Track/Subcategory: Gastrointestinal Cancer—Colorectal and Anal: Colorectal Cancer–Advanced Disease

Abstract ID: 3501

Session Type: Oral Abstract Session

Title: Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) or NIVO monotherapy for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): Expanded analyses from CheckMate 8HW.

Presenter Name: Heinz-Josef Lenz

Abstract Text:

Background: In the phase 3 CheckMate 8HW study (NCT04008030), both dual primary endpoints of
progression-free survival (PFS) for first-line (1L) NIVO + IPI vs chemo (HR 0.21; $P < 0.0001$) and NIVO
+ IPI vs NIVO across all lines (HR 0.62; $P = 0.0003$) in patients (pts) with centrally confirmed MSI-H/dMMR mCRC was met. We report expanded analyses of NIVO + IPI versus NIVO (all lines) and longer follow-up results for NIVO + IPI versus chemotherapy (1L).

Methods: The study design was described previously. Patients with MSI-H/dMMR, as determined by local testing, were enrolled in the study. After randomization, IHC and PCR-based tests were used for central confirmation. PFS2 (time from randomization to progression after subsequent systemic therapy, start of second subsequent systemic therapy, or death) was a key exploratory endpoint.

Results: In all randomized pts (all lines), 296 of 354 (84%) in the NIVO + IPI arm, 286 of 353 (81%) in the NIVO arm, and 113 of 132 (86%) in the chemo arm had centrally confirmed MSI-H/dMMR. In all randomized 1L pts, 171 of 202 (85%) in the NIVO + IPI arm and 84 of 101 (83%) in the chemo arm had centrally confirmed MSI-H/dMMR. Median follow-up was 47.0 mo (range 16.7–60.5). 1L NIVO + IPI continued to show a PFS benefit compared to chemotherapy (Table). Subsequent systemic therapy was received by 27 (16%) and 61 (73%) pts after 1L NIVO + IPI and chemo, respectively; 10 (6%) and 21 (25%) received subsequent non-study immunotherapy. In the 1L chemo arm, 39 (46%) pts crossed over to NIVO + IPI on study. PFS2 continued to favor 1L NIVO + IPI vs chemo (Table). Across all lines, NIVO + IPI demonstrated superior PFS vs NIVO (Table). Subsequent systemic therapy was received by 54 (18%) patients in the NIVO + IPI arm and 83 (29%) in the NIVO arm; 20 (7%) and 31 (11%) received subsequent non-study immunotherapy. PFS2 favored NIVO + IPI vs NIVO across all lines of therapy (Table). In all treated patients, grade 3/4 treatment-related adverse events occurred in 78 (22%) and 50 (14%) pts in the NIVO + IPI and NIVO arms, respectively. Additional analysis will be presented.

Conclusions: NIVO + IPI demonstrated sustained clinical benefit compared to chemo (1L) and NIVO (all lines) despite the use of subsequent therapy, as shown by improved PFS2 in patients with centrally confirmed MSI-H/dMMR mCRC. No new safety signals were observed. These results support NIVO + IPI as a standard of care treatment for MSI-H/dMMR mCRC.

Track/Subcategory: Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary: Esophageal or Gastric Cancer - Advanced/Metastatic Disease

Abstract ID: LBA4002

Session Type: Oral Abstract Session

Title: Trastuzumab deruxtecan (T-DXd) vs ramucirumab (RAM) + paclitaxel (PTX) in second-line treatment of patients (pts) with human epidermal growth factor receptor 2-positive (HER2+) unresectable/metastatic gastric cancer (GC) or gastroesophageal junction adenocarcinoma (GEJA): Primary analysis of the randomized, phase 3 DESTINY-Gastric04 study.

Presenter Name: Kohei Shitara

Abstract Text:

Background: T-DXd 6.4 mg/kg is approved for patients with metastatic HER2+ GC/GEJA who received a prior trastuzumab-based regimen based on previous phase 2 studies. This is the primary efficacy analysis from a planned interim analysis of DESTINY-Gastric04 (NCT04704934), a global, randomized, multicenter, open-label, Phase 3 study evaluating the efficacy and safety of T-DXd versus RAM + PTX in patients with HER2+ unresectable/metastatic gastric or gastroesophageal junction adenocarcinoma in this second-line setting.

Methods: After biopsy-confirmed HER2+ status (IHC 3+ or IHC 2+/ISH+), patients were randomized 1:1 to T-DXd 6.4 mg/kg or RAM + PTX. The primary endpoint was overall survival (OS). OS between the two arms was compared by a log-rank test stratified using randomization factors. Secondary endpoints, as assessed by the investigator, include progression-free survival (PFS), confirmed objective response rate (cORR), disease control rate (DCR), and safety.

Results: At data cutoff (October 24, 2024), 494 pts were assigned (T-DXd, n = 246; RAM + PTX, n = 248). Based on 266 OS events observed (information fraction = 78.5%), efficacy superiority was achieved (2-sided $P < 0.0228$). Median (m) (95% CI) OS follow-up was 16.8 mo (14.0-20.0) for T-DXd and 14.4 mo (13.1-19.7) for RAM + PTX. mOS (95% CI) was 14.7 mo (12.1-16.6) for T-DXd vs 11.4 mo (9.9-
15.5) for RAM + PTX (hazard ratio [HR], 0.70; $P = 0.0044$). Additional efficacy data are in the Table. Median (range) treatment duration was 5.4 mo (0.7-30.3) with T-DXd and 4.6 mo (0.9-34.9) with RAM + PTX. Treatment-emergent adverse events (TEAEs) were reported in 244/244 (100%) patients with T-DXd vs 228/233 patients (97.9%) with RAM + PTX, respectively; 68.0% vs 73.8% were grade (G) ≥3. Serious TEAEs with T-DXd vs. RAM + PTX occurred in 41.0% versus. 43.3% of patients experienced TEAEs associated with drug discontinuation, which occurred in 14.3% of patients compared to 17.2% of patients. Independently adjudicated drug-related interstitial lung disease/pneumonitis occurred in 34 pts (13.9%) with T-DXd (1 G3, 0 G4/5) vs 3 pts (1.3%) with RAM + PTX (2 G3, 1 G5).

Conclusions: T-DXd showed statistically significant and clinically meaningful improvement in OS over RAM + PTX in patients with HER2+ unresectable/metastatic GC/GEJA, reinforcing its use as a second-line standard of care. The safety profile of T-DXd 6.4 mg/kg was consistent with the known safety profile of T-DXd in GC/GEJA, with no new safety signals.

Track/Subcategory: Gastrointestinal Cancer—Colorectal and Anal: Colorectal Cancer–Local-Regional Disease

Abstract ID: LBA1

Session Type: Plenary Session

Title: Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III deficient DNA mismatch repair (dMMR) colon cancer (Alliance A021502; ATOMIC). Presenter Name: Frank Sinicrope

Abstract Text: Background: Standard adjuvant chemotherapy of stage III colon cancer consists of a fluoropyrimidine plus oxaliplatin. In patients (pts) with stage III colon cancer and deficient mismatch repair (dMMR), the benefit of an immune checkpoint inhibitor combined with adjuvant chemotherapy is unknown. The Phase III ATOMIC trial (NCT02912559) was conducted to determine whether atezolizumab (atezo), an anti-PD-L1 antibody, can improve patient outcomes when added to adjuvant 5-fluorouracil, leucovorin, plus oxaliplatin (mFOLFOX6) in patients with stage III dMMR tumors.

Methods: We conducted an NCI-sponsored, multicenter, randomized phase III trial in patients with surgically resected stage III dMMR colon adenocarcinoma (any T, N1, N2, M0). Pts, age ≥ 12 years (yr), were accrued at NCTN sites and the German AIO. Tumor dMMR was determined by local immunohistochemistry and centrally verified. Pts were randomized 1:1 to mFOLFOX6 plus atezo (840 mg IV q2 weeks) for 12 cycles (6 months)[mo] followed by atezo monotherapy for 13 cycles (12 mo total) versus mFOLFOX6 alone for 12 cycles. Randomization stratification factors were N-stage.

(N1/N1c vs N2), T-stage (T1-T3 vs T4) and site (proximal vs distal). The primary endpoint was disease-free survival (DFS); secondary endpoints included overall survival and adverse event (AE) profile, as assessed by the Common Terminology Criteria for Adverse Events (CTCAE) and the Patient-Reported Outcome-CTCAE (PRO-CTCAE) scales. Primary efficacy analysis was done in the intent-to-treat population; DFS was compared by arm (stratified log-rank test). Hazard ratio (HR) and 95% confidence interval (CI) were calculated using a stratified Cox model; 3-year DFS was determined by the Kaplan-Meier method. Among 700 pts., 165 DFS events with two interim analyses (50%, 75% of events) yielded 90% power to detect HR 0.6 (3-yr DFS 75% vs. 84.2%) assuming exponential survival and 1-sided alpha (0.025).

Results: From 9/2017 to 1/2023, 712 pts were randomized (1 pediatric) to either atezo plus mFOLFOX6 (n= 355; atezo arm) or mFOLFOX6 (n= 357). Median patient age was 64 years. 55.1% were female. Among tumors, 83.8% were proximal, 46.1% were classified as clinical low risk (T1-3N1), and 53.9% were classified as high risk (T4 and/or N2). At the second interim analysis, the median patient follow-up was 37.2 months (interquartile range, 24.2 to 55.5), and 124 DFS events were observed. Three-year DFS was 86.4 % (95% CI, 81.8 to 89.9) in the atezo arm and
76.6 % (95% CI, 71.3 to 81.0) in the mFOLFOX6 arm (HR, 0.50; 95% CI, 0.35 to 0.72). Stratified log-rank p-value was <0.0001, crossing the pre-specified efficacy boundary of 0.009. Efficacy for the atezo arm was consistent across subgroups, including patients over 70 years and low- and high-risk groups. Treatment-related≥ grade 3 AEs occurred in 71.7 % of pts in the atezo arm vs 62.1 % in the mFOLFOX6 arm.

Conclusion: The addition of atezolizumab to mFOLFOX6 significantly improved DFS and should be considered the new adjuvant standard of care for patients with dMMR stage III colon cancer.
Support: U10CA180821, U10CA180882, U24CA196171; Genentech, a member of the Roche group; https://acknowledgments.alliancefound.org

Track/Subcategory: Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary: Esophageal or Gastric Cancer - Local-Regional Disease

Abstract ID: 4000

Session Type: Oral Abstract Session

Title: Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): First results of overall survival (OS) from CheckMate 577.

Presenter Name: Ronan Kelly

Abstract Text: Background: At 24.4-month (mo) median follow-up, adjuvant nivolumab demonstrated a statistically significant and clinically meaningful improvement in disease-free survival (DFS) vs placebo with a well-tolerated safety profile in patients (pts) with resected EC/GEJC with residual pathologic disease following neoadjuvant CRT and surgery in the primary analysis from the global, phase 3 CheckMate 577 study (NCT02743494). We report the final analysis of the hierarchically tested secondary endpoint of OS, along with a longer follow-up of DFS.

Methods: Adults with resected (R0) stage II/III EC/GEJC who received neoadjuvant CRT and had residual pathologic disease were randomized 2:1 to nivolumab 240 mg or placebo Q2W for 16 weeks, followed by nivolumab 480 mg or placebo Q4W. Maximum treatment duration was 1 year. The primary endpoint was DFS. OS was a secondary endpoint, and exploration endpoints included safety, distant metastasis-free survival (DMFS), and progression-free survival on subsequent systemic therapy (PFS2).

Results: 794 pts were randomized (nivolumab, n = 532; placebo, n = 262). With a median follow-up of

78.3 (range, 60.1–96.6) mo, adjuvant nivolumab continued to show DFS benefit vs placebo (HR 0.76 [95% CI 0.63–0.91]; Table). Median OS was numerically longer with nivolumab compared to placebo (51.7 vs 35.3 months), although the difference was not statistically significant (HR 0.85 [95% CI 0.70–1.04]; *P* = 0.1064; Table). OS rates at 3 and 5 years with nivolumab versus placebo were 57% versus 50% and 46% versus 41%, respectively. OS subgroup analyses will be presented. Clinically meaningful improvement in DMFS with nivolumab vs placebo was maintained (Table). PFS2 favored nivolumab vs placebo (HR 0.81 [95% CI 0.67–0.98]). In the nivolumab group, 46% of patients received subsequent therapy, compared to 60% in the placebo group; 5% received subsequent immunotherapy, compared to 15% in the placebo group. No new safety signals were identified.

Conclusions: Adjuvant nivolumab demonstrated sustained long-term DFS benefit and numerical improvement in OS vs placebo in patients with resected EC/GEJC and residual pathologic disease following neoadjuvant CRT. The safety profile of adjuvant nivolumab remained well-tolerated with longer follow-up. These results further support the use of adjuvant nivolumab in this patient population.

Track/Subcategory: Gastrointestinal Cancer—Colorectal and Anal: Colorectal Cancer–Advanced Disease

Abstract ID: 3505

Session Type: Oral Abstract Session

Title: Perioperative systemic therapy for resectable colorectal peritoneal metastases: Multicenter

randomized phase 3 trial (CAIRO6). Presenter Name: Ignace De Hingh Abstract Text:

Background: In patients with resectable colorectal peritoneal metastases who qualify for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC), there is a lack of prospective data comparing the efficacy of perioperative systemic therapy with CRS-HIPEC alone.

Methods: In this multicenter phase 3 superiority trial, patients with resectable colorectal peritoneal metastases without extraperitoneal metastases who did not receive systemic therapy within six months before enrollment were randomly assigned (1:1) to receive perioperative CAPOX, FOLFOX, or FOLFIRI with neoadjuvant addition of bevacizumab (perioperative systemic therapy group) or CRS- HIPEC alone (surgery alone group). The primary outcome was overall survival. Key secondary outcomes were progression-free survival and 90-day significant postoperative morbidity and mortality. The trial needed 179 patients in each arm to detect a superior 3-year overall survival of 65% in the perioperative systemic therapy group versus 50% in the surgery alone group (corresponding hazard ratio [HR] for death 0.62) with 80% power, 5% drop-out, and a two-sided log-rank test of $p<0.05$. The primary overall survival analysis was done after 171 events (88% power).

Results: Of 358 randomized patients, 351 were eligible for primary analysis: 173 in the perioperative systemic therapy group and 178 in the surgery alone group. At a median follow-up of 41 months, median and 3-year overall survival were 44 months and 54% in the perioperative systemic therapy group and 39 months and 53% in the surgery alone group, respectively (HR for death 0.85, 95% CI 0.62-1.15, p=0.28). Median and 3-year progression-free survival rates were 13.5 months and 20% in the perioperative systemic therapy group, and 7.0 months and 5% in the surgery-alone group, respectively (HR for progression or death, 0.51; 95% CI, 0.41-0.65). In the per-protocol population of 292 patients who underwent macroscopic complete CRS-HIPEC, median and 3-year overall survival were 54 months and 64% in the perioperative systemic therapy group (138 patients) and 45 months and 59% in the surgery alone group (154 patients), respectively (HR for death 0.73, 95% CI 0.51-1.05). Ninety-day major postoperative morbidity rates were 36% in the perioperative systemic therapy group and 26% in the surgery alone group, with a 90-day postoperative mortality of 1% in both groups.

Conclusions: Among patients with resectable colorectal peritoneal metastases, perioperative systemic therapy did not result in superior overall survival as compared to CRS-HIPEC alone.

Track/Subcategory: Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary: Esophageal or Gastric Cancer - Advanced/Metastatic Disease

Abstract ID: LBA5

Session Type: Plenary Session

Title: Event-free survival (EFS) in MATTERHORN: A randomized, phase 3 study of durvalumab plus five fluorouracil, leucovorin, oxaliplatin, and docetaxel chemotherapy (FLOT) in resectable colon gastric/gastroesophageal junction cancer (GC/GEJC).

Presenter Name: Yelena Janjigian

Abstract Text: Background: FLOT is a perioperative standard of care (SoC) in resectable colon GC/GEJC, yet recurrence rates remain high. Immune checkpoint inhibitors are approved in combination with chemotherapy in metastatic GC/GEJC, but not in the perioperative setting. The randomized, double-blind, global, Phase 3 MATTERHORN study (NCT04592913) assesses the combination of perioperative durvalumab (D) + FLOT vs placebo (P) + FLOT in participants (pts) with locally advanced, resectable GC/GEJC. The primary endpoint is EFS. Pathological complete response (pCR) and overall survival (OS) are key secondary endpoints. The trial previously showed a statistically significant gain in pCR for D + FLOT. Here, we report efficacy and safety from pre-planned interim analysis 2.

Methods: Pts aged ≥18 years with histologically confirmed, resectable (Stage II–IVa per American Joint Committee on Cancer 8th edition) untreated G/GEJ adenocarcinoma were randomized 1:1 to D 1500 mg or P every 4 weeks (Q4W) on Day 1 + FLOT on Days 1 and 15 for four cycles (2 cycles each neoadjuvant/adjuvant), followed by D 1500 mg or P on Day 1 Q4W for 10 cycles. Asia stratified pts vs non-Asia, clinical lymph node status (positive vs negative), and programmed cell death ligand-1 Tumor Area Positivity score (≥1% vs <1%). The data cutoff was December 20, 2024. EFS (time from randomization to progression, local or distant recurrence, or death) superiority for D + FLOT vs P + FLOT was assessed in all randomized pts by a stratified log-rank test (2-sided significance level threshold: 0.0239) on data according to RECIST v1.1 per BICR and/or locally by pathology testing.

Results: In total, 948 pts were randomized to receive D + FLOT (n=474) or P + FLOT (n=474); median

(m) follow-up duration was 31.5 months (mo). Demographic/baseline characteristics were generally similar across treatment arms. D + FLOT demonstrated a statistically significant improvement in EFS compared to P + FLOT (hazard ratio [HR] 0.71; 95% confidence interval [CI], 0.58–0.86; p < 0.001), with mEFS not reached (NR) with D + FLOT versus 32.8 months with P + FLOT. The 24-mo EFS rate was higher for D + FLOT vs P + FLOT (Table). mOS was NR for D + FLOT vs 47.2 mo for P + FLOT (HR 0.78; 95% CI, 0.62–

0.97; p=0.025; 33.9% maturity) and will be formally assessed at the final analysis. Maximum Grade 3 or 4 adverse event rates were similar between treatment arms; D + FLOT did not delay surgery or initiation of adjuvant therapy vs P + FLOT.

Conclusion: D + FLOT demonstrated a statistically significant improvement in EFS compared to P + FLOT in patients with resectable GC/GEJC, with an encouraging OS trend. These results support D + FLOT as a potential new global SoC for resectable GC/GEJC.

Track/Subcategory: Gastrointestinal Cancer—Gastroesophageal, Pancreatic, and Hepatobiliary: Pancreatic Cancer - Local-Regional Disease

Abstract ID: LBA4005

Session Type: Oral Abstract Session

Title: PANOVA-3: Phase 3 study of tumor treating fields (TTFields) with gemcitabine and nab-paclitaxel for locally advanced pancreatic ductal adenocarcinoma (LA-PAC).

Presenter Name: Vincent Picozzi

Abstract Text:

Background: To date, no phase 3 clinical trial has demonstrated an overall survival (OS) benefit in patients with locally advanced pancreatic adenocarcinoma (LA-PAC). TTFields are electric fields that disrupt the division of cancer cells. TTFields therapy is approved for glioblastoma, pleural mesothelioma, and metastatic non-small cell lung cancer. A phase 2 trial in PAC demonstrated the safety and preliminary efficacy of TTFields therapy with gemcitabine with or without nab-paclitaxel. We report final data from PANOVA-3 (NCT03377491), the most significant global, phase 3, randomized, open-label trial in LA-PAC to date.

Methods: Adult patients with newly diagnosed unresectable LA-PAC were randomized 1:1 to receive TTFields therapy (150 kHz) with gemcitabine/nab-paclitaxel (Gapp) or GnP. The primary endpoint was OS. Secondary endpoints included progression-free survival (PFS), local PFS, objective response rate (ORR), and pain-free survival. Distant PFS (metastases beyond the pancreas and regional lymph nodes) was assessed post hoc. Survival data were compared using the Kaplan-Meier method and a log-rank test.

Results: 571 patients were randomized. Baseline characteristics were generally well-balanced between the study arms. OS was significantly longer with TTFields/GnP than with GnP (median 16.2 [95% CI: 15.0, 18.0] vs 14.2 months [95% CI: 12.8, 15.4]; HR 0.82 [95% CI: 0.68, 0.99], p=0.039). One-year survival
rate was also significantly improved with TTFields/GnP vs GnP (68.1% [95% CI: 62.0-73.5] vs 60.2% [95% CI: 54.2-65.7], p=0.029). There was no significant difference in PFS or local PFS between arms. Pain-free survival was significantly longer with TTFields/GnP vs GnP (median 15.2 [95% CI: 10.3, 22.8] vs 9.1 months [95% CI: 7.4, 12.7]; HR 0.74 [95% CI: 0.56, 0.97], p=0.027). Post-hoc analysis showed
significant distant PFS benefit (median 13.9 [95% CI: 12.2, 16.8] vs 11.5 months [95% CI: 10.4, 12.9], HR 0.74 [95% CI: 0.57, 0.96], p=0.022) with TTFields/GnP vs GnP. ORR was similar between arms (36.1% [95% CI: 30.0, 42.4] vs 30.0% [95% CI: 24.3, 36.2], p=0.094). 97.8% and 98.9% of patients who
received TTFields/GnP and GnP, respectively, had adverse events (AEs), and 88.6% and 84.3% had grade
≥3 AEs. The most frequent grade ≥3 AEs were neutropenia (47.8% and 47.6%) and anemia (21.9% and 22.3%). 81% of patients receiving TTFields/GnP had device-related AEs, mostly grade 1/2 skin AEs, e.g., dermatitis (27.7%), rash (17.5%), and pruritus (15.0%); grade 3 and grade 4 device-related AEs occurred in 9.1% and 0.4% of patients, respectively.

Conclusions: PANOVA-3 is the most significant phase 3 trial exclusively performed in patients with LA-PAC and the first to show a statistically significant OS benefit. With no additive systemic toxicity and a statistically significant pain-free survival benefit, TTFields therapy is a potential new standard treatment for LA-PAC.

Track/Subcategory: Gastrointestinal Cancer—Colorectal and Anal: Colorectal Cancer–Advanced Disease

Abstract ID: LBA3500

Session Type: Oral Abstract Session

Title: First-line encorafenib + cetuximab + mFOLFOX6 in BRAF V600E-mutant metastatic colorectal cancer (BREAKWATER): Progression-free survival and updated overall survival analyses.

Presenter Name: Elena Elez

Abstract Text:

Background:

BREAKWATER (NCT04607421) is an open-label, global, randomized, phase 3 study evaluating first-line (1L) encorafenib + cetuximab (EC) ± chemotherapy (chemo) vs standard of care (SOC; chemo ± bevacizumab) in BRAF V600E-mutant metastatic colorectal cancer (mCRC). The study previously met one of its dual primary endpoints (EPs), demonstrating clinically meaningful and statistically significant improvement in confirmed objective response rate (ORR) by anonymous independent central review (BICR) in the ORR subset. These results served as the basis for the FDA's accelerated approval of EC+mFOLFOX6 for BRAF V600E-mutant metastatic colorectal cancer (mCRC), including in the first-line setting, under Project Frontrunner. Here, we report the primary analysis of progression-free survival (PFS) by BICR, updated interim analysis of OS, updated safety, and other analyses.

Methods: Eligible patients (pts) with untreated BRAF V600E-mutant mCRC were randomized 1:1:1 to receive EC, EC+mFOLFOX6, or SOC; EC arm enrollment was closed after a protocol amendment. Dual primary EPs: ORR and PFS by BICR (EC+mFOLFOX6 vs SOC); key secondary EP: OS (EC+mFOLFOX6 vs SOC).

Results: 637 pts were randomized to EC, EC+mFOLFOX6, or SOC. Baseline demographics and disease characteristics were generally balanced between arms. EC+mFOLFOX6 (data cutoff: Jan 6, 2025) demonstrated a clinically meaningful and statistically significant PFS improvement vs SOC, meeting the other dual primary EP; HR=0.53 (95% CI 0.407, 0.677; P<0.0001); median PFS 12.8 vs 7.1 mo. OS was clinically meaningful and statistically significant vs SOC; HR=0.49 (95% CI 0.375, 0.632; P<0.0001); median OS 30.3 vs 15.1 mo. Median PFS and OS in the EC arm were 6.8 and 19.5 months. These data and response data for all random patients are shown on the table. Serious treatment-emergent adverse events occurred in 30%, 46%, and 39% of patients in the safety analysis set. Safety was consistent with that known to each agent.

Conclusions: BREAKWATER demonstrated clinically meaningful and statistically significant improvements in PFS and OS compared to SOC, with EC+mFOLFOX6, and manageable toxicities. EC+mFOLFOX6 is potentially practice-changing as the new SOC.

Track/Subcategory: Gastrointestinal Cancer—Colorectal and Anal: Colorectal Cancer–Local- Regional Disease

Abstract ID: LBA3510

Session Type: Clinical Science Symposium

Title: A randomized phase III trial of the impact of a structured exercise program on disease-free survival (DFS) in stage 3 or high-risk stage 2 colon cancer: Canadian Cancer Trials Group (CCTG) CO.21 (CHALLENGE).

Presenter Name: Christopher Booth

Abstract Text: Background: Multiple observational studies have reported that post-diagnosis physical activity (PA) is associated with reduced recurrence rates in early-stage colon cancer, but epidemiologic data are limited by confounding and reporting bias. CCTG CO.21 was designed to test the hypothesis that a meaningful increase in recreational PA after adjuvant therapy is achievable and will improve DFS in stage 3 or high-risk stage 2 colon cancer.

Methods: CCTG CO.21 enrolled patients at 55 sites in 6 countries. Patients with resected stage 3 or high-risk stage 2 colon cancer who had received adjuvant chemotherapy were randomized to a structured exercise program (SEP) or health education material (HEM). HEM participants received education materials promoting PA and healthy nutrition in addition to standard surveillance. SEP participants worked with a PA consultant who delivered an exercise intervention using behavior change methodology for over 3 years. The SEP goal was to increase recreational PA by at least 10 MET-hours/week from baseline during the first 6 months and sustain this for 3 years. Participants chose the type, frequency, intensity, and duration of aerobic exercise. The primary endpoint is DFS compared by a stratified log-rank test performed on an intention-to-treat basis. Secondary endpoints include overall survival (OS) and patient-reported outcomes (PROs), with the SF-36 physical function scale serving as the primary PRO.

Results: Between 2009 and 2024, 889 participants were randomized to SEP (n=445) or HEM (n=444); 51% female, median age 61 years, 90% stage 3 disease. Compared to HEM, SEP resulted in statistically significant improvements in recreational PA, predicted VO2max, and 6-minute walk distance, all maintained over the 3-year intervention period. With a median follow-up of 7.9 years, 224 DFS events (93 in SEP and 131 in HEM) and 107 deaths (41 in SEP and 66 in HEM) were observed. 5-year DFS was 80% in SEP and 74% in HEM (HR 0.72; 95% CI 0.55-0.94; p=0.017). 8-year OS was 90% in SEP and
83% in HEM (HR=0.63; 95% CI=0.43-0.94; p=0.022). SF-36 physical function was substantially improved with SEP at 6 months (mean change scores: 7.42 vs. 1.10, $p < 0.001$) and remained sustained to 24 months. In the safety analysis, 19% (79/428) of patients on SEP reported any grade of musculoskeletal adverse event (MSK AE) during the study, compared to 12% (50/433) on HEM. 10% (8/79) of MSK AE on SEP were considered to be related to participation in the PA program.

Conclusions: In patients with stage 3 and high-risk stage 2 colon cancer, a 3-year structured exercise program initiated shortly after completion of adjuvant chemotherapy improves DFS, OS, patient-reported physical functioning, and health-related fitness. Health systems should incorporate structured exercise programs as standard of care for this patient population.

Track/Subcategory: Quality Care/Health Services Research: Real-World Data/Outcomes
Abstract ID: 11005
Session Type: Oral Abstract Session
Title: Real-world social determinants of health (SDOH) and outcomes of early-onset colorectal cancer (EO-CRC): An analysis of an extensive, nationally representative US community oncology network.
Presenter Name: Jessica Paulus
Abstract Text: Background: The rise of EO-CRC in individuals under the age of 50 presents a significant public health challenge, as these patients may encounter unique barriers to both screening and treatment. Understanding the drivers and implications of EO-CRC is crucial, and real-world data (RWD) can serve as a valuable tool, offering insights into evolving diagnostic, utilization, and practice landscapes, along with robust information on the social determinants of disease burden. Building on existing disparity concerns, this study leveraged RWD from an extensive, nationally diverse network of US community oncology practices to describe the SDOH and outcomes of patients with EO-CRC.
Methods: This retrospective observational cohort study examined adult CRC patients within The US Oncology Network and non-Network practices, encompassing over 2,500 community-based providers treating more than 1.4 million patients annually. All patients diagnosed with CRC between 2000 and 2024 were included; patients were categorized as EO-CRC if they were < 50 years at first diagnosis and average-onset (AO)-CRC otherwise. Patient characteristics were sourced from iKnowMed, an oncology-specific electronic health record system, and descriptively summarized. Overall survival (OS) was assessed from the time of diagnosis using the Kaplan-Meier method.
Results: A total of 104,281 patients were identified, including 14,611 (14%; median age: 44 years) with EO-CRC and 89,670 (86%; median age: 67 years) with AO-CRC. Patients in the EO-CRC cohort were more likely to be Black (11% vs. 8%), American Indian or Alaska Native race (1.3% vs. 0.9%), of a documented race other than White (20% vs. 15%), and of Hispanic/Latino ethnicity (11% vs. 8%) versus the AO-CRC cohort. Few of the EO-CRC (11%) and AO-CRC (10%) patients were current smokers at the time of diagnosis. More than one-third of the EO-CRC group was obese (36%), slightly higher than in the AO-CRC (31%). EO patients were more commonly located in urban areas (69% vs. 63% of AO patients). Among 2,810 patients with Distress Thermometer data, EO-CRC patients were more likely to report high or moderate distress (29% vs. 22%) and less likely to report low distress (71% vs. 78%). 5-year OS probability was 72% (95% CI: 71-73) for EO-CRC and 64% (95% CI: 63-64) for AO-CRC.
Conclusions: In one of the largest cohorts of patients with EO-CRC to date, this study confirmed that EO-CRC is an emerging concern within the US community oncology setting, particularly regarding
heightened disparities in race, ethnicity, and lifestyle factors. EO patients may face unique burdens related to timely screening and diagnosis, necessitating tailored and cross-disciplinary approaches to their care, and warranting additional investigation into social and clinical drivers of survival outcomes to improve long-term prognosis.

Track/Subcategory: Central Nervous System Tumors: Brain Metastases

Abstract ID: 2011

Session Type: Clinical Science Symposium

Title: Stereotactic radiation versus hippocampal avoiding whole brain radiation in patients with 5-20 brain metastases: A multicenter, phase 3 randomized trial.

Presenter Name: Ayal Aizer

Abstract Text:

Background: Radiation therapy forms the mainstay of management for patients with brain metastases. Published randomized trials have found an improved quality of life with stereotactic radiation (SRS/SRT) compared to whole brain radiation (WBRT) in patients with ≤ 4 brain metastases; comparative trials in patients with >4 brain metastases are lacking. In addition, prior randomized trials have demonstrated the superiority of hippocampal avoidance WBRT (HA-WBRT) over traditional WBRT, but no study has compared SRS/SRT to HA-WBRT. Accordingly, we conducted a multicenter, phase 3 randomized trial comparing SRS/SRT to HA-WBRT in patients with 5-20 brain metastases.

Methods: Eligible patients aged 18-80 with 5-20 brain metastases secondary to a solid primary other than small cell lung cancer, were naïve to prior brain-directed radiation, and lacked leptomeningeal disease. The primary endpoint was the average of patient-reported symptom severity and interference over the first six months post-baseline relative to baseline, using the MD Anderson Symptom Inventory– Brain Tumor (MDASI-BT) module, a validated instrument assessing 22 symptoms and 6 interference measures integral to quality of life, each scored 0-10 with higher scores indicating greater symptomatology/interference in function. The target effect size was a symptom severity of 0.70, corresponding to 50% of the observed difference between patients with a good (90-100) versus poor (≤80) Karnofsky performance status; with 80% power and a two-sided alpha of 0.05, 196 patients were required.

Results: Between 4/2017 and 5/2024, 196 patients enrolled, 98 in each arm. The median number of brain metastases was 14 (IQR, 11-18); 25% of patients had undergone prior neurosurgical resection. Baseline mean MDASI-BT symptom severity scores were 2.2 (SRS/SRT arm) and 1.9 (HA-WBRT arm), p=0.20; respective interference scores were 3.5 and 3.2 (p=0.40). The average weighted post-baseline severity and interference scores relative to baseline indicated lower symptomatology/inference in the SRS/SRT arm, meeting the primary endpoint of the study (difference between SRS/SRT and HA-WBRT: -1.06, $p < 0.001$). Averaged post-baseline symptom severity scores minus baseline were -0.03 and 0.59 in the SRS/SRT and HA-WBRT arms, respectively (difference -0.62, with lower symptom severity in the SRS/SRT arm, $p<0.001$); respective interference estimates were -0.62 and 0.89 (difference -1.50, with lower interference in the SRS/SRT arm, $p<0.001$). Median survival was 8.3 and 8.5 months in the SRS/SRT and HA-WBRT arms, respectively (p=0.30).

Conclusions: The Phase 3 randomized trial indicates that patients with 5-20 brain metastases experience fewer symptoms and less functional interference after SRS/SRT compared to HA-WBRT, without compromising survival, which supports SRS/SRT as the standard of care in this population.

Track/Subcategory: Gynecologic Cancer: Other Gynecologic Cancer

Abstract ID: 5511

Session Type: Rapid Oral Abstract Session

Title: Primary results of a phase 2 study of cisplatin-sensitized radiation therapy and pembrolizumab for unresectable vulvar cancer.

Presenter Name: Oladapo Yeku

Abstract Text: Background: Locally advanced vulvar cancer is a rare but lethal disease, more common in underserved populations. In contrast to other gynecologic cancers, the incidence and mortality of this disease have increased over the past decade. Treatment for locoregional disease involves surgery and chemoradiation, while systemic chemotherapy and immunotherapy are reserved for patients with distant metastases. Cisplatin and radiation (cis-RT) have been reported to have anti-tumor immunomodulatory properties in addition to their cytotoxic effects. We hypothesized that immune checkpoint inhibitors could synergize with chemotherapy and improve outcomes for this disease.

Methods: In this single-arm phase II trial (NCT04430699), patients with primary unresectable, incompletely resected, recurrent, or metastatic squamous cell carcinoma of the vulva undergoing RT were eligible. Patients who had received prior chemotherapy were also eligible. Patients received cisplatin 40 mg/m2 weekly concurrently with intensity modulated (IM) RT, and pembrolizumab 200 mg was administered every three weeks for a total of 12 cycles. The primary endpoint was overall response rate (ORR), and the secondary objective was six-month recurrence-free survival (RFS). PD-L1 expression and T-cell receptor beta clonality were assessed, along with other translational endpoints. An ORR ≥ 60% was considered worthy of further study.

Results: The study closed to accrual on October 11, 2024, after 24 patients had enrolled. Twenty-two patients (92%) had primary unresectable diseases, and two (8%) had recurrent diseases. All patients were treated with definitive intent RT, with a median dose to the primary of 68.4 Gy (range, 26.2, 70.2) and 45 Gy to pelvic, inguinal, and vulva CTV (range, 21.6, 50.4). One patient stopped RT early due to disease progression. At the data cutoff on January 22, 2025, the ORR (CR+PR) was 75%. The 6-month RFS rate was 70% (95% CI: 48 – 85%). The median PFS has not been reached. Any grade adverse events (AE) occurred in all patients. Grade (G) 3 or 4 AEs occurred in 19 (78.6%) patients, most of which were related to cisplatin.

The most common treatment-emergent adverse events were nausea (88%), diarrhea (71%), fatigue (67%), and anemia (50%). There were six serious AEs, only 2 of which were related to the treatment (both AKI).

Most immune-related toxicities were grade 1/2, except for grade 3 diarrhea (4%). Immune-mediated colitis led to discontinuation in 1 patient (4%). PD-L1 (CPS ≥ 1) was positive in all patients. There was an increase in mean TCR clonality after two cycles of treatment.

Conclusions: The study met its primary endpoint. Concurrent treatment with chemoradiation and pembrolizumab improved ORR and 6-month RFS in vulvar cancer. The addition of pembrolizumab did not lead to any unexpected AEs. Chemoradiation with pembrolizumab could be considered in patients with primary unresectable or incompletely resected vulvar cancer.

Track/Subcategory: Melanoma/Skin Cancers: Advanced/Metastatic Disease

Abstract ID: 9506

Session Type: Oral Abstract Session

Title: DREAMseq: A phase III trial of treatment sequences in BRAFV600-mutant (m) metastatic melanoma (MM)Final clinical results.

Presenter Name: Michael Atkins

Abstract Text:

Background: The DREAMseq trial compared efficacy and toxicity of the sequence of nivolumab/ipilimumab (N/I) followed by dabrafenib/trametinib (D/T) to the reverse sequence in patients (pts) with BRAFV600m MM. In 9/2021, with 59% of patients 2+ years (yr) from enrollment, the DSMC and NCI CTEP recommended halting the trial and releasing data that showed a 20% difference in 2-yr OS (72% vs 52%) favoring the N/I first sequence. Here, we update the data to the median ~5 years from entry and report secondary analyses, including time to CNS relapse and percent unconfirmed responses (ucOR).

Methods: Eligible patients with untreated BRAFV600m MM were stratified by ECOG Performance Status 0 or 1 and LDH and randomized 1:1 to Step 1 treatment with either N/I (Arm A) or D/T (Arm B) and at disease progression (PD) were eligible for Step 2 alternate therapy, D/T (Arm C) or N/I (Arm D). Imaging was done at baseline and every 12 weeks (wks). The primary endpoint was 2-year OS. Secondary endpoints included: 3-yr OS, efficacy (PFS, ORR, and DOR), and toxicity.

Results: 267 out of 300 proposed patients were enrolled (135 Arm A; 132 Arm B). As of 7/23/24, median follow-up of 58 months (mo) (range:0-101), 30 pts had switched to Arm C and 52 to Arm D. 2-yr OS for those assigned to Arm A was 68.3% (95% CI: 60.8-76.9) and for Arm B 54.1% (95% CI: 46.1-63.7%) (log-rank $p < 0.01$). 3 and 5-yr OS by sequence and 2, 3, and 5-yr PFS for initial arms, and median PFS, ORR, and DOR for all arms are shown in the Table. There were 125 deaths (Arm A-C:47; Arm B-D:78). 76% of responders in Arm A and 24% in Arm B remain in response. At 12 wks, 59 pts on Arm A and 85 on Arm B had RECIST PR, of which 10 (16.9%) and 35 (41.2%), respectively, were ucOR by week 24. CNS was the first site of PD in 24 pts on Arm A and 44 pts on Arm B. Median time to CNS PD: Arm A 12.2 mo (0.7-46.5); Arm B 8.4 mo (1.3-78.1) ($p< 0.01$).

Conclusions: At nearly 5-year median f/up, the N/I first treatment sequence continues to show superior efficacy over the D/T first sequence for treatment-naïve BRAFV600m MM with a near doubling (30% absolute difference) in 5-year OS and a tripling of 5-year PFS. While confirmed ORR was similar between Arms A and B, shorter DOR and more uCR and more and earlier CNS PD were observed with initial D/T, contributing to its worse efficacy.

Track/Subcategory: Melanoma/Skin Cancers: Advanced/Metastatic Disease

Abstract ID: LBA9507

Session Type: Oral Abstract Session

Title: A randomized phase 2 trial of encorafenib + binimetinib + nivolumab vs ipilimumab + nivolumab in BRAFV600-mutant melanoma brain metastases: SWOG S2000 (NCT04511013).

Presenter Name: Zeynep Eroglu

Abstract Text:

Background: While anti-PD-1 and anti-CTLA4 immunotherapies have efficacy in the treatment of patients (pts) with asymptomatic melanoma brain metastases (MBM), their effectiveness in pts with symptomatic MBM is minimal. In the Checkmate-204 trial of ipilimumab with nivolumab in MBM, the 6-month progression-free survival (PFS) rate was 19% with a median PFS of only 1.2 months in symptomatic pts. In the COMBI-MB study of BRAF/MEK inhibitors in MBM, median PFS was 5.5 months in symptomatic patients (n=17). A head-to-head approach comparing targeted and immunotherapy has not been tested; however, a combination of targeted and immunotherapy is feasible, as demonstrated by prior studies.

Methods: SWOG S2000 is a 1:1 randomized phase 2 trial exploring the efficacy of a front-line triplet regimen of BRAF/MEK inhibitors with anti-PD-1 monotherapy (encorafenib 450 mg qday + binimetinib 30 mg BID + nivolumab 480 mg IV q4w) versus ipilimumab 3 mg/kg + nivolumab 1 mg/kg q3w in pts with symptomatic BRAF-mutant MBM. Pts were ≥18 years old, ECOG 0-2, and prior neoadjuvant or adjuvant anti-PD-1, CTLA-4, or BRAF/MEK inhibitors were permitted, but no systemic treatment in the metastatic setting. Steroids up to 8 mg of dexamethasone/day (or equivalent), leptomeningeal spread, and prior local therapy (radiation or surgery) for MBM were permitted, if there was at least one measurable, progressing MBM ≥ 0.5 cm. Disease assessments were performed at 6 and 12 weeks, and then every 12 weeks from treatment starts until progression. The primary objective was to compare PFS (intracranial + extracranial) per RECIST 1.1 between the arms.

Results: Between September 2020 and June 2024, 30 patients with symptomatic MBM were enrolled; 1 patient was ineligible. Thirteen (45%) received prior corticosteroids, and 14 pts (48%) received prior local therapy for MBM. The six-month PFS rate was 50% (95% CI, 23-72%) with enco/bini/nivo, compared to 29% (95% CI, 9-52%) with ipi/nivo. The study met its primary endpoint with a hazard ratio (HR) of 0.51 (95% CI 0.0 – 0.92), achieving a statistically significant one-sided p-value of 0.07, which is less than the pre-specified alpha of 0.10. Median PFS was 6.2 months (3.0- 20.4) with enco/bini/nivo, vs 1.4 months (0.7 - 13.8) with ipi/nivo. The overall response rate (PR + CR) was 57% (31-83%) with enco/bini/nivo versus 15% (10-15%) with ipi/nivo. With enco/bini/nivo, 69% of pts had grade 3-4 toxicity, and with ipi/nivo, 75% had grade 3-5 toxicity, with one death due to cardiac arrest.

Conclusions: S2000 is the first randomized trial in patients with symptomatic melanoma brain metastases. A first-line triplet regimen of enco/bini/nivo demonstrated a statistically significant improvement in PFS as compared to ipi/nivo, with an HR of 0.51. Both regimens also had toxicity rates consistent with their known profiles. In this difficult-to-treat patient population frequently requiring steroids, a triplet regimen may warrant further study.

Track/Subcategory: Melanoma/Skin Cancers: Advanced/Metastatic Disease

Abstract ID: 9515

Session Type: Rapid Oral Abstract Session

Title: Lifileucel in Patients with Advanced Melanoma: 5-Year Outcomes of the C-144-01 Study.

Presenter Name: Theresa Medina

Abstract Text:

Background: Lifileucel is a personalized, one-time tumor-derived autologous T-cell immunotherapy approved for the treatment of adult patients (pts) with advanced (unresectable or metastatic) melanoma previously treated with a programmed cell death-1 (PD-1)–blocking antibody, and, if *BRAF* V600 mutation–positive, a BRAF inhibitor with or without a MEK inhibitor. In the registrational C-144-01 study (NCT02360579), patients with advanced melanoma who received Lifileucel had an objective response rate (ORR) of 31.4%. Follow-up in therapeutic trials targeting refractory patients with refractory melanoma typically spans months rather than years due to lack of activity. Reflective of the durability of Lifileucel, we now report 5-year survival outcomes from the C-144-01 study.

Methods: C-144-01 (NCT02360579) is a phase 2, multicenter, multicohort, open-label study of Lifileucel. Eligible patients had advanced melanoma that had progressed on or after an immune checkpoint inhibitor and targeted therapy, where appropriate. Before Lifileucel infusion, patients underwent nonmyeloablative lymphodepletion (NMA-LD; cyclophosphamide, 60 mg/kg × 2 days plus fludarabine, 25 mg/m² × 5 days). Pts received cryopreserved Lifileucel followed by up to 6 doses of interleukin-2 (IL-2; 600,000 IU/kg every 8–12 hours). The primary endpoint was ORR assessed by an independent review committee (IRC) using RECIST v1.1. Key secondary endpoints were duration of response (DOR), overall survival (OS), and safety.

Results: Among patients who received Lifileucel (n = 153; median age, 56 years; range, 20–79 years), 54% were male. All patients had an Eastern Cooperative Oncology Group Performance Status of 0 or 1 and had previously received anti-PD-1/PD-1/PD-L1 therapy. Pts had a median of 3 prior lines of therapy (range, 1–9), and 55% were primary refractory to anti-PD-1/PD-1/PD-L1 therapy. At a median follow-up of 57.8 months, all patients have completed or discontinued the study, with 28 (18.3%) patients having completed the 5-year study follow-up. The ORR was 31.4% (complete response, 5.9%; partial response, 25.5%). Median DOR was 36.5 mo (95% confidence interval [CI]: 8.3–not reached), with 31.3% of responders completing the 5-year assessment with a sustained response. The median time to best response was 1.5 months (range, 1.3–30.4 months). Median OS was
13.9 mo (95% CI: 10.6–17.8); the 5-year OS rate was 19.7% (95% CI: 13.3–27.0). Treatment-emergent adverse events were consistent with known safety profiles of NMA-LD and IL-2. The extended follow-up revealed no new safety signals.

Conclusions: This 5-year analysis of the C-144-01 trial is the most extensive follow-up of the largest group of patients with melanoma treated with tumor-infiltrating lymphocytes in a single study. This study illustrates the continued durability of response and survival benefit of Lifileucel up to 5 years after a single administration, without any long-term safety concerns.

Track/Subcategory: Melanoma/Skin Cancers: Advanced/Metastatic Disease

Abstract ID: LBA9508

Session Type: Oral Abstract Session

Title: Comparison of 1 year versus a minimum of two years of anti-PD1-based immunotherapy as first-line
treatment for metastatic melanoma: Results of the DANTE phase III trial.

Presenter Name: Sarah Danson

Abstract Text:

Background: Optimal first-line therapy for patients with metastatic melanoma is an immunotherapy regimen containing an anti-PD1 antibody, regardless of tumour *BRAF* mutation status. Anti-PD1 antibodies are licensed for use until disease progression. Recurrence rarely occurs in responding patients after 2 years of treatment. The optimal duration of anti-PD1-based immunotherapy has not been established. Reduced treatment duration may reduce the risk of long-term side effects and generate cost savings for healthcare systems.

Methods: DANTE (ISRCTN15837212) was a UK academic multi-centre parallel group non-inferiority trial. Adults with unresectable stage III/IV melanoma receiving first-line anti-PD1 +/- anti-CTLA-4 antibody immunotherapy were eligible. Patients who were progression-free after 1 year of treatment were randomised (1:1) to stop treatment (with the option of restarting progression) or to continue therapy for at least two years in the absence of disease progression / unacceptable toxicity (control). The primary endpoint was progression-free survival (PFS) at one-year post-randomization. Secondary endpoints included quality of life, best objective response, overall survival, toxicity, and cost-effectiveness. A qualitative study explored patient acceptance of randomization. A follow-up at four years was planned for PFS, with secondary outcomes collected up to 18 months post-randomization. Assuming a 2-year PFS rate in the control arm of 86% and defining non-inferiority (NI) as a reduction in PFS of no more than 6%, a sample size of 1208 patients (604 per arm) was required (80% power, 5% significance, 5% drop-out). DANTE closed early due to slow patient enrolment. PFS was compared between arms using Cox's proportional hazards model, adjusting for stratification factors.

Results: Between September 2018 and March 2023, 415 patients were registered from 36 UK hospitals, and 166 patients (65.6% male, median age 74, *BRAF* mutant 25.9%) were randomised. Patient characteristics were broadly balanced. As of January 27, 2025, with a median follow-up of 29.1 months (IQR, 17.9-39.3 months), a total of 53 PFS events were observed: 18 in the control arm (15 progressions and three deaths) versus 35 in the stop arm (29 progressions and six deaths). PFS rates at 1-year were 87.6% in the control arm and 80.2% in the stop arm (HR 1.76; 90% CI 1.03-3.03), with an absolute difference of -7.4% and 90% two-sided CI -17.1-2.32, which is within the pre-defined NI margin of 6%. Analyses are ongoing; results for secondary endpoints will be presented at a later time.

Conclusions: DANTE is the largest prospective melanoma trial evaluating immunotherapy duration completed to date. Although the results suggest that stopping immunotherapy at 1 year was non-inferior compared to at least 2 years of treatment, the trial was underpowered due to its early closure. Continuing immunotherapy for at least 2 years should remain the standard treatment.

Track/Subcategory: Quality Care/Health Services Research: Real-World Data/Outcomes
Abstract ID: 11001

Session Type: Oral Abstract Session

Title: Outcomes of an electronic patient-reported outcomes (ePRO)–based symptom management program (eSyM): A cluster randomized trial.

Presenter Name: Michael Hassett

Abstract Text:

Background: Although ePROs have been shown to reduce resource utilization and improve outcomes among individuals with cancer, their adoption has not been widespread. We conducted a pragmatic type II hybrid effectiveness-implementation cluster randomized stepped-wedge trial of an ePRO-based, EHR-integrated symptom management program (eSyM) across six health systems. Here, we report the primary effectiveness outcome comparing patients treated before (control/not exposed) versus after (intervention/exposed) eSyM deployment.

Methods: Eligible patients were adults who started chemotherapy (CHEMO) or were discharged after surgery (SURG) for a suspected or confirmed GI, GYN, or thoracic cancer. The intervention included ePRO questionnaires based on PRO-CTCAE items, severe symptom alerts, self-management tip sheets, and communication support. Outcomes included having an emergency department (ED) visit or inpatient admission (INPT) within 30 and 90 days. Logistic regression models accounted for socio-demographic, clinical, calendar time, health system, and other factors. Secondary analyses stratified results by treatment and health system to assess for effect modification.

Results: From January 2018 to February 2023, the control and intervention conditions accrued 21,112 and 18,830 patients, respectively (median age: 62 vs. 65; female: 68% vs. 63%). Patient enrollment by health system ranged from 3,961 to 14,560. In the intervention cohort, 51% of patients used eSyM to report symptoms. Crude 30-day event rates for the control and intervention cohorts were 5.4% and 6.2% for ED, and 8.5% and 9.1% for INPT, respectively. Accounting for other factors, there were no significant differences in ED or INPT at 30 (Table) or 90 days. Among SURG patients, there were significantly greater odds of ED, but not INPT, for the intervention vs. control cohort. Results varied by health system, with evidence of higher, similar, and lower odds of the intervention compared to the control cohort.

Conclusions: The deployment of eSyM did not significantly reduce ED or INPT events. Only half of the exposed patients used eSyM to report symptoms. Prior analyses found lower odds of acute care utilization among patients who reported symptoms via eSyM; therefore, implementation and engagement barriers may have substantially impacted effectiveness outcomes. Heterogeneity of effect by health system and treatment suggests that healthcare structures, processes, and baseline performance influence the uptake and impact of ePRO-based symptom management systems.

Track/Subcategory: Quality Care/Health Services Research: Health Services Research

Abstract ID: 11003

Session Type: Oral Abstract Session

Title: Randomized trial of a supportive oncology care at home intervention for patients with cancer receiving curative treatment.

Presenter Name: Ryan Nipp

Abstract Text:

Background: Patients with cancer receiving curative treatment often endure substantial symptoms and utilize significant healthcare resources. Symptom monitoring interventions and hospital-at-home care models represent a promising approach for improving the outcomes of these patients.

Methods: We conducted a randomized trial of a Supportive Oncology Care at Home intervention versus usual care in adult patients receiving treatment with curative intent (chemotherapy and/or chemoradiation) for pancreatic, rectal, gastroesophageal, and head and neck cancer, as well as non-Hodgkin lymphoma, who resided in-state, within 50 miles of our hospital. Patients were randomized to receive the Supportive Oncology Care at Home intervention or usual care within two weeks of initiating therapy and remained on trial for up to 6 months. The intervention entailed: 1) remote monitoring of daily patient-reported symptoms, vital signs, and body weight; 2) a hospital-at-home care model for symptom assessment and management; and 3) structured communication with the oncology team. The primary outcome was the proportion of patients requiring inpatient hospital admission or emergency department (ED) visits during the study period. Secondary outcomes included urgent visits to the clinic, treatment delays, and longitudinal changes in monthly assessments of quality of life (QOL; Functional Assessment of Cancer Therapy-General), symptoms (Edmonton Symptom Assessment System [ESAS] and Hospital Anxiety and Depression Scale [HADS]), and daily activities (ADLs).

Results: We enrolled 50.8% (199/392) of potentially eligible patients. One patient withdrew consent, and two became ineligible following consent, resulting in 196 participants (median age, 65.8 [range, 21.1-92.0]; 39.8% female). The cancer types were as follows: 34.2% pancreatic, 27.0% head and neck (H&N), 16.3% lymphoma, 12.8% rectal, and 9.7% gastroesophageal. The proportion of patients requiring hospital admission or ED visit did not differ significantly between the intervention and usual care groups (37.1% v 35.7%, p=.87). Intervention participants were less likely to require an urgent visit (7.2% v 24.5%, p<.01), but there were no differences in rates of treatment delays >7 days (29.9% v 33.0%, p=.62). Compared to baseline assessments, intervention participants had greater improvement in ESAS symptoms (p<.01) and ADLs (p=.04) over time. QOL and HADS depression/anxiety symptoms did not differ longitudinally between groups.

Conclusions: Although this Supportive Oncology Care at Home intervention did not have a significant impact on rates of hospital admissions or ED visits, we found encouraging results for reducing urgent visits to the clinic and substantial improvement in symptom burden and ADLs, underscoring the potential utility of this novel care model for enhancing care delivery and outcomes for patients with cancer receiving curative treatment.

Track/Subcategory: Breast Cancer—Metastatic: Hormone Receptor-Positive

Abstract ID: LBA4

Session Type: Plenary Session

Title: Camizestrant + CDK4/6 inhibitor (CDK4/6i) for the treatment of emergent *ESR1* mutations during first-line (1L) endocrine-based therapy (ET) and ahead of disease progression in patients (pts) with HR+/HER2– advanced breast cancer (ABC): Phase 3, double-blind ctDNA-guided SERENA-6 trial.

Presenter Name: Nicholas Turner

Abstract Text: Background: *ESR1* mutations (*ESR1*m) constitutively activate the estrogen receptor (ER)

and are the most common mechanism of acquired resistance to aromatase inhibitor (AI) + CDK4/6i. Molecular monitoring by ctDNA analysis can detect the emergence of *ESR1*m during 1L AI + CDK4/6i. Camizestrant, the next-generation selective ER degrader (SERD) and complete ER antagonist, has shown anti-tumor activity in patients with and without detectable *ESR1 Mutations*. SERENA-6 is the first global registrational Phase 3 trial assessing a ctDNA-guided approach to detect the emergence of *ESR1*m during 1L AI + CDK4/6i to inform a switch in therapy ahead of disease progression.

Methods: Pts with HR+/HER2– ABC who had received ≥6 months of 1L AI (anastrozole/letrozole) + CDK4/6i (abemaciclib/palbociclib/ribociclib) were enrolled and had ctDNA tested for *ESR1*m every 2–3 months, coinciding with routine imaging. At *ESR1*m detection, patients without evidence of disease progression were randomized 1:1 to switch to camizestrant (75 mg) with continued CDK4/6i (type and dose maintained) plus placebo for AI, or to continue AI plus CDK4/6i plus placebo for camizestrant. The primary endpoint was investigator-assessed PFS (per RECIST v1.1). The prespecified interim analysis data cutoff was November 28, 2024.

Results: 3,256 eligible pts were surveilled for *ESR1*m using ctDNA until 315 eligible pts were randomized to switch to camizestrant (n=157) or continue with AI (n=158). All patients remained on the same CDK4/6 inhibitor. Approximately 50% of randomized patients had *ESR1 Mutations* detected at the first ctDNA test. Baseline characteristics were well balanced between treatments. After 171 PFS events, the hazard ratio for PFS was 0.44 (95% CI 0.31–0.60, p<0.00001; median PFS 16.0 vs 9.2 months). PFS benefit was consistent across subgroups.

PFS rate at 12 months was 60.7% (95% CI 51.1–69.0) vs 33.4% (95% CI 24.9–42.2), and at 24 months

was 29.7% (95% CI 19.0–41.2) vs 5.4% (95% CI 0.7–18.2). PFS2 hazard ratio was 0.52 (95% CI 0.33–

0.81; 27% maturity). OS is immature (12%). Camizestrant + CDK4/6i was well-tolerated, with safety consistent with the known profiles of camizestrant and each CDK4/6 inhibitor. Rates of treatment discontinuation due to adverse events were 1.3% for camizestrant and 1.9% for AI.

Conclusions: Camizestrant + CDK4/6i guided by the emergence of *ESR1*m during 1L AI + CDK4/6i in pts with HR+/HER2– ABC resulted in a statistically significant and clinically meaningful improvement in PFS. SERENA-6 is the first global Phase 3 trial to demonstrate the clinical utility of using ctDNA to detect and treat emerging resistance, ahead of disease progression. These findings represent a potential new treatment strategy to optimize and improve outcomes in 1L patients.

Track/Subcategory: Breast Cancer—Local/Regional/Adjuvant: Adjuvant Therapy

Abstract ID: 505

Session Type: Oral Abstract Session

Title: 15-year outcomes for women with premenopausal hormone receptor-positive early breast cancer (BC) in the SOFT and TEXT trials assessing benefits from adjuvant exemestane (E) + ovarian function suppression (OFS) or tamoxifen (T) + OFS.

Presenter Name: Prudence Francis

Abstract Text:

Background: Long-term follow-up of the SOFT and TEXT randomized trials has shown a persistent reduction of recurrence from inclusion of OFS in adjuvant endocrine therapy, and clinically meaningful improvement in overall survival (OS) among patients at higher baseline risk of recurrence. We report a final update after a median follow-up of 15 years in SOFT and 16.6 years in TEXT.

Methods: SOFT and TEXT enrolled premenopausal women with HR+ early BC from November 2003 to April 2011 (2660 in TEXT, 3047 in SOFT intention-to-treat populations). TEXT randomized women within 12 weeks of surgery to 5y E+OFS vs T+OFS; chemotherapy (CT) was optional and concurrent with OFS. SOFT randomized women to 5y E+OFS vs T+OFS vs T alone, within 12 weeks of surgery if no CT planned, or within 8 months of completing (neo)adjuvant CT. Both trials were stratified by CT use. The primary endpoint was disease-free survival (DFS), which included invasive local, regional, distant, and contralateral breast events, second non-breast malignancies, and deaths. Secondary endpoints included invasive breast cancer-free interval (BCFI), distant recurrence-free interval (DRFI), and OS. A 20-year data collection was completed in Q4 2024: 80% of surviving patients had their final follow-up during or after 2020, with 70% having it between 2023 and 2024. 15y Kaplan-Meier estimates and hazard ratios (HR) with 95% CIs are reported.

Results: There were 815 DFS events and 388 deaths reported in SOFT, and 669 DFS events and 325 deaths in TEXT. In SOFT, a moderate DFS benefit of T+OFS vs T (HR 0.85; 0.72-1.00) persisted; however, 1/6 DFS events were not BC related; BCFI benefit was HR 0.82 (0.69-0.98). E+OFS vs T further reduced DFS events (HR 0.73; 0.61-0.86). The 15y DFS in SOFT was 67.0% for T, 70.5% for T+OFS, and 73.5% for E+OFS. There were consistent but non-significant decreased hazards of death for T+OFS vs T (HR 0.87; 0.68-1.10) and E+OFS vs T (HR 0.85; 0.67-1.08). 15y OS was 85.3%, 86.7%,

86.9% respectively. For the TEXT+SOFT combined analysis of E+OFS vs T+OFS (n=2346 vs 2344) DFS, BCFI, and DRFI continued to be significantly improved for E+OFS over T+OFS. 15y DFS was 74.9% vs 71.3% (HR 0.82; 0.73-0.92). 15y OS was 87.8% vs 87.0% (HR 0.94; 0.80-1.11) respectively.

15y estimates by CT use are tabulated.

Conclusions: The high-level 15-year final results of the SOFT and TEXT confirm a role for OFS- and aromatase inhibitor-containing adjuvant endocrine therapy for premenopausal women. Analysis is ongoing.

Track/Subcategory: Breast Cancer—Metastatic: *HER2*-Positive

Abstract ID: LBA1008

Session Type: Oral Abstract Session

Title: Trastuzumab deruxtecan (T-DXd) + pertuzumab (P) vs taxane + trastuzumab + pertuzumab (THP) for first-line (1L) treatment of patients (pts) with human epidermal growth factor receptor 2–positive (HER2+) advanced/metastatic breast cancer (a/mBC): Interim results from DESTINY-Breast09.

Presenter Name: Sara Tolaney

Abstract Text:

Background:

DESTINY-Breast09 (NCT04784715) is a global, randomized Phase 3 study assessing the efficacy and safety of 1L T-DXd vs THP in 1157 pts with HER2+ a/mBC. The CLEOPATRA study established THP as the standard of care in this setting over a decade ago.

Methods:

Eligible patients had centrally confirmed HER2+ (IHC 3+ or ISH+) a/mBC and no prior chemotherapy or HER2-directed therapy for a/mBC ([neo]adjuvant HER2-directed therapy/chemotherapy with a disease-free interval of >6 months [mo] and ≤1 line of endocrine therapy for metastatic disease permitted). Pts were randomized 1:1:1 to T-DXd 5.4 mg/kg (+ placebo), T-DXd + P, or THP, stratified by de-novo vs recurrent disease, and hormone receptor (HR) and *PIK3CA* mutation status. In this planned interim analysis, data for T-DXd + P vs THP are presented; the T-DXd + placebo arm remains blinded until final PFS analysis. The primary endpoint was progression-free survival (PFS) as determined by an independent central review (ICR) in the intent-to-treat population. Other endpoints included overall survival (OS), PFS by investigator (INV), objective response rate (ORR), duration of response (DOR), and safety.

Results:

Among the patients randomized to T-DXd + P (n = 383) and THP (n = 387), 52% had de novo disease and 54% had HR+ status; demographic and disease characteristics were well-balanced. At this interim data cutoff (Feb 26, 2025; median follow-up 29 months; 38% mature for PFS), T-DXd + P significantly improved PFS by BICR (hazard ratio 0.56; 95% CI 0.44, 0.71; P<0.00001) and INV (Table). PFS benefits were consistent across all subgroups. OS data were immature. Median response duration with T-DXd + P exceeded 3 years (Table). Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 63.5% and 62.3%, and serious TEAEs in 27.0% and 25.1% of patients in the T-DXd + P and THP groups, respectively. Adjudicated drug-related interstitial lung disease/pneumonitis occurred in 46 (12.1%; predominantly Gr 1/2; n=2 [0.5%] Gr 5) pts who received T-DXd + P, and 4 (1.0%; all Gr 1/2) who received THP.

Conclusion: T-DXd + P demonstrated a statistically significant and clinically meaningful improvement in PFS compared to THP, which was consistently observed across all subgroups and may represent a new standard of care in 1L HER2+ a/mBC; no new safety signals were identified.

Track/Subcategory: Breast Cancer—Local/Regional/Adjuvant: Adjuvant Therapy

Abstract ID: 507

Session Type: Oral Abstract Session

Title: The impact of ovarian function suppression with adjuvant endocrine therapy on survival outcomes in young germline *BRCA* mutation carriers with breast cancer: Secondary analysis of an international cohort study.

Presenter Name: Paola Zagami

Abstract Text: Background: In young women with hormone receptor-positive (HR+) breast cancer (BC), ovarian function suppression (OFS) has been shown to improve outcomes when combined with adjuvant endocrine therapy (ET). However, limited evidence exists on its efficacy in germline *BRCA (gBRCA)* carriers. Here, we investigated the association between OFS plus ET and outcomes in the most significant global cohort of young g*BRCA* carriers with BC.

Methods: The BRCA BCY Collaboration (NCT03673306) is an international, multicenter, hospital-based, retrospective cohort study of women harboring germline *BRCA1/2* pathogenic/likely pathogenic variants, diagnosed between 2000 and 2020 with stage I-III invasive BC at the age of ≤ 40 years. The analysis included patients with HR+ BC and available data on ET and OFS. The OFS group included patients treated with luteinizing hormone-releasing hormone agonists (LHRHa) and/or bilateral risk-reducing salpingo-oophorectomy (RRSO) within 1 year of BC diagnosis. Outcome analyses included disease-free survival (DFS), BC-free interval (BCFI), and overall survival (OS). Cox proportional hazard models, stratified for country, year of diagnosis, nodal status, and surgery type, and adjusted for RRSO and bilateral risk-reducing mastectomy (time-dependent), were used to explore the association between OFS use (vs non-use) and outcomes. Sensitivity analysis explored OFS as a time-dependent covariate. To address immortal time bias, an additional Cox model was used to account for left truncation, considering differences in time to *BRCA* testing.

Results: Among 5,660 patients from 109 centers, 1,865 patients with HR+ BC were included, of whom

1,071 (57%) received OFS plus ET (35% with an aromatase inhibitor [AI], 65% with tamoxifen [tam]), and 794 (43%) received tam alone. Patients receiving OFS were more likely to have node-positive disease (56% vs. 47%), receive treatment in the recent years (36% vs. 17%), undergo mastectomy (70% vs. 57%), and be tested for g*BRCA* at diagnosis (46% vs. 30%).

With a median follow-up of 7.8 years (IQR 4.6-12.1), OFS combined with ET was associated with significantly improved DFS (adjusted HR [aHR] 0.79, 95% CI 0.66-0.94), BCFI (aHR 0.74, 95% CI 0.61- 0.89), and OS (aHR 0.66, 95% CI 0.50-0.88) over tam alone. Sensitivity analysis using OFS as a time-dependent factor yielded consistent results. No significant interactions were observed between OFS use and specific g*BRCA* mutations or HER2 status. Sub-analyses by type of ET (OFS + AI vs. OFS + tam vs. tam alone) will be presented at the conference.

Conclusions: In this global cohort of young *BRCA* mutation carriers, OFS combined with ET was associated with improved DFS, BCFI, and OS versus tam without OFS. These findings support the consideration of OFS as a key component of adjuvant therapy in this population.

Track/Subcategory: Breast Cancer—Metastatic: Triple-Negative

Abstract ID: LBA109

Session Type: Oral Abstract Session

Title: Sacituzumab govitecan (SG) + pembrolizumab (pembro) vs chemotherapy (chemo) + pembro in previously untreated PD-L1 positive advanced triple-negative breast cancer (TNBC): Primary results from the randomized phase 3 ASCENT-04/KEYNOTE-D19 study.

Presenter Name: Sara Tolaney

Abstract Text:

Background:

Although PD-1/PD-L1 inhibitors plus chemo have expanded treatment options for previously untreated PD-L1–positive advanced TNBC, there remains a critical unmet need to improve outcomes. SG previously demonstrated significant clinical benefit in pretreated metastatic TNBC (mTNBC). We report results from the ASCENT-04/KEYNOTE-D19 study in patients with previously untreated, PD–L1–positive (CPS ≥ 10; 22C3 assay) locally advanced unresectable or mTNBC.

Methods:

Patients were randomized 1:1 to SG (10 mg/kg IV, days 1 & 8) + pembro (200 mg, day 1, with a maximum of 35 cycles) in 21-day cycles or to chemo (gemcitabine + carboplatin, paclitaxel, or nab-paclitaxel) + pembro until disease progression or unacceptable toxicity. Randomization was stratified by curative treatment-free interval, geography, and prior exposure to anti–PD-(L)1 therapy in the curative setting. The primary endpoint was progression-free survival (PFS) as determined by an independent central review (ICR). Key secondary endpoints include overall survival (OS), objective response rate (ORR), and duration of response (DOR) by BICR, as well as safety.

Results:

443 patients were randomized at a 1:1 ratio: 221 to SG + pembro and 222 to chemo + pembro. The median follow-up was 14 mo. SG + pembro showed a significant improvement in PFS by BICR compared with chemo + pembro (hazard ratio [HR], 0.65; 95% CI, 0.51-0.84; *P* = .0009; Table). Median DOR was 16.5 mo for SG + pembro vs 9.2 mo for chemo + pembro (Table). Although OS data were immature, a positive early trend in OS improvement was also noted. The most frequent (≥ 10% of patients) grade ≥ 3 treatment-emergent adverse events (TEAEs) with SG + pembro were neutropenia (43%) and diarrhea (10%); and with chemo + pembro were neutropenia (45%), anemia (16%), and thrombocytopenia (14%).

Conclusions:

SG + pembro led to a statistically significant and clinically meaningful improvement in PFS compared to chemo + pembro, with durable responses, no new safety concerns for SG or pembro, and a lower rate of treatment discontinuation due to TEAEs in patients with previously untreated, PD-L1–positive advanced TNBC. These data support the use of SG + pembro as a potential new standard of care treatment in this patient population.

Track/Subcategory: Breast Cancer—Metastatic: Hormone Receptor-Positive

Abstract ID: LBA1000

Session Type: Oral Abstract Session

Title: Vepdegestrant, a PROTAC estrogen receptor (ER) degrader, vs fulvestrant in ER-positive/human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer: Results of the global, randomized, phase 3 VERITAC-2 study.

Presenter Name: Erika Hamilton

Abstract Text:

Background: Vepdegestrant, an oral PROTAC (PROteolysis TArgeting Chimera) ER degrader, showed encouraging clinical activity and was well tolerated in a phase 1/2 study in pretreated patients (pts) with aBC, and is the first PROTAC to be evaluated in a phase 3 trial (VERITAC-2).

Methods: Eligible pts (aged ≥18 y) had ER+/HER2- aBC, one prior line of a cyclin-dependent kinase (CDK)4/6 inhibitor plus endocrine therapy (ET) and ≤1 additional line of ET (most recent ET given for ≥6 mo before disease progression); pts with prior chemotherapy in the advanced setting or prior fulvestrant were excluded. Pts were randomized 1:1 to vepdegestrant 200 mg orally once daily continuously or fulvestrant 500 mg intramuscularly (days 1 and 15 of cycle 1; day 1 of subsequent cycles); patients were stratified by *ESR1* mutation status and presence of visceral disease. The primary endpoint was progression-free survival (PFS) by an anonymous independent central review (BICR) in patients

with *ESR1* mutations (*ESR1m*) and all patients. Overall survival (OS) was a key secondary endpoint. PFS was analyzed using a stratified 1-sided log-rank test. Median PFS (mPFS) was estimated by the Kaplan-Meier method and hazard ratio (HR) by a stratified Cox proportional hazard model; the study was designed to detect HR<0.60 with 88% power in pts with *ESR1m* and HR<0.67 with 92.5% power in all pts (1-sided α=0.01875).

Results: 624 pts (median age: 60.0 y [range 26–89]) were randomized (n=313 vepdegestrant; 311 fulvestrant); 43.3% had *ESR1m* tumors (n=136 vepdegestrant; 134 fulvestrant). PFS by BICR was significantly longer with vepdegestrant vs fulvestrant among pts with *ESR1m* (174 events, HR=0.57 [95% CI 0.42–0.77]; *P*=0.0001); mPFS (95% CI) was 5.0 mo (3.7–7.4) vs 2.1 (1.9–3.5). PFS by BICR in all pts

was not significantly different (384 events, HR=0.83 [95% CI 0.68–1.02]; *P*=0.0358); mPFS (95% CI) was 3.7 mo (3.6–5.3) vs 3.6 (2.2–3.8). OS data are immature (20% of targeted events in all pts). In 619 treated patients, treatment-emergent adverse events (TEAEs) were primarily grade 1 or 2. Grade ≥3 TEAEs occurred in 23.4% of pts in the vepdegestrant arm (vs 17.6% fulvestrant). The most common TEAEs in the vepdegestrant arm were fatigue (26.6% vs 15.6% in the fulvestrant arm), increased ALT (14.4% vs 9.8%), increased AST (14.4% vs 10.4%), and nausea (13.5% vs 8.8%). TEAEs led to discontinuation of vepdegestrant in 2.9% of patients (vs 0.7% fulvestrant).

Conclusions: Vepdegestrant demonstrated statistically significant and clinically meaningful improvements in PFS compared to fulvestrant in the *ESR1m* population. No statistically significant improvement in PFS was observed in the all-patients population. Vepdegestrant was generally well tolerated with low discontinuation rates due to TEAEs. Results support vepdegestrant as a potential oral treatment option for previously treated patients with *ESR1m* ER+/HER2- aBC.

Track/Subcategory: Breast Cancer—Local/Regional/Adjuvant: Neoadjuvant Therapy

Abstract ID: LBA500

Session Type: Oral Abstract Session

Title: De-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer (neoCARHP): A multicentre, open-label, randomised, phase 3 trial.

Presenter Name: Kun Wang

Abstract Text:

Background: Neoadjuvant taxane, carboplatin, and trastuzumab plus pertuzumab is associated with excellent treatment outcomes. The neoCARHP study aimed to evaluate the efficacy and safety of a de-escalated neoadjuvant taxane plus trastuzumab and pertuzumab with or without carboplatin in HER2-positive early breast cancer.

Methods: The neoCARHP was a multicenter, open-label, randomized non-inferiority phase 3 trial conducted in 15 hospitals. Eligible patients were ≥18 years old with untreated, stage II-III, invasive HER2-positive breast cancer. Patients were stratified by nodal and hormone receptor status and randomized (1:1) to receive six 3-week cycles of an investigator-selected taxane (docetaxel, paclitaxel or nab-paclitaxel) plus trastuzumab (8 mg/kg loading dose, then 6 mg/kg every three weeks) and pertuzumab (840 mg loading dose, then 420 mg every 3 weeks), with carboplatin (TCbHP; AUC 6 mg/mL per min) or without carboplatin (THP). The primary endpoint was the pathological complete response (pCR) rate in the breast and axilla (ypT0/is ypN0), assessed in the modified intent-to-treat (mITT) population (all randomised patients who received at least one dose of study medication). The primary efficacy analysis was performed using the Cochran-Mantel-Haenszel $\chi 2$ test(stratified by nodal and hormone receptor status), with a prespecified non-inferiority margin of -10%. Assuming a pCR rate of 62.8% for each group, 774 patients would provide 80% power at a one-sided significance level of 0.025, with an assumed 5% dropout rate. Safety was assessed in all patients who received the study drug. The trial is registered with ClinicalTrials.gov (NCT04858529), and adjuvant phase follow-up is ongoing.

Results: Between April 30, 2021, and August 27, 2024, 774 patients were enrolled and randomized (387
per group), with 766 included in the mITT population (382 in THP and 384 in TCbHP). 245 (64.1% [95% CI 59.2-68.8]) patients in the THP group achieved pCR, compared with 253 (65.9% [61.0-70.5]) patients in the TCbHP group (absolute difference -1.8%, 95% CI -8.5 to 5.0: odds ratio 0.93, 95% CI 0.69 to 1.25.
p=0.0089). Patients receiving THP had fewer grade 3–4 adverse events (79 of 382 [20.7%] vs 133 of 384
[34.6%]) and serious adverse events (5 of 382 [1.3%] vs 18 of 384 [4.7%]) compared with those receiving TCbHP. The most common grade 3-4 adverse events with THP were neutropenia (26 of 382 [6.8%] vs 63 of 384 [16.4%] with TCbHP), leukopenia (21 [5.5%] vs 57 [14.8%]), and diarrhea (10 [2.6%] vs 16 [4.2%]). No treatment-associated deaths occurred.

Conclusions: THP provided non-inferior pCR rates and improved tolerability compared with TCbHP. Omitting carboplatin could be an efficacious de-escalated neoadjuvant strategy in the presence of dual HER2 blockade for patients with HER2-positive early breast cancer.

Track/Subcategory: Breast Cancer—Local/Regional/Adjuvant: Neoadjuvant Therapy

Abstract ID: 501

Session Type: Oral Abstract Session

Title: Predicting pathologic complete response (pCR) from clinicopathologic variables and HER2DX genomic test in stage II/III HER2+ breast cancer treated with taxane, trastuzumab, and pertuzumab (THP): Secondary results from the EA1181/CompassHER2 pCR trial.

Presenter Name: Nadine Tung

Abstract Text:

Background:

EA1181 (NCT04266249) is a single-arm trial of neoadjuvant THP for patients with clinical anatomic stage II/III HER2+ breast cancer; patients with cT4 or cN3 disease were excluded. Assessing the primary endpoint, 3-year recurrence-free survival in patients with a pCR (ypT0/Tis, ypN0), requires longer

follow-up. Here, we present results for the secondary objective of pCR rate and its relation to clinicopathologic factors and the HER2DX pCR likelihood score (Reveal Genomics) derived from gene expression and clinical features.

Methods:

Patients received four cycles of trastuzumab and pertuzumab (HP) with weekly paclitaxel (12 weeks) or docetaxel (every three weeks for four cycles), followed by surgery. Clinicopathologic features were assessed for all patients, and the HER2DX pCR score (stratified by estrogen receptor [ER] status) was determined using diagnostic biopsy in a representative subset of study participants.

Results:

Two thousand one hundred seventy-five (2175) patients were enrolled. The median age was 55 years (range, 22-88 years); 58% had clinical stage IIA, 33% had stage IIB, and 9% had stage III. 45% had nodal involvement (mostly cN1). 781 tumors were HER2+/ER- and 1394 HER2+/ER+ (locally tested). Two thousand one hundred forty-one (2141)patients started THP, for whom the overall pCR rate was 44%. This rate was 63.7% in HER2+/ER- tumors and 32.4% in HER2+/ER+ tumors. Disease progressed during THP in 16 patients (0.7%). The pCR rate varied inversely to the proportion of cells staining for ER among patients with HER2+/ER+ breast cancer: 1-10%+, 62.5%; 11-69%, 51.6% ; ≥70%, 22.5% ($p < 0.001$). The pCR

The rate was significantly associated with higher grades, especially in HER2+/ER+ disease. T and N stages did not substantially affect the pCR rate. Among 569 patients assessed for the HER2DX pCR score, the pCR rate was significantly higher for patients with a higher score compared to those with a lower score, regardless of ER status (Table). Further correlations and interactions will be presented.

Conclusions:

Neoadjuvant THP resulted in pCR in nearly two-thirds of patients with clinical stage II/III HER2+/ER- and in one-third with HER2+/ER+ breast cancer. There was no association with clinical stage. Lower ER expression and higher grade were associated with higher rates of pCR. The HER2DX pCR score was a significant predictor of pCR, regardless of ER status.

Track/Subcategory: Breast Cancer—Local/Regional/Adjuvant: Adjuvant Therapy

Abstract ID: 508

Session Type: Oral Abstract Session

Title: Efficacy and safety of elinzanetant for vasomotor symptoms associated with adjuvant endocrine

therapy: Phase 3 OASIS 4 trial. Presenter Name: Fatima Cardoso Abstract Text:

Background: Vasomotor symptoms (VMS) associated with adjuvant endocrine therapy (AET) impact quality of life and decrease treatment adherence, worsening breast cancer outcomes. There are several effective treatment options, but none are currently approved for this indication.

Methods: The 52-week randomized phase 3 trial OASIS 4 (NCT05587296) evaluated the safety and efficacy of elinzanetant (EZN), a dual neurokinin-1 and -3 receptor antagonist, in women aged 18–70 years being treated for, or at high risk of developing, hormone receptor-positive (HR+) breast cancer and experiencing ≥35 moderate-to-severe VMS/week associated with AET. Women were randomized 2:1 to receive once-daily EZN 120 mg for 52 weeks or placebo (P) for 12 weeks, followed by EZN for an additional 40 weeks. The primary endpoints were the mean change in moderate-to-severe VMS frequency from baseline to weeks 4 and 12, analyzed using a mixed-effects model with repeated measures (one-sided p-values). Secondary endpoints included the mean changes from baseline in moderate-to-severe VMS frequency at week 1 and moderate-to-severe VMS severity at weeks 4 and 12. Treatment-emergent adverse events (TEAEs) were reported throughout the study.

Results: Mean (standard deviation [SD]) baseline daily VMS frequency was 11.4 (6.9) in the EZN group (n=316) and 11.5 (6.4) in the P group (n=157). Reductions from baseline in VMS frequency were observed from week 1 (EZN: -4.0 [5.1]; P: -1.8 [3.8]). At week 4, the mean (SD) VMS frequency reduced by

-6.5 (6.1) with EZN and -3.0 (5.0) with P, with statistical significance between EZN and P (least squares [LS] mean difference [95% confidence interval (CI)]: -3.5 [-4.4, -2.6]; $p<0.0001$). At week 12, reductions in VMS frequency were -7.8 (6.2) with EZN and -4.2 (6.1) with P, with statistical significance between EZN and P (LS mean difference [95% CI]: -3.4 [-4.2, -2.5]; $p<0.0001$). Reductions in VMS severity were greater with EZN vs. P (week 4: -0.7 [0.6]; -0.4 [0.4], week 12: -1.0 [0.7]; -0.5 [0.6]). During the placebo-controlled period, 220 (69.8%) patients in the EZN group and 98 (62.0%) patients in the P group reported TEAEs. Somnolence, fatigue, and diarrhea were more frequently reported with EZN (Table). Fewer TEAEs were reported in both groups during weeks 13–52.

Conclusions: EZN was efficacious with a fast onset and well tolerated for the treatment of VMS associated with AET. TEAE frequency was as expected for this type of trial. Effective VMS management can enhance adherence to AET, ultimately improving cancer outcomes and quality of life.

Track/Subcategory: Gynecologic Cancer: Cervical Cancer

Abstract ID: LBA5504

Session Type: Oral Abstract Session

Title: Pembrolizumab with chemoradiotherapy in patients with high-risk locally advanced cervical cancer: Final analysis results of the phase 3, randomized, double-blind ENGOT-cx11/GOG-3047/KEYNOTE-A18 study.

Presenter Name: Linda Duska

Abstract Text:

Background: Prior results from ENGOT-cx11/GOG-3047/KEYNOTE-A18 (NCT04221945) showed that pembro + CCRT and then continued after CCRT provided statistically significant and clinically meaningful improvements in OS and PFS vs CCRT alone in pts with newly diagnosed, previously untreated, high-risk LACC. We present the final analysis (FA) results from this study.

Methods:

Eligible pts with newly diagnosed, previously untreated, high-risk LACC (FIGO 2014 stage IB2-IIB with node-positive disease or stage III-IVA regardless of lymph node status) were randomized 1:1 to 5 cycles of pembro 200 mg or placebo (pbo) Q3W + CCRT, then 15 cycles of pembro 400 mg or pbo Q6W. The CCRT regimen consisted of five cycles (with an optional sixth dose) of cisplatin 40 mg/m² every 1 week, followed by EBRT and then brachytherapy. Pts were stratified by planned EBRT type (intensity-modulated radiotherapy [IMRT] or volumetric-modulated arc therapy [VMAT] vs non-IMRT or non-VMAT), stage at screening (stage IB2- IIB vs III-IVA). They planned total radiotherapy dose (<70 Gy vs ≥70 Gy equivalent dose). Primary endpoints are PFS per RECIST version 1.1 by investigator and OS.

Results:

1060 pts were randomized to pembro + CCRT (n=529) or pbo + CCRT (n=531). At the protocol-specified FA (January 7, 2025, data cutoff), the median follow-up was 41.9 months (range, 24.8-55.0). Eighty-six (86) patients had received post-progression immunotherapy; of those, 64 had received pembrolizumab. Pembro + CCRT continued to show clinically meaningful improvements in OS and PFS vs pbo + CCRT (Table). The benefit of pembrolizumab + CCRT was generally consistent in prespecified subgroups, including patients with stage IB2-IIB node-positive disease (OS HR = 0.92 [95% CI, 0.62-1.38]; PFS HR = 0.84 [95% CI, 0.63-1.14]). The grade ≥3 TRAE
incidence was 69.5% in the pembro + CCRT group and 61.5% in the pbo + CCRT group.

Conclusion:

With an additional 12-month median follow-up, pembro + CCRT continued to show clinically meaningful improvements in OS and PFS vs pbo + CCRT in pts with high-risk LACC and had a manageable safety profile. These data are consistent with the prior interim analysis and provide further support for pembro + CCRT as the new standard of care for this population.

Track/Subcategory: Gynecologic Cancer: Ovarian Cancer
Abstract ID: 5515
Session Type: Rapid Oral Abstract Session
Title: A phase II trial of pembrolizumab and lenvatinib in recurrent or persistent clear cell ovarian carcinoma (NCT05296512).
Presenter Name: Joyce Liu
Abstract Text:
Background: Clear cell ovarian carcinoma (CCOC) is a chemoresistant subtype of ovarian cancer. Immune checkpoint inhibitors have been reported to have clinical activity in CCOC. Additionally, CCOC harbors molecular alterations suggesting a role for anti-angiogenic agents. We therefore conducted a single-arm, two-stage Phase 2 trial to investigate the clinical activity of the combination of the PD-1 inhibitor pembrolizumab with the anti-angiogenic tyrosine kinase inhibitor lenvatinib in patients (pts) with CCOC.
Methods: Patients with CCOC and measurable disease received pembrolizumab 200 mg IV every 3 weeks and lenvatinib 20 mg daily. Pts could have received an unlimited number of prior therapies; prior bevacizumab and immune checkpoint inhibitors were allowed, but prior lenvatinib was exclusionary.
Malignant bowel involvement was not allowed. Co-primary endpoints were the objective response rate.
(H0 5%; Ha 25%) and rate of PFS at six months (mo) per RECIST v1.1 (H0 10%; Ha 30%), restricting the probabilities of type I and type II errors to 10% and 10%, respectively. Two patients with objective responses or three patients progression-free and alive at six months were needed to proceed from stage 1 (n = 18) to stage 2 (n = 13); five patients with objective responses or six patients progression-free and alive at six months were needed to declare the combination worthy of further study.
Results: Data cut-off occurred 22-Oct-2024. Of 30 enrolled patients, 83.3% were white; the mean age among all patients was 54.1 years. 30% of pts (9/30) experienced a confirmed response (2 CR, 7 PR); an additional 3 pts (10%) experienced unconfirmed PRs, and 4 pts (13.3%) had SD ≥6 mo. As of the data cut-off, three patients (10%) had not yet reached their first radiographic assessment, and 17 patients were still receiving study therapy.
With a median follow-up of 9.72 months, 16 patients were alive and progression-free at 6 months. The estimated 6-month PFS was 75.96% (95% CI 53.82-88.51%). Median PFS was 10.9 mo. The estimated 12-month PFS was 48.86% (95% CI 23.67-70.04%). The most common any-grade TRAEs were hypertension (71%), hypothyroidism (66%), and fatigue (60%). There were no unanticipated TRAEs.
Conclusions: The combination of pembrolizumab/lenvatinib demonstrates encouraging evidence of clinical activity in CCOC, with nine patients experiencing a confirmed response and 16 patients alive and progression-free at 6 months. As both co-primary endpoints of the study were met, enrollment closed with 30 patients.
Updated data for all patients will be reported. There were no new safety signals.

Track/Subcategory: Genitourinary Cancer—Kidney and Bladder: Urothelial Cancer - Advanced/Metastatic Disease

Abstract ID: 4500

Session Type: Oral Abstract Session

Title: Nivolumab plus ipilimumab (NIVO+IPI) vs gemcitabine-carboplatin (gem-carbo) chemotherapy for previously untreated unresectable or metastatic urothelial carcinoma (mUC): Final results for cisplatin-ineligible patients from the CheckMate 901 trial.

Presenter Name: Michiel Van Der Heijden

Abstract Text:

Background: Platinum-based chemotherapy is a standard of care (SOC) for unresectable or mUC; patients (pts) ineligible for cisplatin (cis) has worse outcomes. The Phase 3, global, open-label, randomized CheckMate 901 trial (NCT03036098) compared NIVO+IPI with gem-carbo in cis-ineligible patients with previously untreated unresectable or metastatic urothelial carcinoma (mUC). Here, we report final results.

Methods: Pts with previously untreated, histologically confirmed, unresectable or mUC who were cis- ineligible (glomerular filtration rate ≥ 30 to < 60 mL/min) were randomized 1:1 to NIVO 1 mg/kg + IPI 3 mg/kg Q3W up to 4 cycles, then NIVO 480 mg Q4W until disease progression/unacceptable toxicity or up to 2 years, or to gem-carbo Q3W for up to 6 cycles. Patients were stratified by tumor PD-L1 expression and liver metastasis. The primary endpoint was overall survival (OS). Progression-free survival (PFS) determined by an anonymous, independent central review (BICR) was a secondary endpoint. Objective response rate (ORR) and duration of response (DOR) per BICR, as well as safety, were explored.

Results: 445 pts were randomized (NIVO+IPI, n = 221; gem-carbo, n = 224). Median time to treatment discontinuation (95% CI) was 2.2 (2.1–3.5) mo with NIVO+IPI vs 3.8 (3.5–3.9) mo with gem-carbo.

After minimum follow-up (58.3 mo), the primary endpoint of OS did not meet the threshold for significance (median, 19.1 mo with NIVO+IPI vs 13.2 mo with gem-carbo; HR 0.79 [98.27% CI, 0.61– 1.01]; *P* = 0.0245; Table). PFS, ORR, and DOR are shown in the Table. Any-grade treatment-related adverse events (TRAEs) occurred in 89.0% (grade 3–4, 47.2%) of NIVO+IPI-treated and 92.9% (grade 3–4, 76.3%) of gem-carbo-treated pts; any-grade TRAEs leading to discontinuation occurred in 31.2% and 14.2% of pts, respectively. There were eight deaths related to toxicity (NIVO+IPI, 7; gem-carbo, 1).

Conclusions: NIVO+IPI did not meet the threshold of statistical significance for improved OS vs gem-carbo in cis-ineligible pts with untreated unresectable or mUC. Durable response and favorable landmark OS with NIVO+IPI show meaningful activity from a chemotherapy-free regimen of finite duration. No new safety signals were identified.

Track/Subcategory: Genitourinary Cancer—Prostate, Testicular, and Penile: Prostate Cancer– Advanced/Hormone-Sensitive

Abstract ID: LBA5006

Session Type: Oral Abstract Session

Title: Phase 3 AMPLITUDE trial: Niraparib (NIRA) and abiraterone acetate plus prednisone (AAP) for metastatic castration-sensitive prostate cancer (mCSPC) patients (pts) with alterations in homologous recombination repair (HRR) genes. Presenter Name: Gerhardt Attard

Abstract Text: Background: NIRA is a highly selective and potent inhibitor of poly (ADP-ribose) polymerase (PARP)-1/2. In the MAGNITUDE trial, NIRA + AAP significantly improved radiographic progression-free survival (rPFS) in HRR gene–altered metastatic castration-resistant prostate cancer. The double-masked, placebo (PBO)-controlled AMPLITUDE trial (NCT04497844) evaluated the efficacy and safety of NIRA + AAP in HRR gene–altered mCSPC.

Methods: Pts with germline or somatic HRR gene alterations (*BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *PALB2*, *RAD51B*, *RAD54L*) were randomized 1:1 to a dual-action tablet (NIRA 200 mg + abiraterone acetate 1000 mg) plus prednisone 5 mg, or PBO + AAP (hereafter AAP). Eligible pts had received ≤6 mo of androgen deprivation therapy (ADT) ± ≤6 cycles of docetaxel (DOC) ± ≤45 d of AAP with metastatic disease extended beyond lymph nodes. The primary endpoint is investigator-assessed rPFS (time from randomization to radiographic progression or death).

Secondary end points include time to symptomatic progression (TSP), overall survival (OS), and safety. The Kaplan-Meier product limit method and a stratified Cox model were used for time-to-event variables, and the hazard ratio (HR) and stratified log-rank test were employed to estimate the treatment effect. This is the first and final analysis for rPFS and the first interim analysis (of three) for OS (data cutoff: January 7, 2025).

Approximately 261 rPFS events were required (2-sided α, 0.025; power, 91%) for an HR ≤0.64 to demonstrate efficacy.

Results: 696 pts were randomized to NIRA + AAP (n=348) or AAP (n=348). Median age was 68 y (IQR, 61-74); 55.6% had *BRCA1/2* alterations, 78% were high-volume metastatic (M1), 87% were de novo M1, and 16% had prior DOC. Median follow-up is 30.8 mo. The primary end point was met, with rPFS significantly longer with NIRA + AAP (median, not reached [NR]) vs AAP (29.5 mo [95% CI, 25.8-NR]; HR, 0.63 [95% CI, 0.49-0.80], p=0.0001), including in the prespecified *BRCA1/2* subgroup (HR, 0.52 [95% CI, 0.37-0.72], p<0.0001). TSP was significantly improved with NIRA + AAP vs AAP (HR, 0.50 [95% CI, 0.36-0.69], p<0.0001; *BRCA1/2*: HR, 0.44 [95% CI, 0.29-0.68], p=0.0001). A trend in OS was seen at this first interim analysis (193/389 events) favoring NIRA + AAP (HR, 0.79 [95% CI, 0.59-1.04], p=0.10; *BRCA1/2*: HR, 0.75 [95% CI, 0.51-1.11], p=0.15). Grade 3/4 adverse events (AEs) occurred in 75.2% with NIRA + AAP and 58.9% with AAP, most commonly anemia (29.1% vs 4.6%) and hypertension (26.5% vs 18.4%). Treatment discontinuations due to AEs were low: NIRA + AAP: 11.0%; AAP: 6.9%.

Conclusions: NIRA + AAP significantly improved rPFS and TSP vs AAP in pts receiving ADT +/- prior DOC had a favorable effect on OS. There were no new safety signals. AMPLITUDE supports NIRA + AAP as a potential new standard of care for pts with HRR gene–altered mCSPC.

Track/Subcategory: Developmental Therapeutics—Immunotherapy: Other IO-Related Topics

Abstract ID: 2511

Session Type: Clinical Science Symposium

Title: Safety and efficacy of immune checkpoint inhibitors in solid organ transplant recipients: A systematic review and individual patient data meta-analysis.

Presenter Name: Muntaser Al Zyoud

Abstract Text:

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment but pose unique challenges in solid organ transplant (SOT) recipients. Transplant rejection remains the predominant safety concern. We systematically evaluated the safety (with a focus on allograft rejection) and efficacy of ICIs across all organ transplant types and ICI classes, providing updated, evidence-based insights for clinical decision-making.

Methods: A systematic review of PubMed, EMBASE, and SCOPUS databases was conducted in accordance with PRISMA guidelines. Studies reporting rejection or efficacy outcomes in SOT recipients treated with any class of ICI were included. The primary endpoints were the incidence of transplant rejection and survival following ICI therapy. Secondary endpoints included objective response rate (ORR) and progression-free survival (PFS) for malignancies. Analysis was performed using SPSS (version 26.0) and R (version 4.3.0).

Results: Of 2682 screened abstracts, 198 studies involving 331 SOT recipients met the inclusion criteria. The transplanted organs were the liver (n = 175), the Kidney (n = 136), and the heart (n = 15). Rejection rates were highest in Kidney at 46.3% (63/136), followed by the heart at 40.0% (6/15) and the liver at 26.9% (47/175). Across ICI classes, rejection rates were: Anti-CTLA4 (25%), Anti-PD1 (40.6%), and Anti-PDL1 (0%). Rejection rates were lower in patients receiving ICI pre-transplant (25.9%) compared to post-transplant (40.9%). ORR varied by ICI class: Anti-CTLA4 (25%), Anti-PD1 (41.8%), Anti-PD1 + CTLA4 (28%), and Anti-PDL1

(72.7%). Cutaneous squamous cell carcinoma (cSCC) showed the highest ORR (49.1%), followed by hepatocellular carcinoma (40.8%) and melanoma (25.3%). Post-transplant rejection risk was lower with Anti-CTLA4 (OR 0.22), 3rd-line ICI therapy (OR 0.24), and corticosteroids (OR 0.46). Pre-transplant rejection risk decreased with washout periods of more than 60 days (OR 0.10). Multivariate analysis identified key factors influencing rejection risk (Table 1).

Conclusions:

ICI therapy in SOT recipients is high-risk yet promising. Key strategies include prolonged washout periods, anti-CTLA4 therapy, and late-line ICI use. Prospective studies are needed to refine protocols and identify predictive markers to improve outcomes in this population.

Track/Subcategory: Developmental Therapeutics—Immunotherapy: New Targets and New Technologies (IO)

Abstract ID: 2501

Session Type: Oral Abstract Session

Title: First-in-human phase I/II trial evaluating BNT142, a first-in-class mRNA-encoded, bispecific antibody targeting Claudin 6 (CLDN6) and CD3, in patients (pts) with CLDN6-positive advanced solid tumors.

Presenter Name: Timothy Yap

Abstract Text:

Background: CLDN6 is an oncofetal cell surface protein silenced in normal adult tissues but aberrantly activated in testicular, ovarian, non-small cell lung (NSCLC), and other cancers. The investigational therapeutic BNT142 is a novel lipid nanoparticle (LNP)-encapsulated mRNA encoding the anti-CLDN6/CD3 bispecific antibody RiboMab02.1. After intravenous administration, BNT142 RNA-LNPs are taken up by liver cells and are translated into RiboMab02.1. The first results of the dose escalation part of the BNT142-01 trial testing seven dose levels (DL) are presented here.

Methods: BNT142-01 (NCT05262530) is a Phase I/II, open-label, multi-center trial to evaluate weekly BNT142 treatment with premedication (antipyretics, antihistamines, fluids) at the investigators' discretion in pts with CLDN6+ (≥10% of cells with at least weak membrane positivity) advanced solid tumors.

The primary objectives include safety and tolerability, as well as identifying the recommended Phase 2 dose (RP2D). Secondary and exploration objectives encompass pharmacokinetics, pharmacodynamics, and preliminary efficacy (RECIST 1.1).

Results: As of 02 Dec 2024, 65 pts (median age 57 years [range 18 – 79]; 75% female; 60% ECOG 1; 44

ovarian, 10 testicular, 5 NSCLC, six rare cancers) Received≥1 dose (median 7, range 1 – 38) of BNT142. Of 65 pts, 46 (71%) had ≥4 prior lines of systemic therapy. Mostly mild to moderate treatment-related adverse events (TRAEs) occurred in 41 (63%) patients, including 15 (23%) pts with ≥G3 TRAEs. Most common (≥10%) TRAEs were cytokine release syndrome (CRS) in 14 (22%) pts (1 pt [2%] ≥G3), aspartate or alanine aminotransferase (AST, ALT) increased in 12 (19%) pts (8 pts [12%] ≥G3), and pyrexia, chills or fatigue in 8 (12%) pts (0/0/2 pts [0%/0%/3%] ≥G3, respectively). TRAEs leading to dose reduction, treatment interruption, or discontinuation occurred in 1 (2%), 12 (19%), or two patients (3%), respectively (mostly G3; most common related terms AST or ALT increased and infusion-related reaction). Two (3%) patients had a dose-limiting toxicity (G4 ALT increased [DL5], leading to dose reduction, and G5 CRS [DL6]). BNT142 led to transient, dose-dependent increases in inflammatory cytokines.

Translated RiboMab02.1 was detected in serum in a dose-dependent manner, peaking 24 – 72 h post-dose. Across all DLs, the disease control rate (DCR) was 58% with a tendency of higher efficacy in the higher DLs. In ovarian cancer, there were 7 RECIST 1.1 partial responses (PRs), and the DCR was 75%.

Conclusions: BNT142 demonstrated a manageable safety profile and promising anti-tumor activity at the higher DLs, with 7 RECIST 1.1 PRs in CLDN6+ ovarian cancer, a tumor usually refractory to immunotherapy. We provide the first clinical proof-of-concept for an mRNA-encoded bispecific antibody. Dose optimization is ongoing.

Track/Subcategory: Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers: Small Cell Lung Cancer

Abstract ID: 8006

Session Type: Oral Abstract Session

Title: Lurbinectedin (lurbi) + atezolizumab (atezo) as first-line (1L) maintenance treatment (tx) in patients (pts) with extensive-stage small cell lung cancer (ES-SCLC): Primary results of the phase 3 IMforte trial.

Presenter Name: Luis Paz-Ares

Abstract Text:

Background: Despite improved efficacy when adding 1L PD-(L)1 inhibitors to platinum-based chemotherapy for ES-SCLC, long-term survival remains limited. We report primary results from the global, open-label, randomized Phase 3 IMforte study (NCT05091567) of 1L maintenance therapy with lurbi + atezo vs atezo in patients with ES-SCLC.

Methods: Tx-naive patients with ES-SCLC received standard induction therapy with atezolizumab, carboplatin, and etoposide for four 21-day cycles (q3w). After induction, eligible patients without disease progression (PD) were randomized 1:1 to receive maintenance tx q3w with lurbi (3.2 mg/m2 IV; with G-CSF prophylaxis)

+ atezo (1200 mg IV) or atezo alone until PD, unacceptable toxicity, or withdrawal. Pts were stratified by liver metastases at induction baseline (BL; yes/no), receipt of prophylactic cranial irradiation before randomization (yes/no), ECOG PS (0/1), and LDH (≤ULN/>ULN) at maintenance BL. Crossover was not allowed. Primary endpoints were independent review facility (IRF)–assessed PFS per RECIST v1.1, and OS assessed from randomization into the maintenance phase.

Results: Of 660 enrolled pts, 483 were randomized to receive lurbi + atezo (n=242) or atezo (n=241). BL characteristics were generally balanced between arms. With a median 15.0-mo follow-up (data cutoff: Jul 29, 2024), IRF-PFS was significantly improved with lurbi + atezo vs atezo (stratified HR, 0.54 [95% CI: 0.43, 0.67]; *P*<0.0001; Table). A significant OS benefit was observed with lurbi + atezo compared to atezo (stratified HR, 0.73 [95% CI: 0.57, 0.95]; *P = 0.0174*). Median maintenance tx duration was 4.1 mo with lurbi and

4.2 mo with atezo in the lurbi + atezo arm (n=242) and 2.1 mo in the atezo arm (n=240). In the lurbi + atezo and atezo arms, respectively, treatment-related AEs (TRAEs) occurred in 83.5% vs 40.0% of pts, G3/4 TRAEs in 25.6% vs 5.8% and G5 TRAEs in 0.8% (2 pts; sepsis, febrile neutropenia) vs 0.4% (1 pt; sepsis); AEs led to tx discontinuation in 6.2% vs 3.3%.

Conclusions: IMforte met both primary endpoints of IRF-PFS and OS, demonstrating a clinically meaningful benefit with 1L maintenance tx with lurbi + atezo vs atezo in pts with ES-SCLC. Lurbi + atezo was generally well tolerated, with no new or unexpected safety signals. IMforte is the first global Phase 3 study to demonstrate improvements in PFS and OS with 1L maintenance therapy for ES-SCLC, supporting the use of maintenance lurbi + atezo as a new option for patients with this aggressive disease.

Track/Subcategory: Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers: Local-Regional Non–Small Cell Lung Cancer

Abstract ID: LBA8000

Session Type: Oral Abstract Session

Title: Overall survival with neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) in patients with resectable NSCLC in CheckMate 816.

Presenter Name: Patrick Forde

Abstract Text:

Background:

NIVO + chemo is an established standard of care neoadjuvant treatment (tx) for eligible patients (pts) with resectable NSCLC. It has shown statistically significant and clinically meaningful improvements in EFS and pCR in the phase 3 CheckMate 816 study. Here, we report the planned final analysis of OS from CheckMate 816 at 5-year follow-up (f/u).

Methods:

Adults with stage IB (≥ 4 cm)–IIIA (per AJCC v7) resectable NSCLC, ECOG PS ≤ 1, and no known *EGFR*/*ALK* alterations were randomized 1:1 to receive neoadjuvant NIVO + chemo Q3W or chemo alone Q3W for three cycles, followed by surgery. Primary endpoints were EFS and pCR (both by anonymous independent review). OS was a key prespecified, statistically powered secondary endpoint that was tested hierarchically. Exploratory analyses included OS by ctDNA clearance and pCR status.

Results: At a median f/u of 68 mo (range, 60–85; database lock, 23 Jan 2025), neoadjuvant NIVO + chemo demonstrated a statistically significant OS benefit vs chemo alone (median [95% CI], not reached [NR] vs 73.7 mo [47.3–NR]; HR [95% CI], 0.72 [0.523–0.998]; *P* = 0.0479); 5-y OS rates were 65% vs
55%. OS favored NIVO + chemo in the subgroups defined by tumor PD-L1 expression, baseline disease
stage, and histology (Table). In an exploratory analysis in pts with ctDNA+ at baseline (NIVO + chemo, n
= 43; chemo, n = 43), pts with presurgical ctDNA clearance (56% vs 35%) had continued OS improvement vs those without across both tx arms (HR [95% CI]: NIVO + chemo, 0.38 [0.15–1.00]; chemo, 0.39 [0.14–1.11]). Furthermore, pts who had pCR with NIVO + chemo had sustained OS improvement vs those without (HR [95% CI], 0.11 [0.04–0.36]; 5-y OS rates, 95% vs 56%). Neoadjuvant NIVO + chemo continued to improve EFS vs chemo (median [95% CI], 59.6 [31.6–NR] vs 21.1 mo [16.5–36.8]; HR [95% CI], 0.68 [0.51–0.91]); 5-y EFS rates were 49% vs 34%. No new safety signals were observed at this long-term f/u.

Conclusions: CheckMate 816 is the only neoadjuvant-only immunotherapy phase 3 trial to demonstrate a statistically and clinically significant OS benefit at five years for a resectable solid tumor. Patients with pCR with neoadjuvant NIVO + chemo had a ~90% reduction in their risk of death by five years compared with those without pCR. The findings demonstrate a long-term survival benefit from a short course of neoadjuvant NIVO plus chemotherapy and affirm a paradigm shift in the treatment of resectable NSCLC without actionable genomic alterations.

Track/Subcategory: Lung Cancer—Non-Small Cell Local-Regional/Small Cell/Other Thoracic Cancers: Local-Regional Non–Small Cell Lung Cancer

Abstract ID: 8001

Session Type: Oral Abstract Session

Title: Neoadjuvant (neoadj) osimertinib (osi) ± chemotherapy (CT) vs CT alone in resectable (R) epidermal growth factor receptor-mutated (EGFRm) NSCLC: NeoADAURA.

Presenter Name: Jamie Chaft

Abstract Text:

Background:

Based on the Ph 3 ADAURA study, adjuvant (adj) treatment (Tx) with osi, a 3rd-generation, EGFR-TKI, is SoC for resected EGFRm stage (stg) IB–IIIA NSCLC (AJCC 7th ed). Neoadj Tx may improve surgical and long-term outcomes. NeoADAURA (NCT04351555) is a global, Phase 3, randomized, controlled, 3-arm study assessing outcomes with neoadjuvant osi ± CT vs CT alone in EGFRm R-NSCLC.

Methods:

Eligible pts: aged ≥18 yrs; WHO PS ≤1; EGFRm (Ex19del/L858R) stg II–IIIB (AJCC 8th ed) R-NSCLC. Pts were stratified (stg II vs III; non-Asian vs Chinese vs other Asian; Ex19del vs L858R) and randomized 1:1:1 to neoadj osi 80 mg QD (≥9 wks) + CT (cis/carboplatin + pemetrexed; 3 cycles, Q3W), osi monotherapy (mono) 80 mg QD (≥9 wks) or placebo (PBO) QD + CT (3 cycles, Q3W). Osi/PBO + CT: double blind; osi mono: open-label, sponsor blind. Adj osi was offered to all pts who completed surgery (Sx). Primary endpoint: major pathological response (MPR) by anonymous central pathology review. Secondary endpoints included pathological complete response (pCR), event-free survival (EFS), and safety—data cut-off: Oct 15, 2024.

Results:

Overall, 358 pts were randomized: osi + CT n=121/osi mono n=117/PBO + CT n=120; baseline characteristics were generally balanced across the respective arms (stg II: 49%/50%/51%; non-Asian: 27%/26%/25%; Ex19del: 50%/51%/51%). After neoadj Tx, 92%/97%/89% of pts underwent Sx in the osi

+ CT/osi mono/PBO + CT arms. Osi + CT (MPR rate, 26%) and osi mono (25%) showed statistically significant improvements in MPR compared to PBO + CT (2%): odds ratios were 19.8 ($p < 0.0001$) and 19.3 ($p < 0.0001$), respectively. Interim EFS (15% maturity) trended in favor of osi + CT and osi mono vs PBO

+ CT (Table); ≥80% of patients in each arm received adjunctive osimertinib. In the neoadj period, grade ≥3 all-cause AEs and AEs leading to discontinuation of any Tx occurred in 36%/13%/33% and 9%/3%/5% of pts, respectively, for osi + CT/osi mono/PBO + CT. No pts died within 30 days of Sx.

Conclusions: Neoadjuvant OS with or without CT showed a statistically significant improvement in the MPR rate compared to CT alone. EFS data were immature and trended in favor of the OSI containing arms. There were no new safety concerns. Neoadjuvant osi ± CT should be considered when planning Tx for pts with EGFRm stg II–IIIB R- NSCLC

Track/Subcategory: Lung Cancer—Non-Small Cell Metastatic: Targeted (Non-Immunotherapy)
Abstract ID: 8506
Session Type: Oral Abstract Session
Title: Patritumab deruxtecan (HER3-DXd) in resistant *EGFR*-mutated (*EGFR*m) advanced non-small cell lung cancer (NSCLC) after a third-generation EGFR TKI: The phase 3 HERTHENA-Lung02 study.
Presenter Name: Tony Mok
Abstract Text: Background: After disease progression on a 3rd-gen (3G) EGFR TKI for advanced *EGFR*m NSCLC, available therapies provide limited efficacy. HER3-DXd, an antibody-drug conjugate consisting of a fully human mAb to HER3 attached to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker, showed promising efficacy in HERTHENA-Lung01.
Methods: HERTHENA-Lung02 (NCT05338970) is a phase 3, randomized, open-label study of HER3-DXd vs platinum-based chemotherapy (PBC) in patients (pts) with advanced *EGFR*m (Ex19del or L858R) NSCLC following disease progression on a 3G EGFR TKI. The primary endpoint is PFS by BICR, tested using a stratified log-rank test. The key secondary endpoint is OS.
Results: 586 pts were randomized to HER3-DXd or PBC (median age, 64 y; 61% female; 60% Asian). On the 31 May 2024 data cutoff for primary analysis of PFS, median (range) study duration was 10.7 (5.2- 21.9) mo, and treatment duration was 5.5 (0.7-16.8) mo and 4.6 (0.7-16.5) mo with HER3-DXd and PBC, respectively. HER3-DXd provided a significant improvement in PFS compared to PBC (HR, 0.77; 95% CI, 0.63-0.94; *P = .011*). Median PFS (95% CI) with HER3-DXd vs PBC was 5.8 (5.5-6.8) mo vs 5.4 (5.0-5.6) mo. The PFS rate (95% CI) with HER3-DXd vs PBC was 0.50 (0.44-0.56) vs 0.38 (0.32-0.44) at six months; 0.29 (0.23-0.35) vs 0.19 (0.14-0.25) at nine months; and 0.18 (0.12-0.25) vs 0.05 (0.01-0.13) at 12 months. ORR (95%CI) was 35.2% (29.7%-40.9%) with HER3-DXd vs 25.3% (20.4%-30.6%) with PBC. Median DOR (95% CI) was 5.7 (5.1-7.3) mo with HER3-DXd vs 5.4 (4.1-5.6) mo with PBC. OS data were immature at this protocol-specified interim data cut. In pts with brain metastases at baseline (per CNS BICR), median (95% CI) intracranial PFS was 5.4 (4.0-5.9) mo with HER3-DXd (n=105) vs 4.2 (2.8-5.0) mo with PBC (n=95) (HR, 0.75; 95% CI, 0.53-1.06). TEAEs occurred in 100% of patients in the HER3-DXd arm and in 99% of patients in the PBC arm. TEAEs were associated with treatment discontinuation in 33 patients (11%) in the HER3-DXd arm and 27 (10%) in the PBC arm. The most common TEAEs (n [%]) in the HER3-DXd/PBC arms were nausea (168 [57.9]/118 [42.1], thrombocytopenia (151 [52.1]/76 [27.1]), and fatigue (146 [50.3]/118 [42.1]). Grade [G] ≥3 TEAEs occurred in 73% (HER3-DXd) and 57% (PBC) of patients; the difference was driven by a higher rate of G≥3 thrombocytopenia with HER3-DXd (30% vs 7.9%). Each arm had 1 G≥3 bleeding event associated with a G≥3 platelet counts decrease. Adjudicated drug-related ILD occurred in 14 pts (5%; 11 G1/2, 1 G3, 2 G5) in the HER3-DXd arm.
Conclusions: HER3-DXd demonstrated statistically significant improvement in PFS vs PBC in patients with *EGFR*m NSCLC post EGFR TKI therapy. The safety profile was manageable, consistent with prior reports. The most common TEAEs were hematologic and gastrointestinal in nature. Follow-up is ongoing, along with further exploration of secondary/exploratory/biomarker endpoints from this data cut.

Track/Subcategory: Lung Cancer—Non-Small Cell Metastatic: Targeted (Non-Immunotherapy)

Abstract ID: 8503

Session Type: Oral Abstract Session

Title: Efficacy of zipalertinib in NSCLC patients with EGFR exon 20 insertion mutations who received prior platinum-based chemotherapy with or without amivantamab.

Presenter Name: Helena Yu

Abstract Text:

Background: Despite the approval of amivantamab (ami) for EGFR exon 20 insertion (ex20ins) mutant NSCLC, an unmet need remains for well-tolerated oral targeted therapies with durable clinical benefit. Zipalertinib (zipa, CLN-081, TAS6417) is a novel EGFR TKI that showed promising clinical activity and manageable safety in a Phase 1/2a study in patients with exon 20 insertion NSCLC that progressed on platinum-based chemotherapy (platinum-chemo). Here, we report the primary data from the pivotal Phase 2b REZILIENT1 study of zipa in patients (pts) with advanced or metastatic EGFR exon 20 insertion mutant NSCLC that progressed after prior platinum-chemotherapy with or without prior anti-EGFR therapy.

Methods: Pts were enrolled in two parallel cohorts (prior plt-chemo, prior plt-chemo and ami) and treated with zipa 100 mg BID. Tumor response was assessed by an independent central review (ICR) according to RECIST v1.1. Patients with stable, asymptomatic, or treated brain metastases (mets) were allowed.

Results: As of 10 December 2024, data cut off, 176 pts (51 with prior ami and 125 with plt-chemo) were enrolled with median follow-up of 9.3 months: median age: 65 (33-85), median lines of previous therapy: 2 (1-7), prior PD1/L1: 100 (56.8%), history of brain mets: 68 (38.6%). Among all pts treated, zipa demonstrated a confirmed ORR (cORR) of 35.2%, mDoR of 8.8 months, and mPFS of 9.5 months (table 1). In patients with platinum-chemotherapy without amifostine, the cORR was 40.0%. Of the 51 pts with prior ami, 30 had no other ex20ins-directed therapy, while 21 had also received other ex20ins drugs (such as mobocertinib, sunvozertinib, BLU-451, or poziotinib), the cORR was 30.0% and 14.3%, respectively. Among all pts with brain mets, systemic cORR was 30.9%. The most common treatment-emergent AEs (TEAEs, all-grade) were paronychia, rash, anemia, diarrhea, dry skin, nausea, and stomatitis, and the majority of the TEAEs were CTCAE grade 1 or 2.

Conclusions: Zipalertinib demonstrated clinically meaningful efficacy with a manageable safety profile in patients with exon 20-ins NSCLC who had received prior platinum-based chemotherapy, as well as in those who had received prior amivantamab, addressing a significant and growing unmet need.

Track/Subcategory: Symptom Science and Palliative Care: Palliative Care and Symptom Management

Abstract ID: 12001

Session Type: Oral Abstract Session

Title: Phase III randomized placebo-controlled trial on repurposing olanzapine for prevention of radiotherapy-induced nausea and vomiting (RINV): CTRI/2022/01/039723.

Presenter Name: Meenu Vijayan

Abstract Text:

Background: Prospective placebo-controlled randomized study with or without olanzapine, to evaluate

Its role in reducing RINV in patients undergoing abdominal-pelvic radiation therapy.

Methods: Phase III, double-masked, placebo-controlled trial in patients undergoing radiotherapy (RT) [Eligibility: >18 yrs, abdominal/pelvic RT, no prior RT history] were randomized to receive 5mg olanzapine or a matching placebo daily, along with standard care (ondansetron 4mg twice daily) using a simple randomization method. The primary endpoint was nausea prevention. Secondary endpoint was no emesis, no rescue medications, toxicity (CTCAE v5), & QOL. Pearson chi-square test & independent t-test employed for statistical analysis.

Results: Between Feb 2022 and Aug 2024, 683 patients were screened & 301 randomized [153 placebo, 148 experimental/olanzapine]. In placebo & experimental arm, mean age was 63.8 years (+/- 10.8) & 62.3 years (+/-10.4), female 42% & 37%, rectal cancer 77(50%) & 72 (49%), prostate 47 (31%) & 46 (31%),

endometrial cancer 14 (9%) & 14(9.5%), pancreatic cancer 9(6%) & 5(3.4%) (p=NS). In the placebo & experimental arms, Image-guided RT was performed in 89% & 83% (p = NS), and concurrent chemotherapy was administered in 57% & 53% (p = NS). During RT, no nausea' & no vomiting' complaints in the placebo & experimental arms were

16.3 & 85.8% (p= <0.001); 74.5% & 95.9% (p= <0.001). The total number of vomiting episodes, occurring more than 15 times during RT in the placebo & experimental arms, was 9.2% & 2%, respectively (p = 0.002). Rescue therapy during RT was required in 7.8% of the placebo group and 1.4% of the experimental arm (p = 0.008). Grade≥2 nausea in placebo & in experimental arm 67% & 7.4% (p=0.001) and vomiting 7.8% & 1.4% (p=0.001). In rectal cancer, nausea grade ≥2 in the placebo & experimental arm were 85.7% & 2.8% (p=0.001), & in prostate cancer, 19% & 9% (p=0.018). In the experimental arm, significant adverse reactions (grade 1) included drowsiness (p < 0.001), dysarthria (p = 0.003), and orthostatic hypotension (p < 0.001). Mean anxiety score before & after RT in placebo was 13.2 (+/-2.5) &14.5 (+/-2.4) (p<0.001); in experimental arm 13.4 (+/-2.3) & 11.1 (+/-2.2) (p<0.001); Mean depression score before & after RT in placebo & experimental arm were 11.9 (+/-1.6) &

13.7 (+/-1.8) (p<0.001); 11.9 (+/-1.6) & 9.7 (+/-1.6) (p<0.001). The olanzapine group had more sleep hours/day (8.4 ± 1.7 hours vs. 5.29 ± 1.13 hours; p < 0.001). QOL score from baseline to end of RT showed improvement in emotional function, nausea/vomiting, insomnia, & loss of appetite (all p<0.001) in the olanzapine arm. Mean EORTC GHS QOL score at RT completion was 61.6 (+/- 8.6) in the placebo arm and

62.9 (+/-9.2) in experimental arm (p=0.235).

Conclusions: Adding olanzapine 5mg along with standard antiemetics demonstrated a significant reduction in RINV in patients receiving abdominal-pelvic radiation therapy.

Track/Subcategory: Symptom Science and Palliative Care: Toxicities–Prevention and Management Strategies

Abstract ID: LBA12000

Session Type: Oral Abstract Session

Title: PRO-ACTIVE: Results of a pragmatic phase IV randomized trial comparing the effectiveness of
prophylactic swallow intervention for patients receiving radiotherapy for head and neck cancer.

Presenter Name: Katherine Hutcheson

Abstract Text:

Background: Swallowing therapy during radiotherapy (RT) for head and neck cancer (HNC) has gained popularity as a dysphagia mitigation strategy, yet optimal timing and intensity of treatment remain uncertain. The PRO-ACTIVE trial compared the effectiveness of prophylactic and reactive swallowing therapies during RT. We hypothesized that PRO-ACTIVE therapies are more effective than RE-ACTIVE, and that more intensive PRO-ACTIVE (EAT+EXERCISE) is superior to less intensive PRO-ACTIVE (EAT).

Methods: PRO-ACTIVE was an international, multi-site pragmatic phase IV randomized clinical trial (NCT03455608). Eligible adult patients had functional baseline swallowing and received RT ≥60-Gy for HNC with bilateral neck fields. Before RT, patients randomized 1:2:2 to 1) RE-ACTIVE, 2) PRO-ACTIVE EAT, or 3) PRO-ACTIVE EAT+EXERCISE arms and followed for 1 year. RE-ACTIVE received weekly monitoring with therapy only if/when dysphagic, and PRO-ACTIVE arms received bi-weekly therapy pre- and during RT. The primary endpoint was the use of a feeding tube (FT) in days from the end of RT to 1 year. Secondary endpoints were patient-reported and clinician-graded outcomes. Adjusted linear regression compared FT days per intention-to-treat with a gate-keeper approach to test hypotheses in hierarchical order with 80% power to detect a small effect size (≥.21 SD) with type 1 error probability of 0.5 (two-sided).

Results: 952 patients from 13 institutions were randomized to RE-ACTIVE (n=196), PRO-ACTIVE-EAT (n=377), or PRO-ACTIVE-EAT+EXERCISE (n=379). 21 (2.2%) patients exited before intervention; thus, 931 were retained for analysis. The majority had stage I/II disease (552/931, 59.3%), oropharyngeal tumors (647/931, 69.5%), and p16+ and/or HPV+ disease (680/931, 73.0%). Baseline function was excellent (499/931 (53.5%) grade 0 dysphagia, mean [SD] MDADI 86 [14]). All patients received curative-intent radiotherapy (median dose, 70 Gy), with 706/931 (75.8%) receiving chemotherapy and 105/931 (11.3%) undergoing primary site surgery. 364 of 931 (39.1%) required an FT, with a mean of 34.4 days (SD 75.9) of use. Adjusted FT days at 12 months did not meaningfully differ by pro- and re-active timing (∆5.4 days, 95% CI -6.5 to 17.2, p=0.37) or EAT versus EAT+exercise intensity (∆5.9 days, 95% CI -3.8 to 17.6, p=0.21).

Swallowing-related QOL, diet, weight/BMI, and dysphagia symptoms did not differ meaningfully by arm.

Conclusion: FT utilization was lower than expected, and secondary measures of swallowing outcomes were favorable across all arms of the PRO-ACTIVE trial, reflecting the relative effectiveness of EAT and exercise therapies regardless of timing or intensity of therapy delivery during RT for HNC. As a pragmatic trial, we are robustly powered to examine heterogeneous treatment effects in subgroup analyses and image-based swallowing metrics, which are critical next steps.

Track/Subcategory: Symptom Science and Palliative Care: Toxicities–Prevention and Management Strategies

Abstract ID: 12006

Session Type: Oral Abstract Session

Title: A multicenter, randomized, controlled, open-label trial to determine the optimal duration of steroid therapy for mild pneumonitis associated with immune checkpoint inhibitors.

Presenter Name: Daichi Fujimoto

Abstract Text:

Background: The optimal duration of corticosteroid therapy for pneumonitis associated with immune checkpoint inhibitors is clinically relevant. Several guidelines recommend a duration of 4 to 6 weeks for mild immune-related pneumonitis. However, evidence from clinical trials is limited. We conducted the first randomized trial to evaluate whether short-term corticosteroid therapy can achieve comparable efficacy.

Methods: This multicenter, open-label, randomized clinical trial, conducted at 22 institutions in Japan, randomly assigned patients with mild immune-related pneumonitis, as classified by the Common Terminology Criteria for Adverse Events grade 1 or 2, in a 1:1 ratio, to receive either 3-week or 6-week corticosteroid treatment. The primary endpoint was the rate of treatment success 8 weeks after the start of steroid administration, with a noninferiority margin of 16 percentage points. The primary secondary endpoints were safety, percentage of participants with treatment failure, quality of life, and overall survival. The primary hypothesis was that a 3-week treatment would be non-inferior to a 6-week treatment in terms of the primary endpoint.

Results: Overall, 106 patients were randomized, and after excluding one patient without immune-related pneumonitis, 105 were included in the intention-to-treat (ITT) population: 51 patients in the 3-week group and 54 in the 6-week group. In the ITT population, the median age of the patients was 72 years; 81% of the patients were men, and 73% had a baseline grade of 2. The rate of treatment success was 66.7% in the 3-week group and 85.2% in the 6-week group, which did not demonstrate noninferiority in the overall study population (difference, −18.5% percentage points [80% confidence interval {CI}, −29.0% to
-7.9%], p = 0.621), and a predefined exploratory superiority analysis indicated superiority of the 6-week regimen (p = 0.013). Over the entire study period, the relapse or exacerbation rates of pneumonitis were 41.1% in the 3-week group and 24.1% in the 6-week group. Grade 3 or higher adverse events occurred in 12% of patients in the 3-week group and 24% of patients in the 6-week group. The absolute mean changes in the total QOL using the K-BILD score from baseline was 4.78 in the 3-week group and 6.28 in the 6-week group (between-group difference, -1.50 points; 95% CI, −5.91 to 2.91).

Conclusions: In patients with mild immune-related pneumonitis, the noninferiority of 3-week corticosteroid treatment compared to 6 weeks was not confirmed in the overall population, and the relapse or exacerbation rate of pneumonitis was higher in the 3-week group over the entire study period.

Corticosteroid therapy is shorter than the duration recommended by the guidelines.

Track/Subcategory: Symptom Science and Palliative Care: Toxicities–Prevention and Management Strategies

Abstract ID: 12007

Session Type: Oral Abstract Session

Title: Romiplostim for chemotherapy-induced thrombocytopenia (CIT) in colorectal, gastroesophageal, and pancreatic cancers: A global, phase 3, randomized, placebo-controlled trial (RCT). Presenter Name: Hanny Al-Samkari

Abstract Text: Background: CIT is a common consequence of antineoplastic regimens for gastrointestinal (GI) cancers, occurring in >60% of colorectal cancer patients receiving multiagent chemotherapy. CIT can lead to chemotherapy dose reduction, delay, omission, and discontinuation, potentially worsening outcomes. Currently, there are no widely available licensed therapies to address this unmet need. Aim: To evaluate the safety and efficacy of the thrombopoietin receptor agonist romiplostim (ROMI) in patients with GI cancers to limit chemotherapy dose modifications from CIT.

Methods: This was phase 3, placebo (PBO)-controlled RCT of patients receiving oxaliplatin-based multiagent regimens for GI cancers with persistent CIT, i.e., platelets (Plt) ≤85×109/L on day 1 of a scheduled chemotherapy cycle (NCT03362177). Patients from 55 sites in 14 countries were randomized 2:1 to ROMI or PBO for three chemotherapy cycles, stratified by baseline Plt (< or ≥50×109/L) and cancer type. Study drug started at 2 µg/kg subcutaneous weekly, adjusted weekly by 1 µg/kg up to 10 µg/kg to target Plt ≥100×109/L in 12 weeks (≤4 weeks at 10 µg/kg). Chemotherapy started when the platelet count (Plt) was≥100×109/L (platelet response) or after week 4, as per the investigator. The primary endpoint was the absence of CIT-induced dose modifications of any myelosuppressive agent in either the second or third chemotherapy cycle, as determined by independent adjudication committees.

Results: Patients (N=165; 109 ROMI, 56 PBO) had colorectal (75%), gastroesophageal (13%), or pancreatic (12%) cancer; 60% were male, 90% White, 4% Black, and 24% Hispanic, with a mean (SD) age of 61.4 (11.1) years. Baseline median (range) Plt was 69 (8–85)×109/L; 11% had Plt < 50×109/L/L. Stage IV disease rates were ROMI 65%, PBO 55%. Most (75%) patients completed the study drug; 3% discontinued due to adverse events (AEs). The primary endpoint was achieved in 92/109 (84%) patients receiving ROMI versus 20/56 (36%) receiving PBO (odds ratio, 10.2; 95% CI, 4.6-22.5; P < 0.001). Median (range) Plt nadirs were ROMI 87 (14–167)×109/L, PBO 58 (22–95)×109/L; P=0.005. For those with Plt responses (ROMI 97%, PBO 77%), the median (95% CI) time to first Plt response was 1.1 (not estimable) weeks for ROMI and 2.1 (1.1-3.0) weeks for PBO; P < 0.001. Treatment-related (TR) AE rates were as follows: ROMI, 12%; PBO, 7%. The most frequently reported AEs were nausea (2%, 2%) and headache (2%, 0%). TR serious AEs and TRAEs leading to death or discontinuation of study drug or chemotherapy were not observed in either arm.

Conclusions: In this first global Phase 3 RCT of ROMI vs PBO for CIT, ROMI was well-tolerated and efficacious in the treatment and prevention of CIT in GI cancers. These results are potentially practice-changing for a common serious condition encountered routinely in clinical practice worldwide that prevents delivery of on-time, full-dose anticancer therapy. Final results from long-term follow-up will be presented.

Track/Subcategory: Head and Neck Cancer: Local-Regional Disease

Abstract ID: 6012

Session Type: Rapid Oral Abstract Session

Title: Neoadjuvant and adjuvant pembrolizumab plus standard of care (SOC) in resectable locally advanced head and neck squamous cell carcinoma (LA HNSCC): Exploratory efficacy analyses of the phase 3 KEYNOTE-689 study.

Presenter Name: Douglas Adkins

Abstract Text:

Background: The addition of immune checkpoint inhibitors to neoadjuvant/adjuvant SOC has led to efficacy benefits across multiple tumor types. The randomized phase 3 KEYNOTE-689 study (NCT03765918) showed significantly improved event-free survival (EFS) with neoadjuvant/adjuvant pembrolizumab + SOC vs SOC alone for participants (pts) with resectable LA HNSCC independent of PD-L1 combined positive score (CPS ≥10 population: HR 0.66, 95% CI 0.49–0.88, *P*=.00217; CPS ≥1 population: HR 0.70, 95% CI 0.55–0.89, *P*=.00140; all pts: HR 0.73, 95% CI 0.58–0.92, *P*=.00411). We present exploratory efficacy endpoints for the intention-to-treat population of the study.

Methods: Adults with SCC of the larynx/hypopharynx/oral cavity (stage III/IVA) or oropharynx (stage III/IVA p16− or stage III T4 N0-2 p16+) were randomized 1:1 to SOC (consisting of surgery + postoperative radiotherapy [PORT] ± concurrent cisplatin 100 mg/m2 Q3W) with or without two cycles of neoadjuvant pembrolizumab, three cycles of pembrolizumab concurrent with PORT ± cisplatin and 12 cycles of adjuvant pembrolizumab (200 mg IV Q3W). The primary endpoint is EFS, as per RECIST 1.1, as determined by an independent, anonymous central review. Safety is a secondary endpoint. Prespecified exploratory efficacy endpoints include locoregional control (the time from randomization to the first locoregional radiographic progression or recurrence, as determined by imaging or biopsy), distant metastasis-free survival (DMFS; the time from randomization to the first distant metastasis or death), and the incidence of second head and neck or other cancers.

Results: A total of 714 pts were randomized (363 to pembrolizumab + SOC, 351 to SOC). At the first interim analysis (data cutoff date: 25 July 2024), the median follow-up was 38.3 months (range, 9.0–66.5). In all patients, the cumulative incidence of locoregional progression or recurrence at 36 months was 13.4% with pembrolizumab + SOC and 14.3% with SOC. The HR for risk of a locoregional failure event with pembrolizumab + SOC vs SOC was 0.92 (95% CI 0.61–1.41). Median DMFS was 51.8 mo with pembrolizumab + SOC vs 35.7 mo with SOC (HR 0.71, 95% CI 0.56–0.90). The estimated DMFS rate at 36 months was 59.1% versus 49.0%, respectively. Second head and neck or other cancers occurred in 9 (2.5%) and 18 pts (5.1%), respectively. The incidence of treatment-related adverse events was similar with pembrolizumab plus SOC and SOC (any grade, 81.4% vs 81.9%; grade 3 or higher, 44.6% vs 42.9%).

Conclusions: Among all patients with resectable LA HNSCC in KEYNOTE-689, DMFS results, and incidence of second cancers favored the addition of neoadjuvant/adjuvant pembrolizumab to SOC surgery and (chemo)radiotherapy, consistent with the primary EFS results of the study. Locoregional control was similar between arms. No new safety signals for pembrolizumab were observed.

Track/Subcategory: Head and Neck Cancer: Local-Regional Disease

Abstract ID: LBA6003

Session Type: Oral Abstract Session

Title: PD-1 blockade with toripalimab incorporated into induction chemotherapy and radiotherapy with or without concurrent cisplatin in locoregionally advanced nasopharyngeal carcinoma (DIAMOND): A multicenter, non-inferiority, phase 3, randomized controlled trial.

Presenter Name: Jun Ma

Abstract Text:

Background:

This study aimed to assess the efficacy and safety of toripalimab combined with induction chemotherapy and radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma (LANPC).

Methods:

Patients with non-metastatic T4N1 or N2–3 (AJCC 8th edition) NPC were recruited from 13 centers in China from August 2021 to July 2022 and randomly assigned (1:1) to receive either toripalimab plus gemcitabine-cisplatin induction chemotherapy and concurrent cisplatin-radiotherapy (*standard* arm) or standard therapy, excluding concurrent cisplatin (*cisplatin-free* arm). Toripalimab was administered at a dosage of 240 mg every 3 weeks for up to 17 cycles (approximately 1.06 years), encompassing the induction (3 cycles), radiotherapy (3 cycles), and adjuvant (11 cycles) phases. The trial would be considered positive if both coprimary endpoints, failure-free survival (FFS; non-inferiority) and the incidence of all-grade vomiting (superiority), were significantly met, maintaining a 1-sided type I error of 5% without α splitting. A total of 532 patients were required to achieve 80% power to detect an HR of 1.74, with non-inferiority defined as the lower limit of the one-sided 95% CI for the difference in 3-year FFS being greater than -8%. Quality of life (QoL) was assessed based on EORTC and FACT systems. PRO-CTCAE questionnaires measured tolerability.

Results: After a median follow-up of 36 mo, intention-to-treat analysis in 532 patients (266 *vs* 266) showed that the estimated 3-year FFS was 88.3% in the *cisplatin-free* arm and 87.6% in the *standard* arm, with a difference of 0.7% (1-sided 95% CI, -4.8% to ∞; *non-inferiority* = 0.002); the stratified HR was 0.92 (95% CI, 0.66 to 1.79; log-rank $p = 0.731$). The incidence of all-grade vomiting in the safety dataset was 25.6% (68/260) in *the cisplatin-free* arm and 69.0% (156/261) in *the standard* arm ($\chi 2$ $p < 0.001$); the incidence of grade 3–4 vomiting was 3.8% *vs* 10.3%. Acute grade 3–4 adverse events (AEs) occurred in 136 (52.3%)

and 166 (63.6%) patients, including immune-related AEs in 13 (5.0%) and 22 (8.4%) patients, in

the *cisplatin-free* and *standard* arms, respectively. No treatment-related death was observed. Compared to *the standard* arm, *the cisplatin-free* arm had significantly better QoL in global health status, physical function, role function, nausea/vomiting, constipation, swallowing, sexuality, and H&N total score, as well as higher tolerability to nausea, vomiting, constipation, and fatigue during radiotherapy.

Conclusions: Removing concurrent cisplatin from toripalimab plus chemoradiotherapy provides comparable survival, lower toxicity, and better QoL and tolerability for patients with LANPC.