FLORIDA CANCER SPECIALISTS & Research Institute

TOP ARTICLES OF THE MONTH

AUGUST 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. TROPHY-U-01: A Phase II Open-Label Study of Sacituzumab Govitecan in Patients With Metastatic Urothelial Carcinoma Progressing After Platinum-Based Chemotherapy and Checkpoint Inhibitors

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PURPOSE

Patients with metastatic urothelial carcinoma (mUC) who progress on platinum-based combination chemotherapy (PLT) and checkpoint inhibitors (CPIs) have limited options that offer objective response rates (ORRs) of approximately 10% with a median overall survival (OS) of 7-8 months. Sacituzumab govitecan (SG) is a TROP-2–directed antibody-drug conjugate with an SN-38 payload that has shown preliminary activity in mUC.

METHODS

TROPHY-U-01 (ClinicalTrials.gov identifier: NCT03547973) is a multicohort, open-label, phase II, registrational study. Cohort 1 includes patients with locally advanced or unresectable or mUC who had progressed after prior PLT and CPI. Patients received SG 10 mg/kg on days 1 and 8 of 21-day cycles. The primary outcome was centrally reviewed ORR; secondary outcomes were progression-free survival, OS, duration of response, and safety.

RESULTS

Cohort 1 included 113 patients (78% men; median age, 66 years; 66.4% visceral metastases; median of three [range, 1-8] prior therapies). At a median follow-up of 9.1 months, the ORR was 27% (31 of 113; 95% CI, 19.5 to 36.6); 77% had decrease in measurable disease. Median duration of response was 7.2 months (95% CI, 4.7 to 8.6 months), with median progression-free survival and OS of 5.4 months (95% CI, 3.5 to 7.2 months) and 10.9 months (95% CI, 9.0 to 13.8 months), respectively. Key grade ≥ 3 treatment-related adverse events included neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), and febrile neutropenia (10%), with 6% discontinuing treatment because of treatment-related adverse events.

CONCLUSION

SG is an active drug with a manageable safety profile with most common toxicities of neutropenia and diarrhea. SG has notable efficacy compared with historical controls in pretreated mUC that has progressed on both prior PLT regimens and CPI. The results from this study supported accelerated approval of SG in this population.

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3. Homologous Recombination Deficiency in Pancreatic Cancer: A Systematic Review and Prevalence Meta-Analysis

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PURPOSE

To analyze the prevalence of homologous recombination deficiency (HRD) in patients with pancreatic ductal adenocarcinoma (PDAC).

MATERIALS AND METHODS

We conducted a systematic review and meta-analysis of the prevalence of HRD in PDAC from PubMed, Scopus, and Cochrane Library databases, and online cancer genomic data sets. The main outcome was pooled prevalence of somatic and germline mutations in the better characterized HRD genes (BRCA1, BRCA2, PALB2, ATM, ATR, CHEK2, RAD51, and the FANC genes). The secondary outcomes were prevalence of germline mutations overall, and in sporadic and familial cases; prevalence of germline BRCA1/2 mutations in Ashkenazi Jewish (AJ); and prevalence of HRD based on other definitions (ie, alterations in other genes, genomic scars, and mutational signatures). Random-effects modeling with the Freeman-Tukey transformation was used for the analyses. PROSPERO registration number: (CRD42020190813).

RESULTS

Sixty studies with 21,842 participants were included in the systematic review and 57 in the meta-analysis. Prevalence of germline and somatic mutations was BRCA1: 0.9%, BRCA2: 3.5%, PALB2: 0.2%, ATM: 2.2%, CHEK2: 0.3%, FANC: 0.5%, RAD51: 0.0%, and ATR: 0.1%. Prevalence of germline mutations was BRCA1: 0.9% (2.4% in AJ), BRCA2: 3.8% (8.2% in AJ), PALB2: 0.2%, ATM: 2%, CHEK2: 0.3%, and FANC: 0.4%. No significant differences between sporadic and familial cases were identified. HRD prevalence ranged between 14.5%-16.5% through targeted next-generation sequencing and 24%-44% through whole-genome or whole-exome sequencing allowing complementary genomic analysis, including genomic scars and other signatures (surrogate markers of HRD).

CONCLUSION

Surrogate readouts of HRD identify a greater proportion of patients with HRD than analyses limited to gene-level approaches. There is a clear need to harmonize HRD definitions and to validate the optimal biomarker for treatment selection. Universal HRD screening including integrated somatic and germline analysis should be offered to all patients with PDAC.

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4. Pembrolizumab Plus Ipilimumab Following Anti-PD-1/L1 Failure in Melanoma

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PURPOSE

Combination of antiprogrammed cell death protein-1 (PD-1) plus anti–cytotoxic T-cell lymphocyte-4 (anti-CTLA-4) immunotherapy shows greater response rates (RRs) than anti-PD-1 antibody alone in melanoma, but RR after initial anti-PD-1 and programmed death ligand-1 (PD-L1) antibody progression awaits robust investigation. Anti-CTLA-4 antibody alone after anti-PD-1/L1 antibody progression has a historical RR of 13%. We report the results of the first prospective clinical trial evaluating ipilimumab 1 mg/kg plus pembrolizumab following progression on anti-PD-1 immunotherapy.

METHODS

Patients with advanced melanoma who had progressed on anti-PD-1/L1 antibody as immediate prior therapy (including non–anti-CTLA-4 antibody combinations) were eligible. Patients received pembrolizumab 200 mg plus ipilimumab 1 mg/kg once every 3 weeks for four doses, followed by pembrolizumab monotherapy. The primary end point was RR by irRECIST. After 35 patients, the trial met the primary end point and was expanded to enroll a total of 70 patients to better estimate the RR.

RESULTS

Prior treatments included 60 on anti-PD-1 antibody alone and 10 on anti-PD-1/L1 antibody–based combinations. Thirteen patients had progressed in the adjuvant setting. The median length of prior treatment with anti-PD-1/L1 antibody was 4.8 months. Response assessments included five complete and 15 partial responses, making the irRECIST RR 29% among the entire trial population. The median progression-free survival was 5.0 months, and the median overall survival was 24.7 months. The median duration of response was 16.6 months. There was no difference in median time on prior anti-PD1/L1 or time to PD1 + CTLA4 initiation between responders and nonresponders. Grade 3-4 drug-related adverse events occurred in 27% of patients. Responses occurred in PD-L1–negative, non-T-cell–inflamed, and intermediate tumor phenotypes.

CONCLUSION

To our knowledge, this is the first prospective study in melanoma of pembrolizumab plus low-dose ipilimumab after anti-PD-1/L1 immunotherapy failure, demonstrating significant antitumor activity and tolerability.

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5. How I treat chronic lymphocytic leukemia after venetoclax

Thomas E Lew, Constantine S Tam, John F Seymour

ABSTRACT

Venetoclax-based regimens have expanded the therapeutic options for patients with chronic lymphocytic leukemia (CLL), frequently achieving remissions with undetectable measurable residual disease (uMRD) and facilitating time-limited treatment without utilizing chemotherapy. Although response rates are high and durable disease control is common, longer-term follow-up of patients with relapsed and refractory (RR) disease, especially in the presence of TP53 aberrations, demonstrates frequent disease resistance and progression. Although the understanding of venetoclax resistance remains incomplete, progressive disease (PD) is typified by oligoclonal leukemic populations with distinct resistance mechanisms, including BCL2 mutations, upregulation of alternative BCL2 family proteins and genomic instability. Although most commonly observed in heavily pre-treated patients with disease refractory to fludarabine and harboring complex karyotype (CK), Richter transformation (RT) presents a distinct and challenging manifestation of venetoclax resistance. For patients with progressive CLL after venetoclax, treatment options include B-cell receptor pathway inhibitors (BCRis), allogeneic stem cell transplantation (SCT), chimeric antigen receptor (CAR) T-cells, and venetoclax re-treatment for those with disease relapsing after time-limited therapy. However, data to inform clinical decisions for these patients are limited. We review the biology of venetoclax resistance and outline an approach to the common clinical scenarios encountered after venetoclax-based therapy that will increasingly confront practising clinicians.

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6. Brentuximab vedotin in combination with nivolumab in relapsed or refractory Hodgkin lymphoma: 3-year study results

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ABSTRACT

This phase 1-2 study evaluated brentuximab vedotin (BV) combined with nivolumab (Nivo) as first salvage therapy in patients with relapsed or refractory classical Hodgkin lymphoma. In parts 1 and 2, patients received staggered dosing of BV and Nivo in cycle 1, followed by same-day dosing in cycles 2-4. In part 3, both study drugs were dosed same day for all 4 cycles. At end of study treatment, patients could undergo autologous stem cell transplantation (ASCT) per investigator discretion. The objective response rate (N=91) was 85%, with 67% achieving a complete response. At a median follow-up of 34.3 months, the estimated progression-free survival (PFS) rate at 3 years was 77% (95% confidence interval [CI]: 65% to 86%) and 91% (95% CI, 79% to 96%) for patients undergoing ASCT directly after study treatment. Overall survival at 3 years was 93% (95% CI, 85% to 97%). The most common adverse events (AEs) prior to ASCT were nausea (52%) and infusion-related reactions (43%), all grade 1 or 2. A total of 16 patients (18%) had immune-related AEs that required systemic corticosteroid treatment. Peripheral blood immune signatures were consistent with an activated T-cell response. Median gene expression of CD30 in tumors was higher in patients who responded compared with those who did not. Longer-term follow up of BV and Nivo as a first salvage regimen shows durable efficacy and impressive PFS, especially in patients who proceeded directly to transplant, without additional toxicity concerns.

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7. Ensartinib vs Crizotinib for Patients With Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer: A Randomized Clinical Trial

Leora Horn, Ziping Wang, Gang Wu, Elena Poddubskaya, Tony Mok, Martin Reck, Heather Wakelee, Alberto A Chiappori, Dae Ho Lee, Valeriy Breder, Sergey Orlov, Irfan Cicin, Ying Cheng, Yunpeng Liu, Yun Fan, Jennifer G Whisenant, Yi Zhou, Vance Oertel, Kim Harrow, Chris Liang, Li Mao, Giovanni Selvaggi, Yi-Long Wu

IMPORTANCE

Ensartinib, an oral tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), has shown systemic and central nervous system efficacy for patients with ALK-positive non-small cell lung cancer (NSCLC).

OBJECTIVE

To compare ensartinib with crizotinib among patients with advanced ALK-positive NSCLC who had not received prior treatment with an ALK inhibitor.

DESIGN, SETTING, AND PARTICIPANTS

This open-label, multicenter, randomized, phase 3 trial conducted in 120 centers in 21 countries enrolled 290 patients between July 25, 2016, and November 12, 2018. Eligible patients were 18 years of age or older and had advanced, recurrent, or metastatic ALK-positive NSCLC.

INTERVENTIONS

Patients were randomized (1:1) to ensartinib, 225 mg once daily, or crizotinib, 250 mg twice daily.

MAIN OUTCOMES AND MEASURES

The primary end point was blinded independent review committee-assessed progression-free survival (PFS). Secondary end points included systemic and intracranial response, time to central nervous system progression, and overall survival. Efficacy was evaluated in the intent-to-treat (ITT) population as well as a prespecified modified ITT (mITT) population consisting of patients with central laboratory-confirmed ALK-positive NSCLC.

RESULTS

A total of 290 patients (149 men [51.4%]; median age, 54 years [range, 25-90 years]) were randomized. In the ITT population, the median PFS was significantly longer with ensartinib than with crizotinib (25.8 [range, 0.03-44.0 months] vs 12.7 months [range, 0.03-38.6 months]; hazard ratio, 0.51 [95% CI, 0.35-0.72]; log-rank P < .001), with a median follow-up of 23.8 months (range, 0-44 months) for the ensartinib group and 20.2 months (range, 0-38 months) for the crizotinib group. In the mITT population, the median PFS in the ensartinib group was not reached, and the median PFS in the crizotinib group was 12.7 months (95% CI, 8.9-16.6 months; hazard ratio, 0.45; 95% CI, 0.30-0.66; log-rank P < .001). The intracranial response rate confirmed by a blinded independent review committee was 63.6% (7 of 11) with ensartinib vs 21.1% (4 of 19) with crizotinib for patients with target brain metastases at baseline. Progression-free survival for patients without brain metastases was not reached with ensartinib vs 16.6 months with crizotinib as a result of a lower central nervous system progression rate (at 12 months: 4.2% with ensartinib vs 23.9% with crizotinib; cause-specific hazard ratio, 0.32; 95% CI, 0.16-0.63; P = .001). Frequencies of treatment-related serious adverse events (ensartinib: 11 [7.7%] vs crizotinib: 9 [6.1%]), dose reductions (ensartinib: 34 of 143 [23.8%] vs crizotinib: 29 of 146 [19.9%]), or drug discontinuations (ensartinib: 13 of 143 [9.1%] vs crizotinib: 10 of 146 [6.8%]) were similar, without any new safety signals.

CONCLUSIONS AND RELEVANCE

In this randomized clinical trial, ensartinib showed superior efficacy to crizotinib in both systemic and intracranial disease. Ensartinib represents a new first-line option for patients with ALK-positive NSCLC.

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8. Projected Association of Human Papillomavirus Vaccination With Oropharynx Cancer Incidence in the US, 2020-2045

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IMPORTANCE

Oropharynx cancer (OPC) incidence has increased for several decades in the US. It is unclear when and how this trend will be affected by current HPV vaccination trends.

OBJECTIVE

To assess the association of HPV vaccination with future OPC incidence in the US.

DESIGN, SETTING, AND PARTICIPANTS

This population-based age-period-cohort analysis obtained OPC incidence data from the Surveillance, Epidemiology, and End Results program from 69 562 patients 34 to 83 years of age diagnosed with OPC. The HPV vaccination data were obtained from the National Immunization Survey-Teen (60 124 participants) and National Health Interview Survey (16 904 participants). Data were collected from January 1, 1992, to December 31, 2017. Age-period-cohort forecasting models projected expected 2018 to 2045 OPC incidence under a counterfactual scenario of no HPV vaccination and current levels of HPV vaccination, stratifying by sex. Data analyses were completed by December 2020.

EXPOSURES

Age- and sex-specific cumulative prevalence of HPV vaccination in 2016 to 2017 projected forward.

MAIN OUTCOMES AND MEASURES

Projected OPC incidence and number of OPC cases expected to be prevented by HPV vaccination.

RESULTS

Under current HPV vaccination rates, between 2018 and 2045, OPC incidence is projected to decrease in younger individuals (36-45 years of age: from 1.4 to 0.8 per 100 000 population; 46-55 years of age: from 8.7 to 7.2 per 100 000 population) but continue to increase among older individuals (70-83 years of age: from 16.8 to 29.0 per 100 000 population). The association of HPV vaccination with overall OPC incidence through 2045 will remain modest (no vaccination vs vaccination: 14.3 vs 13.8 per 100 000 population in 2045). By 2045 HPV vaccination is projected to reduce OPC incidence among individuals 36 to 45 years of age (men: 48.1%; women: 42.5%) and 46 to 55 years of age (men: 9.0%; women: 22.6%), but among those 56 years or older, rates are not meaningfully reduced. Between 2018 and 2045, a total of 6334 OPC cases will be prevented by HPV vaccination, of which 88.8% of such cases occur in younger age (≤55 years) groups.

CONCLUSIONS AND RELEVANCE

According to the projections of this population-based age-period-cohort study, current HPV vaccination rates will have a limited association with overall OPC incidence through 2045 because older individuals who have not yet been vaccinated remain at high risk for OPC. However, reductions in OPC incidence should occur among young and middle-aged adults, the group at lowest risk of diagnosis. These findings forecast a continued shift in the landscape of OPC to an older population.

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9. Prognosis of Patients With Early Breast Cancer Receiving 5 Years vs 2 Years of Adjuvant Bisphosphonate Treatment: A Phase 3 Randomized Clinical Trial

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IMPORTANCE

Bisphosphonate treatment in patients with early breast cancer has become part of care, but the optimal treatment duration is still unclear.

OBJECTIVE

To compare 2 vs 5 years of zoledronate treatment following adjuvant chemotherapy in patients with early breast cancer.

DESIGN, SETTING, AND PARTICIPANTS

The SUCCESS A phase 3 multicenter randomized open-label clinical trial with a 2 × 2 factorial design enrolled 3754 patients from September 21, 2005, to March 12, 2007 (last patient out, May 7, 2014). Final data analysis was conducted from September 2019 to October 2020. In 250 German study centers, patients were eligible for participation in the SUCCESS A trial if they had either node-positive or high-risk node-negative (defined as at least 1 of the following: tumor size ≥ pT2, histologic grade 3, negative hormone receptor status, or age ≤35 years) primary invasive breast cancer.

INTERVENTIONS

Patients were first randomized to adjuvant chemotherapy with 3 cycles of fluorouracil, epirubicin, and cyclophosphamide followed by 3 cycles of docetaxel with or without gemcitabine (not presented in this report). After chemotherapy, patients underwent a second randomization of 5 years of zoledronate treatment (4 mg intravenously every 3 months for 2 years, followed by 4 mg intravenously every 6 months for 3 years) vs 2 years of zoledronate treatment (4 mg intravenously every 3 months for 2 years).

MAIN OUTCOMES AND MEASURES

The primary end point of the study was disease-free survival; secondary end points were overall survival, distant disease-free survival, and the incidence of skeletal-related adverse events. Survival times were measured from 2 years after the start of zoledronate treatment (landmark analysis).

RESULTS

Overall, data on 2987 patients were available for analysis; median age was 53 (range, 21-86) years. Disease-free survival, overall survival, and distant disease-free survival did not differ significantly between the 2 treatment arms (5 vs 2 years) as shown by adjusted multivariable Cox proportional hazards regression models (disease-free survival: hazard ratio [HR], 0.97; 95% CI, 0.75-1.25; P = .81; overall survival: HR, 0.98; 95% CI, 0.67-1.42; P = .90; distant disease-free survival: HR, 0.87; 95% CI, 0.65-1.18; P = .38). Adverse events were observed more often in the 5-year (46.2%) vs 2-year (27.2%) zoledronate treatment arm, which was particularly true for the skeletal-related events bone pain (5 years, 8.3% vs 2 years, 3.7%) and arthralgia (5 years, 5.1% vs 2 years, 3.1%).

CONCLUSIONS AND RELEVANCE

The results of this phase 3 randomized clinical trial indicate that extending the zoledronate treatment beyond 2 years does not improve the prognosis of high-risk patients with early breast cancer receiving chemotherapy, suggesting that the currently recommended bisphosphonate treatment duration of 3 to 5 years could be reduced.

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10. Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non-Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy: The Phase 3 PORT-C Randomized Clinical Trial

Zhouguang Hui, Yu Men, Chen Hu, Jingjing Kang , Xin Sun, Nan Bi, Zongmei Zhou, Jun Liang, Jima Lv, Qinfu Feng, Zefen Xiao, Dongfu Chen, Yan Wang, Junling Li, Jie Wang, Shugeng Gao, Luhua Wang, Jie He

IMPORTANCE

The role of postoperative radiotherapy (PORT) has not been well defined in resected pIIIA-N2 non-small cell lung cancer (NSCLC).

OBJECTIVE

To evaluate the effect of PORT using modern techniques on survival and safety in patients with pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy.

DESIGN, SETTING, AND PARTICIPANTS

The PORT-C randomized clinical trial was conducted in 394 patients with pIIIA-N2 NSCLC treated with complete resection and 4 cycles of platinum-based chemotherapy between January 2009 and December 2017. Data were analyzed between March 2019 and December 2020.

INTERVENTIONS

Patients were randomized equally into the PORT arm (n = 202) or the observation arm (n = 192). The total dose of PORT was 50 Gy.

MAIN OUTCOMES AND MEASURES

The primary end point was disease-free survival (DFS). Secondary end points included overall survival (OS), locoregional recurrence-free survival (LRFS), distant metastasis-free survival, and toxic effects.

RESULTS

In total, 394 patients were enrolled and 364 were eligible, with a median (range) age of 55 (25-70) years. There were 202 (55.5%) male and 162 (44.5%) female patients. The median follow-up was 46.0 (95% CI, 41.9-51.4) months, and 230 DFS events were reported. There were 184 patients in the PORT arm and 180 patients in the observation arm. The 3-year DFS rates were 40.5% with PORT vs 32.7% with observation (median, 22.1 vs 18.6 months), and the difference in DFS was not statistically significant without adjustment (hazard ratio [HR], 0.84; 95% CI, 0.65-1.09; P = .20), though it was significant with preplanned yet exploratory analysis (stratified analysis by the number of detected lymph nodes and positive lymph nodes, HR, 0.75; log-rank P = .04). The 3-year OS rates were 78.3% vs 82.8% (HR, 1.02; P = .93), and LRFS was 66.5% vs 59.7% (HR, 0.71; 95% CI, 0.51-0.97; P = .03), respectively. For 310 per-protocol patients (140 with PORT and 170 with observation), PORT significantly improved DFS (42.8% vs 30.6%; HR, 0.75; 95% CI, 0.57-1.00; P = .05) but not OS (HR, 0.83; 95% CI, 0.53-1.30; P = .41). The 3-year local recurrence only rates were 9.5% and 18.3% in the 2 arms, respectively (Fine-Gray HR, 0.55; Gray test P = .04). No radiotherapy-related grade 4 or 5 adverse event was observed.

CONCLUSIONS AND RELEVANCE

In this phase 3 randomized clinical trial of patients with pIIIA-N2 NSCLC after complete resection and adjuvant chemotherapy, PORT did not improve DFS. Further studies exploring patients who might best benefit from PORT are needed.