastases rates were 9.9%/8.6% with cisplatin and 17.3%/11.7% with cetuximab. Acute grade 3-4/5 adverse events were 82%/0.8% and 77%/1.3% with cisplatin and cetuximab, respectively. The distribution of grade 3-4 adverse events varied by treatment with anemia, hearing loss, nausea, vomiting, neutropenia, and kidney injury more common with cisplatin, and rash being more common with cetuximab. Long-term severe dysphagia was 4% for the cisplatin arm and 6% for the cetuximab arm. Extensive quality of life measures were collected and will be reported separately.

Conclusion: This study failed to establish the non-inferiority of radiation/cetuximab for patients with locoregionally advanced HPV-related oropharynx cancer . Radiation/cetuximab resulted in inferior overall and

progression-free survival. Radiation with concurrent cisplatin remains the standard of care in these patients.

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LBA5

Short Term Androgen Deprivation Therapy Without or With Pelvic Lymph Node Treatment Added to Prostate Bed Only Salvage Radiotherapy: The NRG Oncology/RTOG 0534 SPPORT Trial

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Purpose/Objective(s): To determine in a three-arm randomized trial whether there are incremental gains in freedom from progression (FFP) from the addition of 4-6 months of short term androgen deprivation therapy (STADT) using antiandrogen plus an LHRH agonist, without or with pelvic lymph node treatment (PLNRT), to prostate bed salvage radiotherapy (PBRT).

Materials/Methods: Patients were randomized to PBRT alone (Arm 1), PBRT + STAD (Arm 2), and PLNRT + PBRT + STAD (Arm 3). The FFP primary endpoint included PSA nadir+2, clinical failure, or death from any cause, with censoring for secondary salvage therapy initiated prior to these events. The sample size provided 90% statistical power to detect a 10% absolute FFP improvement at 5 yr in Arm 2 compared to Arm 1 and a 10% absolute improvement at 5 yr in Arm 3 compared to Arm 2 at an overall alpha level of 0.025. On the third planned interim analysis for efficacy and futility based on 1191 eligible patents with 5 yr minimum follow-up, the treatment arms were compared in a stepwise approach to determine if the Haybittle-Peto (HP) threshold boundary of $p < 0.001$ (one sided) was crossed. Futility evaluation tested the alternative hypotheses at $p < 0.001$. Adverse events were graded using CTCAEv3.0.

Results: There were 1792 patients enrolled from 2008 − 2015. Median follow-up for those living is 5.4 yr. Ineligible patients included 18, 17, and 21 in Arms 1, 2, and 3. The patient and tumor characteristics for the 1736 eligible patients include a median age of 64 yr (range 39-84), black in 13%, baseline Zubrod status of 0 in 93%, seminal vesicle involvement in 15%, pre-radiotherapy PSA of ≤1.0 ng/ml in 89%, Gleason score < 8 in 83%, and pT2 margin positive or pT3 in 72%. Arms 1, 2, and 3 had 5 yr FFP rates of 71.1%, 82.7% and 89.1%. Arm 3 had the highest rate compared to Arm 1 ($p < 0.0001$), exceeding the HP boundary. The hazard ratio (HR) between arms 3 and 1 was 0.44 (95% CI: 0.32-0.59). Arm 3 was then compared to Arm 2, yielding a difference of 6.4% ($p = 0.0063$) and a HR of 0.71 (95% CI: 0.51-0.98). In all eligible patients followed for up to 8 years, there were 45, 38 and 25 patients who developed distant metastasis (DM) in Arms 1, 2 and 3. Without second salvage censoring, the DM hazard ratio for Arm 3 vs Arm 1 was 0.52 (95% CI: 0.32-0.85) and for Arm 3 vs. Arm 2 was 0.64 (95% CI: 0.39-1.06). With IMRT use in 87% of cases, highest late grade 3+ toxicity was observed in 4.3%, 4.9% and 6.0% for renal/genitourinary events and 0.7%, 0.4%, and 1.1% for gastrointestinal events in Arms 1, 2, and 3.

Conclusion: This is the first report of the primary endpoint and is the first randomized trial to show significant incremental improvements in FFP going from PBRT only to PBRT+STAD to PLNRT+PBRT+STAD. The addition of PLNRT resulted in early, meaningful, reductions in failure. Follow-up of patients will further elucidate the magnitude of the differences between arms 2 and 3.

LBA6

Plasma Circulating Tumor HPV DNA for the Surveillance of Cancer Recurrence in HPV-associated Oropharyngeal Cancer

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Purpose/Objective(s): To assess the performance of plasma circulating tumor HPV DNA (ctHPVDNA) as a surveillance blood test in patients with p16 positive oropharyngeal squamous cell carcinoma (OPSCC).

Materials/Methods: A prospective biomarker trial was conducted in 89 patients with p16 positive OPSCC who had no evidence of distant metastatic disease at baseline. All patients received definitive chemoradiotherapy (CRT) with 78 receiving de-intensified CRT on clinical trial (60Gy). Remaining patients received standard CRT (70Gy). All patients had a 3 month post-CRT PET/CT and were thereafter surveilled with clinical examinations every 2 - 4 months for years 1 - 2, then every 6 months for years 3 - 5. Chest x-rays or chest CT's were performed every 6 months. Blood specimens were collected at baseline (58/89), weekly during treatment (30/89), and with each follow-up visit (89) for plasma circulating nucleic acid extraction (Qiagen). Multianalyte droplet digital PCR assays were developed for ultra-sensitive detection of ctHPVDNA -16, -18, -31, -33, and -35 DNA on the Bio-Rad QX200 platform. Additional imaging was obtained if ctHPVDNA became detectable in the blood. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of ctHPVDNA testing at detecting recurrence were calculated. Events were defined as recurrence after the 3 month post-CRT PET/CT.

Results: Clinical characteristics were the following: 89% T0-2, 80% N2, 80% never/≤ 10 pack years. Mean f/u was 19.8 months (range 3.7 − 44.7). Baseline ctHPVDNA was detectable in 51/58 (88%), with a median value of 582 copies/mL (range 8 - 22,579). 53/58 evaluable patients had undetectable ctHPVDNA within 3 months of completing CRT. 73/89 patients in the surveillance cohort had undetectable ctHPVDNA at all timepoints beyond 3 months post-CRT. 16/89 patients developed a positive ctHPVDNA test result with a median interval from CRT of 16.7 months (range 7.8 − 30.4) and a median value of 75 copies/mL (range 9 − 28,369). 8/16 patients who developed a positive ctHPVDNA test result during surveillance were diagnosed with recurrence (0 local, 1 regional, 7 distant). 8 patients currently have detectable ctHPVDNA (range 23 − 28,369 copies/ml) but have no evidence of recurrence and are being

monitored with repeat ctHPVDNA and imaging. 0/73 patients with undetectable ctHPVDNA at all follow-up visits have developed recurrence. Sensitivity, specificity, NPV, and PPV of ctHPVDNA testing was: 100%, 90%, 100%, 50%.

Conclusion: Performance of an optimized multianalyte ctHPVDNA blood test for the detection of cancer recurrence was exceptional (NPV = 100%). Future studies should be done to evaluate whether ctHPVDNA testing may improve early detection of cancer recurrence while also reducing costs by targeting radiographic surveillance to the subset of patients who are at greatest risk of relapse.

LBA7

Act.in.Sarc: An International Randomized Phase III Trial Evaluating Efficacy and Safety of First-in-Class NBTXR3 Hafnium Oxide Nanoparticles Activated By Preoperative Radiotherapy in Locally Advanced Soft Tissue Sarcoma

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Purpose/Objective(s): A subset of soft tissue sarcoma (STS) patients achieve significant therapeutic benefit from preoperative radiotherapy (RT). Yet, this treatment paradigm may be associated with limited efficacy and increased toxicity, highlighting the necessity of novel multimodal therapies aimed at local control with few adverse events (AEs). NBTXR3 is a first-in-class Hafnium-Oxide nanoparticle. Designed for cancer cell uptake, it is injected intratumorally (IT) and activated by ionizing radiation to yield a tumor-localized high energy deposit and increased cell death compared to the same dose of RT alone. We report now the first phase II/III randomized clinical trial of NBTXR3 given as preoperative treatment to patients with locally advanced STS of the extremity and trunk wall.

Materials/Methods: In this multicenter, open-label phase II/III trial [NCT02379845], patients (pts) were randomized 1:1 to receive a single IT preoperative NBTXR3 injection followed by RT or RT alone and then surgical resection. RT consisted of Intensity Modulated RT or 3D-RT of 2Gy*25 fractions (total 50 Gy). The primary endpoint was pathological Complete Response Rate (pCRR) defined as the percentage proportion of pts presenting $\leq$5% of residual viable cancer cells (EORTC guidelines) evaluated by a blind Central Review Board. Key secondary endpoints included negative surgical margins (R0) and safety.

Results: In 180 included pts, the pCRR was 16.1% in the NBTXR3 plus RT group compared with 7.9% in the RT alone group (p=0.0448) in the intent-to-treat full analysis set population, which included all pts who were randomized and stratified by STS histological subtype. In the same population, 77.0% in the experimental arm achieved an R0 versus 64.0% in the control arm (p=0.0424). NBTXR3 showed very good local tolerance without any modification of RT alone safety profile. In all the treated pts, who were randomly assigned and received any amount of NBTXR3 or at least one RT dose, the IT administration of NBTXR3 caused injection-site pain in 12 (13.5%) pts. NBTXR3 was also associated with grade 3-4 acute immune reactions in 7 (7.9%) pts, but these AEs were of short duration, manageable, and resolved spontaneously in some cases.

Conclusion: This trial met its primary and secondary endpoints of pCRR and R0 rates, respectively. NBTXR3 with RT demonstrated an acceptable safety profile compared to RT alone. As pCR is a known indicator of long-term treatment response with a positive correlation to both progression free and overall survival, NBTXR3 represent a new option for preoperative treatment for locally advanced STS. Acknowledgments: These data support ongoing studies investigating NBTXR3 in recurrent/metastatic HNSCC or metastatic non-small cell lung cancer [NCT03589339]; HNSCC [NCT01946867; NCT02901483]; prostate [NCT02805894], liver [NCT02721056] and rectal cancers [NCT02465593].

LBA8

Preoperative Chemoradiotherapy Potentially Improves Outcome for (Borderline) Resectable Pancreatic Cancer: Preliminary Results of the Dutch Randomized Phase III PREOPANC Trial

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Purpose/Objective(s): For patients with (borderline) resectable pancreatic adenocarcinoma standard treatment is resection followed by adjuvant chemotherapy. Previous studies suggest a benefit of preoperative treatment. The aim of this multicenter phase III, superiority, randomized controlled trial is to test the hypothesis that median overall survival of patients with (borderline) resectable pancreatic cancer improves with preoperative chemoradiotherapy.

Materials/Methods: Patients with pathologically confirmed (borderline) resectable pancreatic cancer $>$ 2 cm were randomized between immediate surgery (arm A) and preoperative chemoradiotherapy (arm B), both followed by adjuvant chemotherapy. After diagnostic laparoscopy, the preoperative chemoradiotherapy consisted of 15 daily fractions of 2.4 Gray combined with gemcitabine, 1,000 mg/m^2 on days 1, 8 and 15, preceded and followed by modified courses of gemcitabine. The adjuvant chemotherapy consisted of 6 cycles of gemcitabine in arm A versus 4 cycles in arm B. Primary endpoint was overall survival (OS) by intention to treat, secondary endpoints were (R0) resection rate, disease free survival (DFS), distant metastases free interval (DMFI), locoregional recurrence free interval (LRFI) and toxicity. Accrual took place between April 23, 2013 and July 25, 2017.

Results: In total, 246 patients were included in the intention-to-treat analysis (127 patients in arm A and 119 in arm B). At this analysis, 149 of the 176 required events for the primary outcome were observed. The primary outcome OS was not significantly improved in arm B (median 13.5 vs. 17.1 months; HR 0.74; p=0.074). In arm A, 120/127 patients underwent an exploratory laparotomy, versus 81/119 in arm B. The most common reason not having exploratory laparotomy in arm B was metastatic disease found at laparoscopy or progression during the preoperative treatment. Resection rates were 72% (91/127) in arm A vs. 61% (72/119) in arm B (p= 0.087). However, there was improvement in R0 resection rate (31% vs. 63%, p=$<$0.001), DFS (median 7.9 vs. 9.9 months; HR 0.71; p=0.023), DMFI (median 10.6 vs 18.4 months; HR 0.64; p=0.013)

and LRFI (median 11.8 vs not reached; HR 0.55; p<0.001) after preoperative treatment (arm B). No significant difference was observed in adverse events between both groups (p= 0.28). A subgroup analysis of patients who actually underwent a resection and started adjuvant gemcitabine (61/127 (48%) in arm A and 55/119 (46%) in arm B) was performed which showed a median OS of 19.1 in arm A, compared to 42.1 months in arm B (p<0.001).

Conclusion: Our preliminary data suggest a benefit in outcome of preoperative chemoradiotherapy in (borderline) resectable pancreatic cancer compared to immediate surgery. The final analysis is expected within half a year.

LBA9

Preservation of Neurocognitive Function (NCF) with Conformal Avoidance of the Hippocampus during Whole-Brain Radiotherapy (HA-WBRT) for Brain Metastases: Preliminary Results of Phase III Trial NRG Oncology CC001

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Purpose/Objective(s): Based on preliminary evidence that radiation to the neuroregenerative hippocampal stem cells plays a role in NCF decline, the phase II NRG/RTOG 0933 trial demonstrated memory-preservation following HA-WBRT. The phase III NRG-CC001 trial of WBRT plus memantine without (WBRT+M) or with hippocampal avoidance (HA-WBRT+M) sought to validate these findings.

Materials/Methods: Adult patients with brain metastases were stratified by RPA and receipt of prior radiosurgery/surgery and randomized to WBRT+M versus HA-WBRT+M (30 Gy in 10 fractions). Standardized NCF tests were performed at baseline, 2, 4, 6, and 12 months (mos). The primary endpoint was time to NCF failure defined as decline using the reliable change index on at least one of the following tests: Hopkins Verbal Learning Test-Revised, Trail Making Test, or Controlled Oral Word Association. Cumulative incidence was used to estimate time to NCF failure (death without NCF failure was treated as a competing risk). Between-arms differences were tested using Gray's test. To detect an 11% absolute reduction in 6-month NCF failure, 382 analyzable patients were required for 90% power with two-sided $\alpha=0.05$. Due to possible non-compliance, the sample size was increased by 25% (510 patients).

Results: 518 patients were randomized from July 2016 to March 2018. Median age was 61.5 years. Treatment arms did not differ in baseline characteristics. Grade≥3 toxicity did not differ (p=0.88). Median follow-up for alive patients was 6.1mos. NCF testing compliance was 69% at 6mos and 61% at 12mos. Treatment arms did not differ in baseline NCF, overall survival (hazard ratio (HR)=1.13, 95% confidence interval (CI): 0.89-1.44, p=0.31) or intracranial progression-free survival (HR 1.12, 95% CI 0.90-1.39, p=0.33). Time to NCF failure was significantly longer in favor of HA-WBRT+M. The NCF failure rates following WBRT+M vs. HA-WBRT+M were 12.8% (95% CI 8.5-18.0%) vs. 11.2% (7.1-16.3%) at 2mos, 63.0% (55.6-69.5%) vs. 53.7% (46.1-60.8%) at 4mos, and 69.1% (61.8-75.3%) vs. 58.0% (50.2-64.9%) at 6mos (p=0.012). In analyses adjusted for stratification factors, HA-WBRT+M (HR=0.72; 95% CI: 0.56-0.94, p=0.016) and age ≤61 years (HR=0.61, 95% CI: 0.46-0.81, p=0.0006) predicted for longer time to NCF failure. Test for interaction between treatment arm and age was non-significant (p=0.67).

Conclusion: Preliminary analysis confirms our hypothesis that conformal avoidance of the hippocampal neuro-regenerative stem cell niche during WBRT preserves NCF while achieving similar intracranial control and survival. While age independently predicts for NCF, the NCF benefit of hippocampal avoidance does not differ by age.

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LBA10

PACIFIC: Overall Survival with Durvalumab versus Placebo after Chemoradiotherapy in Stage III NSCLC

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Purpose/Objective(s): In the global, Phase 3 PACIFIC study (Antonia 2017; NCT02125461), durvalumab significantly improved progression-free survival (PFS) versus placebo in Stage III, unresectable NSCLC patients without progression after concurrent chemoradiotherapy (CRT) (stratified HR, 0.52; 95% CI, 0.42−0.65; P<0.001). This was the first major advance in this disease setting for many years. Here we report the second primary endpoint of overall survival (OS) for PACIFIC.

Materials/Methods: Patients (any PD-L1 tumor status) with WHO PS 0/1 who received ≥2 cycles of platinum-based CRT were randomized (2:1) 1−42 days post-CRT to durvalumab 10 mg/kg IV Q2W or placebo up to 12 months, stratified by age, sex, and smoking history. Primary endpoints were PFS from randomization (blinded independent central review; RECIST v1.1) and OS (interim analysis reported). Secondary endpoints included time to death or distant metastasis (TTDM) and PFS2 (time to second progression) from randomization and safety. Time to first/second subsequent therapy or death (TFST/TSST) were supportive assessments for PFS/PFS2.

Results: Between May 2014 and April 2016, 713 patients were randomized; 709 received treatment (durvalumab, n=473; placebo, n=236). As of March 22, 2018 (data cutoff), median follow-up duration was 25.2 months (range, 0.2−43.1). After discontinuation, 41.0% and

54.0% in the durvalumab and placebo groups received subsequent anticancer therapy; overall, 8.0% and 22.4% received additional immunotherapy. Durvalumab significantly improved OS versus placebo (stratified HR 0.68, 99.73% CI, 0.469−0.997; P = 0.00251), with the median not reached (NR; 95% CI, 34.7 months−NR) and 28.7 months (95% CI, 22.9−NR), respectively. Durvalumab improved OS in all prespecified subgroups. Updated PFS remained similar (stratified HR 0.51, 95% CI, 0.41−0.63), with medians of 17.2 and 5.6 months with durvalumab and placebo, respectively. Durvalumab improved updated TTDM (stratified HR 0.53, 95% CI, 0.41−0.68), and PFS2 (stratified HR 0.58, 95% CI, 0.46−0.73), TFST (stratified HR 0.58, 95% CI, 0.47−0.72) and TSST (stratified HR 0.63, 95% CI, 0.50−0.79). Within the durvalumab and placebo groups, 30.5% and 26.1% had grade 3/4 any-causality AEs, 15.4% and 9.8% discontinued due to AEs, and no new safety signals were identified; any-grade (grade 3/4) pneumonitis/radiation pneumonitis occurred in 33.9% (3.6%) and 24.8% (3.0%). Exploratory analyses characterizing outcome based on features of previous CRT will be presented.

Conclusion: Durvalumab demonstrated statistically significant and clinically meaningful improvement in OS compared with placebo, supported by secondary endpoints such as PFS2. PACIFIC is the first study to show a survival advantage following CRT in this locally advanced NSCLC population, providing compelling evidence for the unprecedented benefit of durvalumab treatment as the standard of care.