LBA1
Randomized Trial Evaluating Radiation following Surgical Excision for “Good Risk” DCIS: 12-Year Report from NRG/RTOG 9804

B. McCormick; Memorial Sloan Kettering Cancer Center, New York, NY

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 = 0.50. 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 (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% (7.5, 15.8) 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)

A.M. Brunt,1 J. Haviland,2 M. Sydenham,3 H. Alquirafi,3 A. Alhasso,4 P. Bliss,4 D. Bloomfield,5 M. Emerson,4 A. Goodman,7 A. Harnett,8 H. Passant,9 Y.M. Tsang,10 D. Wheatley,11 J. Bliss,2 and J. Yarnold12; 1Institute of Cancer Research, London, United Kingdom, 2The Institute of Cancer Research, Sutton, United Kingdom, 3Southend Hospital, Southend, United Kingdom, 4Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom, 5Torbay General Hospital, Torbay, United Kingdom, 6Royal Sussex County Hospital, Brighton, United Kingdom, 7Royal Devon and Exeter Hospital, Exeter, United Kingdom, 8Norfolk and Norwich University Hospital, Norwich, United Kingdom, 9Vellindre Hospital, Cardiff; United Kingdom, 10Mount Vernon Cancer Centre, London, United Kingdom, 11Royal Cornwall Hospital, Truro, United Kingdom, 12Division of Radiotherapy and Imaging, the Institute of Cancer Research, London, United Kingdom

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 cyto-toxic 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 50 Gy excess of moderate/marked effects for 30 Gy 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 13.0% 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
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**

D.R. Gomez, 1,2 C. Tang, 1,3 J. Zhang, 1,4 G.R. Blumenschein, 3 M. Hernandez, 3 J.J. Lee, 2 R. Yé, 1,4 D.R. Camidge, 5,6 E. Skoulidis, 1,6 R. Doebele, 4 L.E. Gaspar, 1,5 D.L. Gibbons, 3,8 J. Karam, 2,9 B.D. Kavanagh, 1,9,11 D.A. Palma, 12 A.V. Louie, 13 A. Tsao, 14 B. Sepesi, 15 S.G. Swisher, 16 and J. Heymach 1,13

1 The University of Texas MD Anderson Cancer Center, Houston, TX, 2 Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, 3 MD Anderson Cancer Center, Houston, TX, 4 Department of Medical Oncology, University of Colorado, Denver, CO, 5 University of Colorado, Aurora, CO, 6 Department of Radiation Oncology, University of Colorado Denver, Aurora, CO, 7 Department of Thoracic/Head and Neck Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, 8 University of Colorado, Denver, CO, 9 London Health Sciences Centre, University of Western Ontario, London, ON, Canada, 10 Department of Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX.

**Purpose/Objective(s):** We previously observed that LCT improves progression free survival (PFS) in patients with oligometastic NSCLC after front-line systemic therapy without progression (Gomez et al, Lancet Oncol Oncology). 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) ≤ 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 or 3 or more months of EGFR or ALK inhibitors for patients with EGFR mutations/ALK rearrangements, respectively. 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 (ctuximab/cisplatin) upper confidence bound was ≤ 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 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 compared to cisplatin in HPV-related cancer. Radiation/cetuximab resulted in inferior overall and 95% CI 14.4, 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).
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

A. Pollack,1 T.G. Karrison,2 A.G. Balogh, Jr,3 D. Low,4 D.W. Bruner,5 J.S. Wefel,6 L.G. Gomella,7 E. Vigneault,8 J.M. Michalski,9 S. Angyalfi,10 H. Lukka,11 S.L. Faria,12 G. Rodrigues,13 M.C. Beaucournu,14 S.A. Seaward,15 A.M. Allen,16 D.C. Monitto,17 W. Seiferheld,18 and H.M. Sandler19; 1University of Miami Sylvester Comprehensive Cancer Center, Miami, FL; 2NRG Oncology SDMC, Philadelphia, PA; 3University of Calgary, Calgary, AB, Canada; 4UCLA, Los Angeles, CA; 5Nell Hodgson Woodruﬀ School of Nursing, and Winship Cancer Institute at Emory University, Atlanta, GA; 6University of Texas MD Anderson Cancer Center, Houston, TX; 7Sidney Kimmel Cancer Center of Thomas Jefferson University, Philadelphia, PA; 8CHU de Quebec, University of Laval, Quebec, QC, Canada; 9Washington University School of Medicine, St. Louis, MO, 10Tom Baker Cancer Centre, Calgary, AB, Canada; 11McMaster University, Hamilton, ON, Canada; 12McGill University Health Centre, Montreal, QC, Canada; 13London Health Sciences Center, London, ON, Canada; 14Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; 15Kaiser Permanente, Vallejo, CA; 16Davidoff Center, Rabin Medical Center, Tel Aviv, Israel; 17Spartanburg Regional Medical Center, Spartanburg, SC; 18Cedars Sinai Medical Center, Los Angeles, CA

**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 (STAD) using an 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 PBRT 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% increase in FFP at 5 yr in Arm 2 compared to Arm 1 and a 10% increase in FFP at 5 yr in Arm 2 compared to Arm 1 at an overall significant test 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

B.S. Chena,1 S. Kumar,2 C. Shen,3 R.J. Amdurd,4 R. Dagan,5 J. Weiss,6 J. Grillly-Olson,7 A. Zanation,8 T. Hackman,9 J. Blumberg,10 S. Patel,11 B. Thorp12, M. Weisser13, N.C. Sheets,14 W.M. Mendenhall,15 and G.P. Gupta16; 1Lineberger Comprehensive Cancer Center, University of North Carolina Hospitals, Chapel Hill, NC; 2The University of North Carolina, Chapel Hill, NC; 3Department of Radiation Oncology, University of North Carolina School of Medicine, Chapel Hill, NC; 4Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL; 5Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, FL; 6University of North Carolina Hospitals, Chapel Hill, NC; 7Department of Medicine, Division of Hematology Oncology, University of North Carolina School of Medicine, Chapel Hill, NC; 8Department of Otolaryngology/Head and Neck Surgery, University of North Carolina School of Medicine, Chapel Hill, NC

**Purpose/Objective(s):** To assess the performance of plasma circulating tumor HPV DNA (cHPV-DNA) 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 cHPV-DNA -16, -18, -31, -33, and -35 DNA on the Bio-Rad QX200 platform. Additional imaging was obtained if cHPV-DNA became detectable in the blood. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of cHPV-DNA 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 cHPV-DNA was detectable in 51/58 (88%), with a median value of 382 copies/mL (range 8 - 22.579). 53/58 evaluable patients had undetectable cHPV-DNA within 3 months of completing CRT. 73/89 patients in the surveillance cohort had undetectable cHPV-DNA at all timepoints beyond 3 months post-CRT. 16/89 patients developed a positive cHPV-DNA 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 cHPV-DNA test result during surveillance were diagnosed with recurrence (0 local, 1 regional, 7 distant). 8 patients currently have detectable cHPV-DNA (range 23 - 28,369 copies/mL) but have no evidence of recurrence and are being
monitored with repeat cHPVDNA and imaging. 0/73 patients with undetectable cHPVDNA at all follow-up visits have developed recurrence. Sensitivity, specificity, NPV, and PPV of cHPVDNA testing was: 100%, 90%, 100%, 50%.

**Conclusion:** Performance of an optimized multianalyte cHPVDNA blood test for the detection of cancer recurrence was exceptional (NPV = 100%). Future studies should be done to evaluate whether cHPVDNA 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

S. Bonvalot, 1 P. Rutkowski, 2 J.O. Thariat, 3 S. Carrere, 4 M.P. Sunyach, 5 E. Saada, 6 P. Agoston, 7 A. Hong, 8 A. Mervoyer, 9 M. Rastrelli, 10 C. Le Pechoux, 11 V. Moreno, 12 R. Li, 13 B. Tiangoo, 14 A. Casado, 15 A. Gronchi, 16 L.C. Mangel, 17 P. Hohenberger, 18 M. Delannes, 19 and Z. Papai 20

**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 uptake, it is injected intratumorally (IT) and activated by ionizing radiation to yield a tumor-localized high energy deposit and increased cell death.

**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 2 Gy*25 fractions (total 50 Gy). The primary endpoint was pathological Complete Response Rate (pCRR) defined as the percentage proportion of pts presenting ≤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 pCRR 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**


**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 a 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/m² on days 1, 8, and 15, 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 9.7 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


1Northwestern Medicine Chicago Proton Center and Northwestern Medicine Cancer Center, Warrenville, Warrenville, IL, 2American College of Radiology, Philadelphia, PA, 3Department of Radiation Oncology, Mayo Clinic, Rochester, MN, 4University of Texas MD Anderson Cancer Center, Houston, TX, 5Department of Radiation Oncology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, 6Nell Hodgson Woodruff School of Nursing, and Winship Cancer Institute at Emory University, Atlanta, GA, 7Medical College of Wisconsin, Milwaukee, WI, 8Washington University School of Medicine, Department of Radiation Oncology, St. Louis, MO, 9East Bay Radiation Oncology Center/Eden Medical Center, Castro Valley, CA, 10Chester County Hospital, West Chester, PA, 11Centre Hospitalier de l’Université de Montréal (CHUM), Montréal, QC, Canada, 12Saskatoon Cancer Centre, Saskatoon, SK, Canada, 13Wayne State University/McLaren Cancer Institute, Flint, MI, 14Duke University, Durham, NC, 15University of California, San Francisco, CA, 16AstraZeneca, Cambridge, United Kingdom, 17AstraZeneca, Cambridge, United Kingdom, 18Woodruff School of Nursing, and Winship Cancer Institute at Emory University, Atlanta, GA.

**Purpose/Objective(s):** Based on preliminary evidence that radiation to the hippocampal neuro-regenerative stem cells plays a role in NCF decline, the sample size was increased by 25% (510 patients). The phase III NRG-CC001 trial demonstrated memory-preservation with(WBRT+M) or without hippocampal avoidance (HA-WBRT). The phase II NRG/RTOG 0933 trial demonstrated memory-preservation (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**

D. Raben,1 C. Faivre-Finn,2 D. Spigel,3 D. Daniel,4 A. Villegas,5 D. Vincente,6 R. Hui,7 J. de Castro Carpeno,8 S. Murakami,9 L. Paz-Ares,10 M. Özgüeroğlu,11 T. Kurata,12 A. Chiappori,13 K.H. Lee,14 M. de Wit,15 L. Poole,16 C. Wadsworth,17 P.A. Dennis,18 and S.J. Antonia13

1University of Colorado Cancer Center, Aurora, CO, 2Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom, 3Sarah Cannon Research Institute, Nashville, TN, 4Tennessee Oncology, Chattanooga, TN, 5Cancer Specialists of North Florida, Jacksonville, FL, 6Hospital Universitário Virgem Macarena, Sevilla, Spain, 7Westmead Hospital and the University of Sydney, Sydney, Australia, 8Hospital Universitário La Paz, Madrid, Spain, 9Kanagawa Cancer Center, Yokohama, Japan, 10Hospital Universitario 12 de Octubre, CiberOnc, Universidad Complutense and CNIO, Madrid, Spain, 11Istanbul University — Cerrahpasa, Cerrahpasa School of Medicine, Istanbul, Turkey, 12Kansai Medical University Hospital, Hirakata, Japan, 13H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, 14Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea, Republic of (South), 15Vivantes Klinikum Neukoelln, Berlin, Germany, 16AstraZeneca, Cambridge, United Kingdom, 17AstraZeneca, Alderley Park, United Kingdom, 18AstraZeneca, Gaithersburg, MD

**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 pre-specified 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.