FLORIDA CANCER SPECIALISTS & Research Institute

TOP ARTICLES OF THE MONTH

APRIL 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 (JCO)

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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. Impact of a Genomic Test on Treatment Decision in a Predominantly African American Population With Favorable-Risk Prostate Cancer: A Randomized Trial (JCO)

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PURPOSE

The Genomic Prostate Score (GPS), performed on biopsy tissue, predicts adverse outcome in prostate cancer (PCa) and has shown promise for improving patient selection for active surveillance (AS). However, its impact on treatment choice in high-risk populations of African Americans is largely unknown and, in general, the effect of the GPS on this difficult decision has not been evaluated in randomized trials.

METHODS

Two hundred men with National Comprehensive Cancer Network very low to low-intermediate PCa from three Chicago hospitals (70% Black, 16% college graduates) were randomly assigned at diagnosis to standard counseling with or without a 12-gene GPS assay. The primary end point was treatment choice at a second postdiagnosis visit. The proportion of patients choosing AS was compared, and multivariable modeling was used to estimate the effects of various factors on AS acceptance.

RESULTS

AS acceptance was high overall, although marginally lower in the intervention group (77% v 88%; P = .067), and lower still when men with inadequate specimens were excluded (P = .029). Men with lower health literacy who received a GPS were seven-fold less likely to choose AS compared with controls, whereas no difference was seen in men with higher health literacy (Pinteraction = .022). Among men with low-intermediate risk, 69% had GPS values consistent with unfavorable intermediate or high-risk cancer. AS choice was also independently associated with a family history of PCa and having health insurance.

CONCLUSION

In contrast to other studies, the net effect of the GPS was to move patients away from AS, primarily among men with low health literacy. These findings have implications for our understanding of how prognostic molecular assays that generate probabilities of poor outcome can affect treatment decisions in diverse clinical populations.

3. Updated Integrated Analysis of the Efficacy and Safety of Entrectinib in Locally Advanced or Metastatic *ROS1* Fusion–Positive Non–Small-Cell Lung Cancer (JCO)

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PURPOSE

Genetic rearrangements of the tyrosine receptor kinase ROS proto-oncogene 1 (ROS1) are oncogenic drivers in non-small-cell lung cancer (NSCLC). We report the results of an updated integrated analysis of three phase I or II clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2) of the ROS1 tyrosine kinase inhibitor, entrectinib, in ROS1 fusion–positive NSCLC.

METHODS

The efficacy-evaluable population included adults with locally advanced or metastatic ROS1 fusion–positive NSCLC with or without CNS metastases who received entrectinib ≥ 600 mg orally once per day. Co-primary end points were objective response rate (ORR) assessed by blinded independent central review and duration of response (DoR). Secondary end points included progression-free survival (PFS), overall survival (OS), intracranial ORR, intracranial DoR, intracranial PFS, and safety.

RESULTS

In total, 161 patients with a follow-up of ≥ 6 months were evaluable. The median treatment duration was 10.7 months (IQR, 6.4-17.7). The ORR was 67.1% (n = 108, 95% CI, 59.3 to 74.3), and responses were durable (12-month DoR rate, 63%, median DoR 15.7 months). The 12-month PFS rate was 55% (median PFS 15.7 months), and the 12-month OS rate was 81% (median OS not estimable). In 24 patients with measurable baseline CNS metastases by blinded independent central review, the intracranial ORR was 79.2% (n = 19; 95% CI, 57.9 to 92.9), the median intracranial PFS was 12.0 months (95% CI, 6.2 to 19.3), and the median intracranial DoR was 12.9 months (12-month rate, 55%). The safety profile in this updated analysis was similar to that reported in the primary analysis, and no new safety signals were found.

CONCLUSION

Entrectinib continued to demonstrate a high level of clinical benefit for patients with ROS1 fusion–positive NSCLC, including patients with CNS metastases.

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4. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer—The Penelope-B Trial (JCO)

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PURPOSE

About one third of patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative breast cancer who have residual invasive disease after neoadjuvant chemotherapy (NACT) will relapse. Thus, additional therapy is needed. Palbociclib is a cyclindependent kinase 4 and 6 inhibitor demonstrating efficacy in the metastatic setting.

PATIENTS AND METHODS

PENELOPE-B (NCT01864746) is a double-blind, placebo-controlled, phase III study in women with hormone receptor–positive, human epidermal growth factor receptor 2–negative primary breast cancer without a pathological complete response after taxane-containing NACT and at high risk of relapse (clinical pathological

staging-estrogen receptor grading score ≥ 3 or 2 and ypN+). Patients were randomly assigned (1:1) to receive 13 cycles of palbociclib 125 mg once daily or placebo on days 1-21 in a 28-day cycle in addition to endocrine therapy (ET). Primary end point is invasive disease-free survival (iDFS). Final analysis was planned after 290 iDFS events with a two-sided efficacy boundary P < .0463 because of two interim analyses.

RESULTS

One thousand two hundred fifty patients were randomly assigned. The median age was 49.0 years (range, 19-79), and the majority were ypN+ with Ki-67 ≤ 15%; 59.4% of patients had a clinical pathological staging-estrogen receptor grading score ≥ 3. 50.1% received aromatase inhibitor, and 33% of premenopausal women received a luteinizing hormone releasing hormone analog in addition to either tamoxifen or an aromatase inhibitor. After a median follow-up of 42.8 months (92% complete), 308 events were confirmed. Palbociclib did not improve iDFS versus placebo added to ET-stratified hazard ratio, 0.93 (95% repeated CI, 0.74 to 1.17) and two-sided weighted log-rank test (Cui, Hung, and Wang) P = .525. There was no difference among the subgroups. Most common related serious adverse events were infections and vascular disorders in 113 (9.1%) patients with no difference between the treatment arms. Eight fatal serious adverse events (two palbociclib and six placebo) were reported.

CONCLUSION

Palbociclib for 1 year in addition to ET did not improve iDFS in women with residual invasive disease after NACT.

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5. Venous Thromboembolism In Cancer Patients: A Population-Based Cohort Study (Blood)

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- The 12-month cumulative incidence of VTE is currently 3% after cancer diagnosis, which is ninefold higher than in the general population.
- For the past 2 decades, cancer patients' VTE risk increased threefold overall and sixfold in those using chemotherapy or targeted therapy.

ABSTRACT

The incidence of venous thromboembolism (VTE) in cancer patients may have changed in the past decade, possibly due to novel cancer therapies, improved survival, and high-resolution imaging. Danish medical registries were used to identify 499 092 patients with a first-time cancer diagnosis between 1997 and 2017, who were matched to 1 497 276 comparison individuals without cancer from the general population. We computed cumulative incidences of VTE 6 and 12 months after the diagnosis/index date. Hazard ratios (HRs) were calculated using Cox regression. Risk factors were examined by computing subdistribution hazard ratios (SHRs) in a competing-risk analysis. Cumulative incidence of VTE 12 months after the cancer diagnosis/index date was 2.3% (95% confidence interval [CI], 2.2% to 2.3%) in the cancer cohort and 0.35% (95% CI, 0.34% to 0.36%) in the comparison cohort (HR, 8.5; 95% CI, 8.2-8.8). Important risk factors for cancer patients were prior VTE (SHR, 7.6; 95% CI, 7.2-8.0), distant metastasis (SHR, 3.2; 95% CI, 2.9-3.4), and use of chemotherapy (SHR, 3.4; 95% CI, 3.1-3.7), protein kinase inhibitors (SHR, 4.1; 95% CI, 3.4-4.9), antiangiogenic therapy (SHR, 4.4; 95% CI, 3.8-5.2), and immunotherapy (SHR, 3.6; 2.8-4.6). Twelve-month incidence in the cancer cohort increased from 1.0% (95% CI, 0.9% to 1.2%) in 1997 to 3.4% (95% CI, 2.9% to 4.0%) in 2017, which was paralleled by improved 12-month survival and increased use of computed tomography scans, chemotherapy, and targeted therapies. In conclusion, the risk of VTE in cancer patients is increasing steadily and is ninefold higher than in the general population

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6. Ten-Year Outcome of Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: The Randomized Controlled CROSS Trial (JCO)

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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.

7. Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451 (JCO)

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PURPOSE

In extensive-disease small-cell lung cancer (ED-SCLC), response rates to first-line platinum-based chemotherapy are robust, but responses lack durability. CheckMate 451, a double-blind phase III trial, evaluated nivolumab plus ipilimumab and nivolumab monotherapy as maintenance therapy following first-line chemotherapy for ED-SCLC.

METHODS

Patients with ED-SCLC, Eastern Cooperative Oncology Group performance status 0-1, and no progression after ≤ 4 cycles of first-line chemotherapy were randomly assigned (1:1:1) to nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks for 12 weeks followed by nivolumab 240 mg once every 2 weeks, nivolumab 240 mg once every 2 weeks, or placebo for ≤ 2 years or until progression or unacceptable toxicity. Primary end point was overall survival (OS) with nivolumab plus ipilimumab versus placebo. Secondary end points were hierarchically tested.

RESULTS

Overall, 834 patients were randomly assigned. The minimum follow-up was 8.9 months. OS was not significantly prolonged with nivolumab plus ipilimumab versus placebo (hazard ratio [HR], 0.92; 95% CI, 0.75 to 1.12; P = .37; median, 9.2 v 9.6 months). The HR for OS with nivolumab versus placebo was 0.84 (95% CI, 0.69 to 1.02); the median OS for nivolumab was 10.4 months. Progression-free survival HRs versus placebo were 0.72 for nivolumab plus ipilimumab (95% CI, 0.60 to 0.87) and 0.67 for nivolumab (95% CI, 0.56 to 0.81). A trend toward OS benefit with nivolumab plus ipilimumab was observed in patients with tumor mutational burden ≥ 13 mutations per megabase. Rates of grade 3-4 treatment-related adverse events were nivolumab plus ipilimumab (52.2%), nivolumab (11.5%), and placebo (8.4%).

CONCLUSION

Maintenance therapy with nivolumab plus ipilimumab did not prolong OS for patients with ED-SCLC who did not progress on first-line chemotherapy. There were no new safety signals.

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8. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer (NEJM)

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BACKGROUND

Patients with metastatic triple-negative breast cancer have a poor prognosis. Sacituzumab govitecan is an antibody-drug conjugate composed of an antibody targeting the human trophoblast cell-surface antigen 2 (Trop-

2), which is expressed in the majority of breast cancers, coupled to SN-38 (topoisomerase I inhibitor) through a proprietary hydrolyzable linker.

METHODS

In this randomized, phase 3 trial, we evaluated sacituzumab govitecan as compared with single-agent chemotherapy of the physician's choice (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with relapsed or refractory metastatic triple-negative breast cancer. The primary end point was progression-free survival (as determined by blinded independent central review) among patients without brain metastases.

RESULTS

A total of 468 patients without brain metastases were randomly assigned to receive sacituzumab govitecan (235 patients) or chemotherapy (233 patients). The median age was 54 years; all the patients had previous use of taxanes. The median progression-free survival was 5.6 months (95% confidence interval [CI], 4.3 to 6.3; 166 events) with sacituzumab govitecan and 1.7 months (95% CI, 1.5 to 2.6; 150 events) with chemotherapy (hazard ratio for disease progression or death, 0.41; 95% CI, 0.32 to 0.52; P<0.001). The median overall survival was 12.1 months (95% CI, 10.7 to 14.0) with sacituzumab govitecan and 6.7 months (95% CI, 5.8 to 7.7) with chemotherapy (hazard ratio for death, 0.48; 95% CI, 0.38 to 0.59; P<0.001). The percentage of patients with an objective response was 35% with sacituzumab govitecan and 5% with chemotherapy. The incidences of key treatment-related adverse events of grade 3 or higher were neutropenia (51% with sacituzumab govitecan and 33% with chemotherapy), leukopenia (10% and 5%), diarrhea (10% and <1%), anemia (8% and 5%), and febrile neutropenia (6% and 2%). There were three deaths owing to adverse events in each group; no deaths were considered to be related to sacituzumab govitecan treatment.

CONCLUSIONS

Progression-free and overall survival were significantly longer with sacituzumab govitecan than with single-agent chemotherapy among patients with metastatic triple-negative breast cancer. Myelosuppression and diarrhea were more frequent with sacituzumab govitecan. (Funded by Immunomedics; ASCENT ClinicalTrials.gov number, NCT02574455; EudraCT number, 2017-003019-21.).

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9. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma (NEJM)

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BACKGROUND

Lenvatinib in combination with pembrolizumab or everolimus has activity against advanced renal cell carcinoma. The efficacy of these regimens as compared with that of sunitinib is unclear.

METHODS

In this phase 3 trial, we randomly assigned (in a 1:1:1 ratio) patients with advanced renal cell carcinoma and no previous systemic therapy to receive lenvatinib (20 mg orally once daily) plus pembrolizumab (200 mg intravenously once every 3 weeks), lenvatinib (18 mg orally once daily) plus everolimus (5 mg orally once daily), or sunitinib (50 mg orally once daily, alternating 4 weeks receiving treatment and 2 weeks without treatment). The primary end point was progression-free survival, as assessed by an independent review committee in accordance with Response Evaluation Criteria in Solid Tumors, version 1.1. Overall survival and safety were also evaluated.

RESULTS

A total of 1069 patients were randomly assigned to receive lenvatinib plus pembrolizumab (355 patients), lenvatinib plus everolimus (357), or sunitinib (357). Progression-free survival was longer with lenvatinib plus pembrolizumab than with sunitinib (median, 23.9 vs. 9.2 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.32 to 0.49; P<0.001) and was longer with lenvatinib plus everolimus than with sunitinib (median, 14.7 vs. 9.2 months; hazard ratio, 0.65; 95% CI, 0.53 to 0.80; P<0.001). Overall survival was longer with lenvatinib plus pembrolizumab than with sunitinib (hazard ratio for death, 0.66; 95% CI, 0.49 to 0.88; P=0.005) but was not longer with lenvatinib plus everolimus than with sunitinib (hazard ratio, 1.15; 95% CI, 0.88 to 1.50; P=0.30). Grade 3 or higher adverse events emerged or worsened during treatment in 82.4% of the patients who received lenvatinib plus pembrolizumab, 83.1% of those who received lenvatinib plus everolimus, and 71.8% of those who received sunitinib. Grade 3 or higher adverse events occurring in at least 10% of the patients in any group included hypertension, diarrhea, and elevated lipase levels.

CONCLUSION

Lenvatinib plus pembrolizumab was associated with significantly longer progression-free survival and overall survival than sunitinib. (Funded by Eisai and Merck Sharp and Dohme; CLEAR ClinicalTrials.gov number, NCT02811861.)

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10. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination (NEJM)

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BACKGROUND

Several cases of unusual thrombotic events and thrombocytopenia have developed after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ChAdOx1 nCov-19, AstraZeneca). More data were needed on the pathogenesis of this unusual clotting disorder.

METHODS

We assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)–heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events, with 28 testing positive on a screening PF4–heparin immunoassay.

RESULTS

Of the 11 original patients, 9 were women, with a median age of 36 years (range, 22 to 49). Beginning 5 to 16 days after vaccination, the patients presented with one or more thrombotic events, with the exception of 1 patient, who presented with fatal intracranial hemorrhage. Of the patients with one or more thrombotic events, 9 had cerebral venous thrombosis, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thromboses; of these patients, 6 died. Five patients had disseminated intravascular coagulation. None of the patients had received heparin before symptom onset. All 28 patients who tested positive for antibodies against PF4–heparin tested positive on the platelet-activation assay in the presence of PF4 independent of heparin. Platelet activation was inhibited by high levels of heparin, Fc receptor–blocking monoclonal antibody, and

immune globulin (10 mg per milliliter). Additional studies with PF4 or PF4–heparin affinity purified antibodies in 2 patients confirmed PF4-dependent platelet activation.

CONCLUSIONS

Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia. (Funded by the German Research Foundation.)