FLORIDA CANCER SPECIALISTS & Research Institute

TOP ARTICLES OF THE MONTH

JUNE - JULY 2021 | Lucio N. Gordan, MD

1. Pembrolizumab in Patients With Metastatic Breast Cancer With High Tumor Mutational Burden: Results From the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

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PURPOSE

The TAPUR Study is a phase II basket trial that aims to identify signals of antitumor activity of commercially available targeted agents in patients with advanced cancers harboring genomic alterations known to be drug targets. Results in a cohort of patients with metastatic breast cancer (mBC) with high tumor mutational burden (HTMB) treated with pembrolizumab are reported.

METHODS

Patients with advanced mBC received standard doses of either 2 mg/kg or 200 mg infusions of pembrolizumab every 3 weeks. Simon's two-stage design was used with a primary study end point of disease control (DC) defined as objective response or stable disease of at least 16 weeks duration. If two or more patients in stage I achieved DC, the cohort would enroll 18 additional patients in stage II. Secondary end points include progression-free survival (PFS), overall survival, and safety.

RESULTS

Twenty-eight patients were enrolled from October 2016 to July 2018. All patients' tumors had HTMB ranging from 9 to 37 mutations/megabase. DC and objective response were noted in 37% (95% CI, 21 to 50) and 21% of patients (95% CI, 8 to 41), respectively. Median PFS was 10.6 weeks (95% CI, 7.7 to 21.1); median overall survival was 30.6 weeks (95% CI, 18.3 to 103.3). No relationship was observed between PFS and tumor mutational burden. Five patients experienced ≥ 1 serious adverse event or grade 3 adverse event at least possibly related to pembrolizumab consistent with the product label.

CONCLUSION

Pembrolizumab monotherapy has antitumor activity in heavily pretreated patients with mBC characterized by HTMB. Our findings support the recent US Food and Drug Administration approval of pembrolizumab for treatment of patients with unresectable or metastatic solid tumors with HTMB without alternative treatment options.

2. Randomized Phase III Trial of Gemcitabine and Cisplatin With Bevacizumab or Placebo in Patients With Advanced Urothelial Carcinoma: Results of CALGB 90601 (Alliance)

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PURPOSE

The combination of gemcitabine and cisplatin (GC) is a standard therapy for metastatic urothelial carcinoma. Based on data that angiogenesis plays a role in urothelial carcinoma growth and progression, a randomized placebo-controlled trial was performed with the primary objective of testing whether patients treated with GC and bevacizumab (GCB) have superior overall survival (OS) than patients treated with GC and placebo (GCP).

PATIENTS AND METHODS

Between July 2009 and December 2014, 506 patients with metastatic urothelial carcinoma without prior chemotherapy for metastatic disease and no neoadjuvant or adjuvant chemotherapy within 12 months were randomly assigned to receive either GCB or GCP. The primary end point was OS, with secondary end points of progression-free survival, objective response, and toxicity.

RESULTS

With a median follow-up of 76.3 months among alive patients, the median OS was 14.5 months for patients treated with GCB and 14.3 months for patients treated with GCP (hazard ratio for death = 0.87; 95% CI, 0.72 to 1.05; two-sided stratified log-rank P = .14). The median progression-free survival was 8.0 months for GCB and 6.7 months for GCP (hazard ratio = 0.77; 95% CI, 0.63 to 0.95; P = .016). The proportion of patients with grade 3 or greater adverse events did not differ significantly between both arms, although increased bevacizumab-related toxicities such as hypertension and proteinuria occurred in the bevacizumab-treated arm.

CONCLUSION

The addition of bevacizumab to GC did not result in improved OS. The observed median OS of about 14 months is consistent with prior phase III trials of cisplatin-based chemotherapy.

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3. Phase II Study of Maintenance Rucaparib in Patients With Platinum-Sensitive Advanced Pancreatic Cancer and a Pathogenic Germline or Somatic Variant in *BRCA1, BRCA2,* or *PALB2*

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PURPOSE

Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor (PARPi), is approved as maintenance therapy for patients with advanced pancreatic cancer (PC) and a germline BRCA1 or BRCA2 pathogenic variant (PV).

This investigator-initiated, single-arm phase II study assessed the role of the PARPi rucaparib as maintenance therapy in advanced PC with germline or somatic PV in BRCA1, BRCA2, or PALB2.

PATIENTS AND METHODS

Eligible patients had advanced PC; germline (g) or somatic (s) PVs in BRCA1, BRCA2, or PALB2, and received at least 16 weeks of platinum-based chemotherapy without evidence of platinum resistance. Chemotherapy was discontinued and patients received rucaparib 600 mg orally twice a day until progression. The primary end point was the progression-free survival (PFS) rate at 6 months (PFS6). Secondary end points included safety, ORR, disease control rate, duration of response, and overall survival.

RESULTS

Of 46 enrolled patients, 42 were evaluable (27 gBRCA2, seven gBRCA1, six gPALB2, and two sBRCA2). PFS6 was 59.5% (95% CI, 44.6 to 74.4), median PFS was 13.1 months (95% CI, 4.4 to 21.8), and median overall survival was 23.5 months (95% CI, 20 to 27). The PFS at 12 months was 54.8%. ORR of the 36 patients with measurable disease was 41.7% (3 complete responses; 12 partial responses; 95% CI, 25.5 to 59.2), and disease control rate was 66.7% (95% CI, 49.0 to 81.4). Median duration of response was 17.3 months (95% CI, 8.8 to 25.8). Responses occurred in patients with gBRCA2 (41%, 11 out of 27), gPALB2 (50%, 3 out of 6), and sBRCA2 (50%, 1 out of 2). No new safety signals were noted.

CONCLUSION

Maintenance rucaparib is a safe and effective therapy for platinum-sensitive, advanced PC with a PV in BRCA1, BRCA2, or PALB2. The finding of efficacy in patients with gPALB2 and sBRCA2 PVs expands the population likely to benefit from PARPi beyond gBRCA1/2 PV carriers

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4. Pembrolizumab Plus Ipilimumab or Placebo for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%: Randomized, Double-Blind Phase III KEYNOTE-598 Study

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PURPOSE

Pembrolizumab monotherapy is standard first-line therapy for metastatic non–small-cell lung cancer (NSCLC) with programmed death ligand 1 (PD-L1) tumor proportion score (TPS) ≥ 50% without actionable driver mutations. It is not known whether adding ipilimumab to pembrolizumab improves efficacy over pembrolizumab alone in this population.

METHODS

In the randomized, double-blind, phase III KEYNOTE-598 trial (ClinicalTrials.gov identifier: NCT03302234), eligible patients with previously untreated metastatic NSCLC with PD-L1 TPS ≥ 50% and no sensitizing EGFR or ALK aberrations were randomly allocated 1:1 to ipilimumab 1 mg/kg or placebo every 6 weeks for up to 18 doses; all participants received pembrolizumab 200 mg every 3 weeks for up to 35 doses. Primary end points were overall survival and progression-free survival.

RESULTS

Of the 568 participants, 284 were randomly allocated to each group. Median overall survival was 21.4 months for pembrolizumab-ipilimumab versus 21.9 months for pembrolizumab-placebo (hazard ratio, 1.08; 95% CI, 0.85 to 1.37; P = .74). Median progression-free survival was 8.2 months for pembrolizumab-ipilimumab versus 8.4 months for pembrolizumab-placebo (hazard ratio, 1.06; 95% CI, 0.86 to 1.30; P = .72). Grade 3-5 adverse events occurred in 62.4% of pembrolizumab-ipilimumab recipients versus 50.2% of pembrolizumab-placebo recipients and led to death in 13.1% versus 7.5%. The external data and safety monitoring committee recommended that the study be stopped for futility and that participants discontinue ipilimumab and placebo.

CONCLUSION

Adding ipilimumab to pembrolizumab does not improve efficacy and is associated with greater toxicity than pembrolizumab monotherapy as first-line treatment for metastatic NSCLC with PD-L1 TPS ≥ 50% and no targetable EGFR or ALK aberrations. These data do not support use of pembrolizumab-ipilimumab in place of pembrolizumab monotherapy in this population.

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5. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%

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**M.R. and D.R.-A. contributed equally to this work.*

PURPOSE

We report the first 5-year follow-up of any first-line phase III immunotherapy trial for non–small-cell lung cancer (NSCLC). KEYNOTE-024 (ClinicalTrials.gov identifier: NCT02142738) is an open-label, randomized controlled trial of pembrolizumab compared with platinum-based chemotherapy in patients with previously untreated NSCLC with a programmed death ligand-1 (PD-L1) tumor proportion score of at least 50% and no sensitizing EGFR or ALK alterations. Previous analyses showed pembrolizumab significantly improved progression-free survival and overall survival (OS).

METHODS

Eligible patients were randomly assigned (1:1) to pembrolizumab (200 mg once every 3 weeks for up to 35 cycles) or platinum-based chemotherapy. Patients in the chemotherapy group with progressive disease could cross over to pembrolizumab. The primary end point was progression-free survival; OS was a secondary end point.

RESULTS

Three hundred five patients were randomly assigned: 154 to pembrolizumab and 151 to chemotherapy. Median (range) time from randomization to data cutoff (June 1, 2020) was 59.9 (55.1-68.4) months. Among patients initially assigned to chemotherapy, 99 received subsequent anti–PD-1 or PD-L1 therapy, representing a 66.0% effective crossover rate. Median OS was 26.3 months (95% CI, 18.3 to 40.4) for pembrolizumab and 13.4 months (9.4-18.3) for chemotherapy (hazard ratio, 0.62; 95% CI, 0.48 to 0.81). Kaplan-Meier estimates of the 5-year OS rate were 31.9% for the pembrolizumab group and 16.3% for the chemotherapy group. Thirty-nine patients received 35 cycles (ie, approximately 2 years) of pembrolizumab, 82.1% of whom were still alive at data cutoff (approximately 5 years). Toxicity did not increase with longer treatment exposure.

CONCLUSION

Pembrolizumab provides a durable, clinically meaningful long-term OS benefit versus chemotherapy as first-line therapy for metastatic NSCLC with PD-L1 tumor proportion score of at least 50%.

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6. Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial

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PURPOSE

The ATEMPT trial was designed to determine if treatment with trastuzumab emtansine (T-DM1) caused less toxicity than paclitaxel plus trastuzumab (TH) and yielded clinically acceptable invasive disease-free survival (iDFS) among patients with stage I human epidermal growth factor receptor 2–positive (HER2+) breast cancer (BC).

METHODS

Patients with stage I centrally confirmed HER2+ BC were randomly assigned 3:1 to T-DM1 or TH and received T-DM1 3.6 mg/kg IV every 3 weeks for 17 cycles or T 80 mg/m2 IV with H once every week × 12 weeks (4 mg/kg load →2 mg/kg), followed by H × 39 weeks (6 mg/kg once every 3 weeks). The co-primary objectives were to compare the incidence of clinically relevant toxicities (CRTs) in patients treated with T-DM1 versus TH and to evaluate iDFS in patients receiving T-DM1.

RESULTS

The analysis population includes all 497 patients who initiated protocol therapy (383 T-DM1 and 114 TH). CRTs were experienced by 46% of patients on T-DM1 and 47% of patients on TH (P = .83). The 3-year iDFS for T-DM1 was 97.8% (95% CI, 96.3 to 99.3), which rejected the null hypothesis (P < .0001). Serially collected patient-reported outcomes indicated that patients treated with T-DM1 had less neuropathy and alopecia and better work productivity compared with patients on TH.

CONCLUSION

Among patients with stage I HER2+ BC, one year of adjuvant T-DM1 was associated with excellent 3-year iDFS, but was not associated with fewer CRT compared with TH.

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7. Brentuximab Vedotin Combined With Chemotherapy in Patients With Newly Diagnosed Early-Stage, Unfavorable-Risk Hodgkin Lymphoma

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PURPOSE

To improve curability and limit long-term adverse effects for newly diagnosed early-stage (ES), unfavorable-risk Hodgkin lymphoma.

METHODS

In this multicenter study with four sequential cohorts, patients received four cycles of brentuximab vedotin (BV) and doxorubicin, vinblastine, and dacarbazine (AVD). If positron emission tomography (PET)-4–negative, patients received 30-Gy involved-site radiotherapy in cohort 1, 20-Gy involved-site radiotherapy in cohort 2, 30-Gy consolidation-volume radiotherapy in cohort 3, and no radiotherapy in cohort 4. Eligible patients had ES, unfavorable-risk disease. Bulk disease defined by Memorial Sloan Kettering criteria (> 7 cm in maximal transverse or coronal diameter on computed tomography) was not required for cohorts 1 and 2 but was for cohorts 3 and 4. The primary end point was to evaluate safety for cohort 1 and to evaluate complete response rate by PET for cohorts 2-4.

RESULTS

Of the 117 patients enrolled, 116 completed chemotherapy, with the median age of 32 years: 50% men, 98% stage II, 86% Memorial Sloan Kettering–defined disease bulk, 27% traditional bulk (> 10 cm), 52% elevated erythrocyte sedimentation rate, 21% extranodal involvement, and 56% > 2 involved lymph node sites. The complete response rate in cohorts 1-4 was 93%, 100%, 93%, and 97%, respectively. With median follow-up of 3.8 years (5.9, 4.5, 2.5, and 2.2 years for cohorts 1-4), the overall 2-year progression-free and overall survival were 94% and 99%, respectively. In cohorts 1-4, the 2-year progression-free survival was 93%, 97%, 90%, and 97%, respectively. Adverse events included neutropenia (44%), febrile neutropenia (8%), and peripheral neuropathy (54%), which was largely reversible.

CONCLUSION

BV + AVD × four cycles is a highly active and well-tolerated treatment program for ES, unfavorable-risk Hodgkin lymphoma, including bulky disease. The efficacy of BV + AVD supports the safe reduction or elimination of consolidative radiation among PET-4–negative patients.

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8. Adjuvant Versus Early Salvage Radiation Therapy for Men at High Risk for Recurrence Following Radical Prostatectomy for Prostate Cancer and the Risk of Death

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PURPOSE

Adjuvant compared with early salvage radiation therapy (sRT) following radical prostatectomy (RP) has not been shown to reduce progression-free survival in randomized controlled trials. However, these trials might have missed a benefit in men with adverse pathology at RP given that these men were under-represented and immortal time bias might have been present; herein, we investigate this possibility.

METHODS

We evaluated the impact of adjuvant versus early sRT on all-cause mortality (ACM) risk in men with adverse pathology defined as positive pelvic lymph nodes (pN1) or pGleason score 8-10 prostate cancer (PC) and disease extending beyond the prostate (pT3/4). We used a treatment propensity score to minimize potential treatment selection bias when estimating the causal effect of adjuvant versus early sRT on ACM risk and a sensitivity analysis to assess the impact that varying definitions of adverse pathology had on ACM risk adjusting for age at RP, PC prognostic factors, site, and the time-dependent use of post-RP androgen deprivation therapy.

RESULTS

After a median follow-up (interquartile range) of 8.16 (6.00-12.10) years, of the 26,118 men in the study cohort, 2,104 (8.06%) died, of which 539 (25.62%) were from PC. After excluding men with a persistent prostate-specific antigen, adjuvant compared with early sRT was associated with a significantly lower ACM risk among men with adverse pathology at RP when men with pN1 PC were excluded (0.33 [0.13-0.85]; P = .02) or included (0.66 [0.44-0.99]; P = .04).

CONCLUSION

Adjuvant radiation therapy should be considered in men with pN1 or pGleason score 8 to 10 and pT3/4 PC given the possibility that a significant reduction in ACM risk exists.

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9. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study

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**K.N.C. and N.A. contributed equally to this work.*

PURPOSE

The first interim analysis of the phase III, randomized, placebo-controlled TITAN study showed that apalutamide significantly improved overall survival (OS) and radiographic progression-free survival in patients with metastatic castration-sensitive prostate cancer (mCSPC) receiving ongoing androgen deprivation therapy (ADT). Herein, we report final efficacy and safety results after unblinding and placebo-to-apalutamide crossover.

METHODS

Patients with mCSPC (N = 1,052) were randomly assigned 1:1 to receive apalutamide (240 mg QD) or placebo plus ADT. After unblinding in January 2019, placebo-treated patients were allowed to receive apalutamide. Efficacy end points were updated using the Kaplan-Meier method and Cox proportional-hazards model without

formal statistical retesting and adjustment for multiplicity. Change from baseline in Functional Assessment of Cancer Therapy-Prostate total score was assessed.

RESULTS

With a median follow-up of 44.0 months, 405 OS events had occurred and 208 placebo-treated patients (39.5%) had crossed over to apalutamide. The median treatment duration was 39.3 (apalutamide), 20.2 (placebo), and 15.4 months (crossover). Compared with placebo, apalutamide plus ADT significantly reduced the risk of death by 35% (median OS not reached v 52.2 months; hazard ratio, 0.65; 95% CI, 0.53 to 0.79; P < .0001) and by 48% after adjustment for crossover (hazard ratio, 0.52; 95% CI, 0.42 to 0.64; P < .0001). Apalutamide plus ADT delayed second progression-free survival and castration resistance (P < .0001 for both). Health-related quality of life, per total Functional Assessment of Cancer Therapy-Prostate, in both groups was maintained through the study. Safety was consistent with previous reports.

CONCLUSION

The final analysis of TITAN confirmed that, despite crossover, apalutamide plus ADT improved OS, delayed castration resistance, maintained health-related quality of life, and had a consistent safety profile in a broad population of patients with mCSPC.

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10. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial

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PURPOSE

Preoperative chemoradiotherapy according to the chemoradiotherapy for esophageal cancer followed by surgery study (CROSS) has become a standard of care for patients with locally advanced resectable esophageal or junctional cancer. We aimed to assess long-term outcome of this regimen.

METHODS

From 2004 through 2008, we randomly assigned 366 patients to either five weekly cycles of carboplatin and paclitaxel with concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week) followed by surgery, or surgery alone. Follow-up data were collected through 2018. Cox regression analyses were performed to compare overall survival, cause-specific survival, and risks of locoregional and distant relapse. The effect of neoadjuvant

chemoradiotherapy beyond 5 years of follow-up was tested with time-dependent Cox regression and landmark analyses.

RESULTS

The median follow-up was 147 months (interquartile range, 134-157). Patients receiving neoadjuvant chemoradiotherapy had better overall survival (hazard ratio [HR], 0.70; 95% CI, 0.55 to 0.89). The effect of neoadjuvant chemoradiotherapy on overall survival was not time-dependent (P value for interaction, P = .73), and landmark analyses suggested a stable effect on overall survival up to 10 years of follow-up. The absolute 10-year overall survival benefit was 13% (38% v 25%). Neoadjuvant chemoradiotherapy reduced risk of death from esophageal cancer (HR, 0.60; 95% CI, 0.46 to 0.80). Death from other causes was similar between study arms (HR, 1.17; 95% CI, 0.68 to 1.99). Although a clear effect on isolated locoregional (HR, 0.40; 95% CI, 0.21 to 0.72) and synchronous locoregional plus distant relapse (HR, 0.43; 95% CI, 0.26 to 0.72) persisted, isolated distant relapse was comparable (HR, 0.76; 95% CI, 0.52 to 1.13).

CONCLUSION

The overall survival benefit of patients with locally advanced resectable esophageal or junctional cancer who receive preoperative chemoradiotherapy according to CROSS persists for at least 10 years.