FLORIDA CANCER SPECIALISTS & Research Institute

TOP ARTICLES OF THE MONTH

JANUARY - FEBRUARY 2021 | Lucio N. Gordan, MD

1. Standardization of ^{18}F-FDG–PET/CT According to Deauville Criteria for Metabolic Complete Response Definition in Newly Diagnosed Multiple Myeloma

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PURPOSE

^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) is currently the standard technique to define minimal residual disease (MRD) status outside the bone marrow (BM) in patients with multiple myeloma (MM). This study aimed to define criteria for PET complete metabolic response after therapy, jointly analyzing a subgroup of newly diagnosed transplantation-eligible patients with MM enrolled in two independent European randomized phase III trials (IFM/DFCI2009 and EMN02/HO95).

PATIENTS AND METHODS

Two hundred twenty-eight patients were observed for a median of 62.9 months. By study design, PET/CT scans were performed at baseline and before starting maintenance (premaintenance [PM]). The five-point Deauville scale (DS) was applied to describe BM (BM score [BMS]) and focal lesion (FL; FL score [FS]) uptake and tested a posteriori in uni- and multivariable analyses for their impact on clinical outcomes.

RESULTS

At baseline, 78% of patients had FLs (11% extramedullary), 80% with an FS ≥ 4. All patients had BM diffuse uptake (35.5% with BMS ≥ 4). At PM, 31% of patients had visually detectable FLs (2% extramedullary), 24% and 67.7% of them with an FS of 3 and ≥ 4, respectively. At PM, 98% of patients retained residual BM diffuse uptake, which was significantly lower than at baseline (mainly between BMS 2 and 3, BMS was ≥ 4 in only 8.7% of patients). By both uni- and multivariable analysis, FS and BMS < 4 were associated with prolonged progression-free survival (PFS) and overall survival (OS) at PM (OS: hazard ratio [HR], 0.6 and 0.47, respectively; PFS: HR, 0.36 and 0.24, respectively)

CONCLUSION

FL and BM FDG uptake lower than the liver background after therapy was an independent predictor for improved PFS and OS and can be proposed as the standardized criterion of PET complete metabolic response, confirming the value of the DS for patients with MM.

2. Nivolumab Plus Ipilimumab for Treatment-Naïve Metastatic Uveal Melanoma: An Open-Label, Multicenter, Phase II Trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402)

José María Piulats, Enrique Espinosa, Luis de la Cruz Merino, Mar Varela, Lorenzo Alonso Carrión, Salvador Martín-Algarra, Rafael López Castro, Teresa Curiel, Delvys Rodríguez-Abreu, Miriam Redrado, Montserrat Gomà, Antonio José Rullán, Alfonso Calvo González, Alfonso Berrocal-Jaime

PURPOSE

This study aimed to assess the efficacy of the combination of nivolumab (nivo) plus ipilimumab (ipi) as a first-line therapy with respect to the 12-month overall survival (OS) in patients with metastatic uveal melanoma (MUM) who are not eligible for liver resection.

METHODS

This was a single-arm, phase II trial led by the Spanish Multidisciplinary Melanoma Group (GEM) on nivo plus ipi for systemic treatment-naïve patients of age > 18 years, with histologically confirmed MUM, Eastern Cooperative Oncology Group-PS 0/1, and confirmed progressive metastatic disease (M1). Nivo (1 mg/kg once every 3 weeks) and ipi (3 mg/kg once every 3 weeks) were administered during four inductions, followed by nivo (3 mg/kg once every 2 weeks) until progressive disease, toxicity, or withdrawal. The primary end point was 12-month OS. OS, progression-free survival (PFS), and overall response rate were evaluated every 6 weeks using RECIST (v1.1). Safety was also evaluated. Logistic regression and Cox proportional hazard models comprising relevant clinical factors were used to evaluate the potential association with response to treatment and survival. Cytokines were quantified in serum samples for their putative role in immune modulation/angiogenesis and/or earlier evidence of involvement in immunotherapy.

RESULTS

A total of 52 patients with a median age of 59 years (range, 26-84 years) were enrolled. Overall, 78.8%, 56%, and 32% of patients had liver M1, extra-liver M1, and elevated lactate dehydrogenase. Stable disease was the most common outcome (51.9%). The primary end point was 12-month OS, which was 51.9% (95% CI, 38.3 to 65.5). The median OS and PFS were 12.7 months and 3.0 months, respectively. PFS was influenced by higher LDH values.

CONCLUSIONS

Nivo plus ipi in the first-line setting for MUM showed a modest improvement in OS over historical benchmarks of chemotherapy, with a manageable toxicity profile.

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3. ARTSCAN III: A Randomized Phase III Study Comparing Chemoradiotherapy With Cisplatin Versus Cetuximab in Patients With Locoregionally Advanced Head and Neck Squamous Cell Cancer

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MATERIALS AND METHODS

Eligible patients were randomly assigned 1:1 to receive either intravenous cetuximab 400 mg/m^2 1 week before start of RT followed by 250 mg/m^2/wk, or weekly intravenous cisplatin 40 mg/m^2, during RT. RT was conventionally fractionated. Patients with T3-T4 tumors underwent a second random assignment 1:1 between standard RT dose

68.0 Gy to the primary tumor or dose escalation to 73.1 Gy. Primary end point was overall survival (OS) evaluated using adjusted Cox regression analysis. Secondary end points were locoregional control, local control with dose-escalated RT, pattern of failure, and adverse effects.

RESULTS

Study inclusion was prematurely closed after an unplanned interim analysis when 298 patients had been randomly assigned. At 3 years, OS was 88% (95% CI, 83% to 94%) and 78% (95% CI, 71% to 85%) in the cisplatin and cetuximab groups, respectively (adjusted hazard ratio, 1.63; 95% CI, 0.93 to 2.86; *P* = .086). The cumulative incidence of locoregional failures at 3 years was 23% (95% CI, 16% to 31%) compared with 9% (95% CI, 4% to 14%) in the cetuximab versus the cisplatin group (Gray's test *P* = .0036). The cumulative incidence of distant failures did not differ between the treatment groups. Dose escalation in T3-T4 tumors did not increase local control.

CONCLUSION

Cetuximab is inferior to cisplatin regarding locoregional control for concomitant treatment with RT in patients with locoregionally advanced HNSCC. Additional studies are needed to identify possible subgroups that still may benefit from concomitant cetuximab treatment.

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4. Randomized Phase II Trial of Nivolumab With Stereotactic Body Radiotherapy Versus Nivolumab Alone in Metastatic Head and Neck Squamous Cell Carcinoma

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PURPOSE

The objective response rate (ORR) for single-agent anti–programmed death receptor 1 (anti–PD-1) therapy is modest in patients with metastatic or recurrent head and neck squamous cell carcinoma (HNSCC). We aimed to test whether radiotherapy may act synergistically with anti–PD-1 therapy to improve response through the abscopal effect.

PATIENTS AND METHODS

We conducted a single-center, randomized, phase II trial of nivolumab (anti–PD-1 therapy) versus nivolumab plus stereotactic body radiotherapy (SBRT) in patients with metastatic HNSCC. Patients had at least two metastatic lesions: one that could be safely irradiated and one measurable by RECIST version 1.1. Patients were randomly assigned (1:1), stratified by human papillomavirus status, to nivolumab (3 mg/kg intravenously every 2 weeks) or nivolumab (same dose) plus SBRT (9 Gy × 3) to 1 lesion. The primary end point was ORR in nonirradiated lesions, which was assessed by RECIST in patients with at least one available set of on-treatment images; safety was assessed in a per-protocol population.

RESULTS

Between March 11, 2016, and June 22, 2018, 62 patients were randomly assigned to nivolumab (n = 30) or nivolumab plus SBRT (n = 32). There was no statistically significant ORR difference between arms (34.5% [95% CI, 19.9% to 52.7%] v 29.0% [95% CI, 16.1% to 46.6%]; *P* = .86). There was no significant difference in overall survival (*P* = .75), progression-free survival (*P* = .79), or response duration (*P* = .26). Grade 3-5 toxicities were similar (13.3% v 9.7%; *P* = .70).

CONCLUSION

We found no improvement in response and no evidence of an abscopal effect with the addition of SBRT to nivolumab in unselected patients with metastatic HNSCC.

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5. Randomized Phase III Study of Irinotecan Plus Cisplatin Versus Etoposide Plus Cisplatin for Completely Resected High-Grade Neuroendocrine Carcinoma of the Lung: JCOG1205/1206

Hirotsugu Kenmotsu, Seiji Niho, Masahiro Tsuboi, Masashi Wakabayashi, Genichiro Ishii, Kazuo Nakagawa, Haruko Daga, Hiroshi Tanaka, Haruhiro Saito, Keiju Aokage, Toshiaki Takahashi, Toshi Menju, Takashi Kasai, Ichiro Yoshino, Koichi Minato, Morihito Okada, Junko Eba, Hisao Asamura, Yuichiro Ohe, Shun-Ichi Watanabe Investigators

PURPOSE

To verify the superiority of irinotecan plus cisplatin over etoposide plus cisplatin as postoperative adjuvant chemotherapy for patients with pathologic stage I-IIIA, completely resected, high-grade neuroendocrine carcinoma (HGNEC) of the lung.

METHODS

This was a randomized, open-label, phase III study on patients with completely resected stage I-IIIA HGNEC of the lung. They were randomly assigned to receive either etoposide (100 mg/m^2, days 1-3) plus cisplatin (80 mg/m^2, day 1) or irinotecan (60 mg/m^2, days 1, 8, 15) plus cisplatin (60 mg/m^2, day 1) up to four cycles. The primary end point was relapse-free survival (RFS) in the intention-to-treat population. This trial was registered with the Japan Registry of Clinical Trials (jRCTs031180216).

RESULTS

Between April 2013 and October 2018, 221 patients were enrolled (etoposide plus cisplatin arm, 111 patients; irinotecan plus cisplatin arm, 110 patients). In the second interim analysis, early termination of the trial was recommended because of futility. At a median follow-up of 24.1 months, the 3-year RFS was 65.4% for etoposide plus cisplatin and 69.0% for irinotecan plus cisplatin, with a hazard ratio of 1.076 (95% CI, 0.666 to 1.738; one-sided log-rank P = .619). Grade 3-4 adverse events were more frequent in the etoposide plus cisplatin arm, with febrile neutropenia (20% of 109 patients v 4% of 107 patients) and neutropenia (97% v 36%) being the most common. Meanwhile, grade 3-4 anorexia (6% v11%) and diarrhea (1% v 8%) were more frequently observed in the irinotecan plus cisplatin arm.

CONCLUSION

Irinotecan plus cisplatin is not superior to etoposide plus cisplatin for improving RFS in patients with completely resected HGNEC; thus, etoposide plus cisplatin remains the standard treatment.

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6. Randomized Phase III KEYNOTE-181 Study of Pembrolizumab Versus Chemotherapy in Advanced Esophageal Cancer

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PATIENTS AND METHODS

In this open-label, phase III study, we randomly assigned (1:1) 628 patients with advanced/metastatic squamous cell carcinoma or adenocarcinoma of the esophagus, that progressed after one prior therapy, to pembrolizumab 200 mg every 3 weeks for up to 2 years or chemotherapy (investigator's choice of paclitaxel, docetaxel, or irinotecan). Primary end points were overall survival (OS) in patients with programmed death ligand-1 (PD-L1) combined positive score (CPS) ≥ 10, in patients with squamous cell carcinoma, and in all patients (one-sided α 0.9%, 0.8%, and 0.8%, respectively).

RESULTS

At final analysis, conducted 16 months after the last patient was randomly assigned, OS was prolonged with pembrolizumab versus chemotherapy for patients with CPS ≥ 10 (median, 9.3 v 6.7 months; hazard ratio [HR], 0.69 [95% CI, 0.52 to 0.93]; P = .0074). Estimated 12-month OS rate was 43% (95% CI, 33.5% to 52.1%) with pembrolizumab versus 20% (95% CI, 13.5% to 28.3%) with chemotherapy. Median OS was 8.2 months versus 7.1 months (HR, 0.78 [95% CI, 0.63 to 0.96]; P = .0095) in patients with squamous cell carcinoma and 7.1 months versus 7.1 months (HR, 0.89 [95% CI, 0.75 to 1.05]; P = .0560) in all patients. Grade 3-5 treatment-related adverse events occurred in 18.2% of patients with pembrolizumab versus 40.9% in those who underwent chemotherapy.

CONCLUSION

Pembrolizumab prolonged OS versus chemotherapy as second-line therapy for advanced esophageal cancer in patients with PD-L1 CPS ≥ 10, with fewer treatment-related adverse events.

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7. Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial

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PURPOSE

To report the long-term results of external-beam accelerated partial-breast irradiation (APBI) intensity-modulated radiation therapy (IMRT) Florence phase III trial comparing whole-breast irradiation (WBI) to APBI in early-stage breast cancer.

PATIENTS AND METHODS

The primary end point was to determine the 5-year difference in ipsilateral breast tumor recurrence (IBTR)

between 30 Gy in 5 once-daily fractions (APBI arm) and 50 Gy in 25 fractions with a tumor bed boost (WBI arm) after breast-conserving surgery.

RESULTS

Five hundred twenty patients, more than 90% of whom had characteristics associated with low recurrence risk, were randomly assigned (WBI, n = 260; APBI, n = 260) between 2005 and 2013. Median follow-up was 10.7 years. The 10-year cumulative incidence of IBTR was 2.5% (n = 6) in the WBI and 3.7% (n = 9) in the APBI arm (hazard ratio [HR], 1.56; 95% CI, 0.55 to 4.37; P = .40). Overall survival at 10 years was 91.9% in both arms (HR, 0.95; 95% CI, 0.50 to 1.79; P = .86). Breast cancer–specific survival at 10 years was 96.7% in the WBI and 97.8% in the APBI arm (HR, 0.65; 95% CI, 0.21 to 1.99; P = .45). The APBI arm showed significantly less acute toxicity (P = .0001) and late toxicity (P = .0001) and improved cosmetic outcome as evaluated by both physician (P = .0001) and patient (P = .0001).

CONCLUSION

The 10-year cumulative IBTR incidence in early breast cancer treated with external APBI using IMRT technique in 5 once-daily fractions is low and not different from that after WBI. Acute and late treatment-related toxicity and cosmesis outcomes were significantly in favor of APBI.

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8. Randomized Trial of Irinotecan and Cetuximab With or Without Vemurafenib in BRAF-Mutant Metastatic Colorectal Cancer (SWOG S1406)

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PURPOSE

BRAFV600E mutations are rarely associated with objective responses to the BRAF inhibitor vemurafenib in patients with metastatic colorectal cancer (CRC). Blockade of BRAFV600E by vemurafenib causes feedback upregulation of EGFR, whose signaling activities can be impeded by cetuximab.

METHODS

One hundred six patients with BRAFV600E-mutated metastatic CRC previously treated with one or two regimens were randomly assigned to irinotecan and cetuximab with or without vemurafenib (960 mg PO twice daily).

RESULTS

Progression-free survival, the primary end point, was improved with the addition of vemurafenib (hazard ratio, 0.50, P = .001). The response rate was 17% versus 4% (P = .05), with a disease control rate of 65% versus 21% (P < .001). A decline in circulating tumor DNA BRAFV600E variant allele frequency was seen in 87% versus 0% of patients (P < .001), with a low incidence of acquired RAS alterations at the time of progression. RNA profiling suggested that treatment benefit did not depend on previously established BRAF subgroups or the consensus molecular subtype.

CONCLUSION

Simultaneous inhibition of EGFR and BRAF combined with irinotecan is effective in BRAFV600E-mutated CR.

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9. A Population-Based Study of Genes Previously Implicated in Breast Cancer

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BACKGROUND

Population-based estimates of the risk of breast cancer associated with germline pathogenic variants in cancer-predisposition genes are critically needed for risk assessment and management in women with inherited pathogenic variants.

METHODS

In a population-based case–control study, we performed sequencing using a custom multigene amplicon-based panel to identify germline pathogenic variants in 28 cancer-predisposition genes among 32,247 women with breast cancer (case patients) and 32,544 unaffected women (controls) from population-based studies in the Cancer Risk Estimates Related to Susceptibility (CARRIERS) consortium. Associations between pathogenic variants in each gene and the risk of breast cancer were assessed.

RESULTS

Pathogenic variants in 12 established breast cancer–predisposition genes were detected in 5.03% of case patients and in 1.63% of controls. Pathogenic variants in BRCA1 and BRCA2 were associated with a high risk of breast cancer, with odds ratios of 7.62 (95% confidence interval [CI], 5.33 to 11.27) and 5.23 (95% CI, 4.09 to 6.77), respectively. Pathogenic variants in PALB2 were associated with a moderate risk (odds ratio, 3.83; 95% CI, 2.68 to 5.63). Pathogenic variants in BARD1, RAD51C, and RAD51D were associated with increased risks of estrogen receptor–negative breast cancer and triple-negative breast cancer, whereas pathogenic variants in ATM, CDH1, and CHEK2 were associated with an increased risk of estrogen receptor–positive breast cancer. Pathogenic variants in 16 candidate breast cancer–predisposition genes, including the c.657_661del5 founder pathogenic variant in NBN, were not associated with an increased risk of breast cancer.

CONCLUSIONS

This study provides estimates of the prevalence and risk of breast cancer associated with pathogenic variants in known breast cancer–predisposition genes in the U.S. population. These estimates can inform cancer testing and screening and improve clinical management strategies for women in the general population with inherited pathogenic variants in these genes. (Funded by the National Institutes of Health and the Breast Cancer Research Foundation.)

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10. Aspirin Use and Risk of Colorectal Cancer Among Older Adults

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FINDINGS

In this pooled analysis of 2 cohort studies with a total of 94 540 participants, regular use of aspirin at or after age 70 years was associated with a lower risk of colorectal cancer compared with nonregular use. However, this reduction in risk was evident only among individuals who initiated use at a younger age.

MEANING

These results suggest that the initiation of aspirin use at an older age for the sole purpose of primary prevention of colorectal cancer should be discouraged; however, the findings support recommendations to continue using aspirin if initiated at a younger age.

ABSTRACT

Importance Although aspirin is recommended for the prevention of colorectal cancer (CRC) among adults aged 50 to 59 years, recent data from a randomized clinical trial suggest a lack of benefit and even possible harm among older adults.

OBJECTIVE

To examine the association between aspirin use and the risk of incident CRC among older adults.

DESIGN, SETTING, AND PARTICIPANTS

A pooled analysis was conducted of 2 large US cohort studies, the Nurses' Health Study (June 1, 1980–June 30, 2014) and Health Professionals Follow-up Study (January 1, 1986–January 31, 2014). A total of 94 540 participants aged 70 years or older were included and followed up to June 30, 2014, for women or January 31, 2014, for men. Participants with a diagnosis of any cancer, except nonmelanoma skin cancer, or inflammatory bowel disease were excluded. Statistical analyses were conducted from December 2019 to October 2020.

MAIN OUTCOMES AND MEASURES

Cox proportional hazards models were used to calculate multivariable adjusted hazard ratios (HRs) and 95% CIs for incident CRC.

RESULTS

Among the 94 540 participants (mean [SD] age, 76.4 [4.9] years for women, 77.7 [5.6] years for men; 67 223 women [71.1%]; 65 259 White women [97.1%], 24 915 White men [96.0%]) aged 70 years or older, 1431 incident cases of CRC were documented over 996 463 person-years of follow-up. After adjustment for other risk factors, regular use of aspirin was associated with a significantly lower risk of CRC at or after age 70 years compared with nonregular use (HR, 0.80; 95% CI, 0.72-0.90). However, the inverse association was evident only among aspirin users who initiated aspirin use before age 70 years (HR, 0.80; 95% CI, 0.67-0.95). In contrast, initiating aspirin use at or after 70 years was not significantly associated with a lower risk of CRC (HR, 0.92; 95% CI, 0.76-1.11).

CONCLUSIONS AND RELEVANCE

Initiating aspirin at an older age was not associated with a lower risk of CRC in this pooled analysis of 2 cohort studies. In contrast, those who used aspirin before age 70 years and continued into their 70s or later had a reduced risk of CRC.