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Scientific Article

Differential Effect of Consolidative Thoracic Radiation Therapy in Extensive-Stage Small Cell Lung Cancer Based on Sex

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Purpose: The landmark randomized trial on chest irradiation in extensive disease small cell lung cancer (CREST) demonstrated that consolidative thoracic radiation therapy (cTRT) improved overall (OS) and progression-free survival (PFS) after initial chemotherapy (chemo) in extensive-stage small cell lung cancer, with potentially increased benefit in women compared with men. It is unknown whether similar findings would apply after chemoimmunotherapy became the standard first-line treatment. In this analysis, we report national practice patterns and survival outcomes of cTRT according to patient sex.

Methods and Materials: We included patients from de-identified electronic health record-derived database diagnosed with stage IV small cell lung cancer (2014-2021) who completed 4 to 6 cycles of first-line systemic therapy (platinum-doublet chemotherapy or chemoimmunotherapy). We evaluated OS and PFS using multivariable Cox proportional hazards regression with receipt of cTRT as an independent variable and stratified by sex. As a sensitivity analysis, we weighted the models by the inverse probability of receiving cTRT.

Results: A total of 1227 patients were included (850 chemotherapy, 377 chemoimmunotherapy). There were no statistically significant differences in baseline characteristics between patients who did and did not receive cTRT. Among women, cTRT was associated with superior OS (adjusted hazard ratio [HR], 0.67; 95% CI, 0.52-0.87) and PFS (HR, 0.63; 95% CI, 0.49-0.82) compared with those not receiving cTRT. Conversely, no OS or PFS benefit with cTRT was observed in men (OS HR, 1.03; 95% CI, 0.80-1.31; PFS HR, 1.12; 95% CI, 0.85-1.47). Findings were similar in weighted analyses.

Conclusions: The survival efficacy of cTRT may be moderated by sex, with female patients appearing more likely to benefit than male patients. These findings reflect sex-based survival trends with similar effect sizes to those observed in the CREST trial. Although the underpinnings of this association need to be elucidated, stratification by sex should be considered for randomized-controlled trials studying cTRT in extensive-stage small cell lung cancer.

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The de-identified data used to conduct this study were obtained from Flatiron Health, Inc. Investigators wishing to gain access should submit a proposal for approval along with a signed data access agreement. Any further inquiries can be sent to DataAccess@flatiron.com.

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Introduction

Extensive-stage small cell lung cancer (ES-SCLC), defined as distant metastases or disease extending beyond the borders of a standard radiation field, accounts for almost two-thirds of cases of small cell lung cancer (SCLC).[1] ES-SCLC remains a challenging disease to treat, with a median overall survival (OS) of <14 months and a 3-year survival up to 18%.[2,3] The standard-of-care first-line systemic therapy was previously platinum-based doublet chemotherapy alone but has recently evolved to chemotherapy with concurrent and maintenance immunotherapy.

In the chemotherapy era, consolidative thoracic radiation therapy (cTRT) has been associated with a survival benefit in multiple randomized controlled trials, most notably the landmark CREST trial in 2014.[4] Although there was no statistically significant difference in the primary endpoint of 1-year overall survival (33% cTRT vs 28% no cTRT, $P = .07$), an exploratory analysis showed a statistically significant difference in 2-year overall survival (13% cTRT vs 3% no cTRT). The initially reported analysis of the CREST trial did not identify any cohorts that had an OS benefit with cTRT, although a nonstatistically significant trend toward improved survival was observed among women compared with men. Furthermore, secondary analyses showed that patients with residual intrathoracic disease (vs those without) and less than 3 distant metastases after chemotherapy benefited the most from cTRT.[5,6]

Nevertheless, controversy exists over the utility and efficacy of cTRT in ES-SCLC. Because the CREST trial did not meet its primary 1-year survival endpoint, but rather showed benefit in a secondary 2-year survival analysis, some have felt this does not conclusively prove the benefit of cTRT.[7] Furthermore, the landscape of systemic therapy changed considerably with the advent of chemoimmunotherapy, which has raised further questions regarding both the safety and efficacy of cTRT.[8,9] It is unknown whether the benefit of cTRT would persist given the survival improvements conferred by chemoimmunotherapy.

There are several important knowledge gaps regarding the clinical efficacy of cTRT. Guidelines vary in strength of recommendation for cTRT, with the National Comprehensive Cancer Network listing it as category 2A after complete or partial response to initial systemic therapy,[10] and the American College of Chest Physicians cites cTRT as grade 2C, suggesting weak evidence to support this practice.[11] The American Radium Society Appropriate Use Criteria and American Society of Clinical Oncology considered cTRT after chemoimmunotherapy as usually appropriate while acknowledging that the strength of evidence is limited.[12,13] Finally, it is plausible that the CREST trial was underpowered to demonstrate a survival benefit among women compared with men, and that a study containing a larger sample size may help to corroborate these findings.

To clarify the role of cTRT in ES-SCLC in the modern treatment landscape, we conducted a retrospective cohort study using Flatiron Health's national data set, which offers data on timing of disease progression as well as more recent data through 2021 that cover the chemoimmunotherapy era. Although multiple retrospective studies suggest thoracic radiation therapy can be safely combined with immunotherapy,[14,15] it is unknown what benefit cTRT confers in this setting. In this analysis, we describe the uptake of cTRT in ES-SCLC over time and compare real-world OS and progression-free survival (PFS) among patients who did or did not receive cTRT, stratified by sex.

Methods and Materials

Data source and study design

We conducted a retrospective cohort study of patients who received a diagnosis of stage IV SCLC between January 1, 2014, and October 31, 2021, and had received systemic cancer treatment. We used the Flatiron Health electronic health record-derived de-identified database, which comprises de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction.[16,17] During the study period, the de-identified data originated from approximately 280 US cancer clinics (~800 sites of care). Most patients in the database originate from community oncology settings; relative community/academic proportions may vary depending on study cohort. This study was considered nonhuman subjects research by the Yale Institutional Review Board.

Sample selection

We restricted the sample to those who had an interaction with the health care system within 90 days of diagnosis, to ensure that patients received their treatment within the Flatiron Health network. We further restricted the sample to those who had 4 to 6 cycles of oncologist-defined, rule-based first-line systemic therapy from January 1, 2014, to July 31, 2021, consistent with the inclusion criteria from previous trials in ES-SCLC.[8,9] Systemic therapy included either platinum doublet chemotherapy or platinum doublet chemoimmunotherapy. To restrict the sample to only those who would be eligible for cTRT, we excluded patients who progressed within 14 days of their last cycle as well as those who died within 90 days after completion of systematic therapy to account for immortal time bias, which would favor the cTRT arm because patients who survive longer have more opportunity to

receive the treatment. Finally, we excluded anyone who started cTRT within 14 days of their last cycle, which was determined a priori as a reasonable minimum time between completion of chemotherapy and start of cTRT (Fig. E1).

Study variables

The primary outcomes were receipt of cTRT for the utilization analysis, and OS and PFS for the outcome analysis. For the former, we evaluated receipt of cTRT in the 15 through 90 days after last cycle date. PFS was ascertained as a composite outcome incorporating either disease progression or death. Flatiron Health data include information on "real-world progression," which is based on clinician documentation of worsening of disease within the electronic health record.[18] Patients' sociodemographic and clinical characteristics included sex, age at diagnosis, race, Eastern Cooperative Oncology Group (ECOG) performance status, insurance, year of diagnosis, and region of residence. Race (categorized as White vs non-White because of the lower numbers of non-White patients) was included as a social rather than biologic construct and examined given previous work that has shown race-based differences in outcomes in SCLC.[19] Age at diagnosis was dichotomized as <70 or ≥70 years, and insurance status was divided into 4 categories: 1) Medicare, 2) commercial, 3) Medicaid and other, and 4) uninsured/unknown. Smoking status was not included as a covariate because 98.0% of patients in our cohort were smokers.

Statistical analysis

First, we performed a descriptive analysis (frequency and percentage) of patients' characteristics by receipt of cTRT (yes vs no). Next, bivariable and multivariable logistic regression were conducted to determine which patient factors were associated with receipt of cTRT. We then performed a time-to-event analysis using Cox proportional hazard regressions for the outcomes of OS and PFS. Index time for both survival analyses was last cycle date of first-line systemic therapy. For OS, patients were censored on the date of last confirmed activity as determined from the Flatiron Health data. For PFS, patients were censored on the date of their last clinic note in the data because progression dates are abstracted from clinic notes. For patients with multiple progression dates, we analyzed time to first progression. We restricted the PFS analysis to patients who did not progress during the 90 days after last cycle because this was the window during which we evaluated receipt of cTRT and patients who progressed during this time would not have been eligible to receive cTRT. This excluded 35.5% of the sample. We evaluated the proportional hazards assumption using the ASSESS statement in SAS's PROC PHREG procedure, which is based on the martingale residuals.

We used the Kaplan-Meier estimator and the log-rank test to compare OS and PFS between cohorts. We performed multivariable unweighted time to event Cox proportional hazards analysis adjusted for age, race, region of residence, diagnosis year, ECOG score, insurance, and type of systemic therapy (chemotherapy vs chemoimmunotherapy). All survival models were stratified by sex. Because sex violated the proportional hazards model, we did not run any models in which both sexes were combined. Because we hypothesized that systemic therapy type might moderate the effect of cTRT on OS and PFS, we included an interaction test between these 2 variables in each of the sex-stratified OS and PFS models.

We also performed weighted analysis using inverse probability of treatment weighting (IPTW).[20] This procedure addresses confounding in the receipt of cTRT by weighting the populations that did and did not receive cTRT such that the distribution of their baseline covariates is equal. We elected to use IPTW rather than propensity score matching due to very small sample sizes after restricting to matched pairs; IPTW allowed us to retain most patients for analysis. The propensity score of receiving cTRT was constructed using the same covariates that were included in the unweighted logistic regression model. We evaluated the balance using standardized differences and included covariate adjustment in the survival models for any covariates with a standardized difference (absolute value) >10% after weighting.[21] All analyses were performed using SAS version 9.4 and Stata version 17.

Results

Patient characteristics and receipt of cTRT

A total of 1227 patients with ES-SCLC were included in our cohort. Most patients were <70 years old (58.4%), male (50.6%), White (75.2%), had an ECOG performance status of 0 to 1 (65.7%), resided in the South (43.6%), and had Medicare insurance (64.0%). A total of 850 (69.3%) patients were treated with chemotherapy alone, and 377 (30.7%) were treated with chemoimmunotherapy (Table 1). Overall, 202 (16.5%) patients received cTRT. At the beginning of our study period (2014, coinciding with the publication of the CREST trial), 11.7% of patients received cTRT. This increased to a high of 20.7% in 2017, before decreasing to 16.4% in 2021 (Fig. 1). This decrease coincided with the publication of IMpower133 in September 2018.

There were no significant differences in any baseline characteristics between patients who did and did not

Table 1 Receipt of radiation therapy among patients with extensive stage small cell lung cancer (N = 1227)

Characteristic	Overall (N = 1227) N (%)	Receipt of cTRT		*P* value*
		No (N = 1025) N (%)	Yes (N = 202) N (%)	
Sex				
Female	606 (49.4)	504 (83.2)	102 (16.8)	.73
Male	621 (5.6)	521 (83.9)	100 (16.1)	
Age group, y				
<70	717 (58.4)	591 (82.4)	126 (17.6)	.21
≥70	510 (41.6)	434 (85.1)	76 (14.9)	
Race				
White	923 (75.2)	768 (83.2)	155 (16.8)	.53
Non-White	187 (15.2)	155 (82.9)	32 (17.1)	
Unknown	117 (9.5)	102 (87.2)	15 (12.8)	
ECOG performance status				
0	271 (22.1)	222 (81.9)	49 (18.1)	.52
1	535 (43.6)	446 (83.4)	89 (16.6)	
2-3	242 (19.7)	211 (87.2)	31 (12.8)	
Unknown	179 (14.6)	146 (81.6)	33 (18.3)	
Region				
Northeast	196 (16.0)	159 (81.1)	37 (18.9)	.22
South	535 (43.6)	460 (86.0)	75 (14.0)	
Midwest	220 (17.9)	185 (84.1)	35 (15.9)	
West	121 (9.9)	98 (81.0)	23 (19.00)	
Unknown	155 (12.6)	123 (79.3)	32 (2.7)	
Insurance type				
Medicare	785 (64.0)	660 (84.1)	125 (15.9)	.29
Commercial	184 (15.0)	145 (78.8)	39 (21.2)	
Other, including Medicaid	100 (8.2)	85 (85.0)	15 (15.0)	
Uninsured/unknown	158 (12.8)	135 (85.4)	23 (14.6)	
Treatment group				
Doublet platinum therapy	850 (69.3)	700 (82.3)	150 (17.7)	.09
Doublet platinum therapy + Immunotherapy	377 (3.7)	325 (86.2)	52 (13.8)	
Year of diagnosis				
2014	128 (1.4)	113 (88.3)	15 (11.7)	.33
2015	166 (13.5)	135(81.3)	31 (18.7)	
2016	166 (13.5)	133 (8.1)	33 (19.9)	
2017	179 (14.6)	142 (79.3)	37 (2.7)	
2018	185 (15.1)	159 (86.0)	26 (14.0)	
2019	187 (15.2)	159 (85.0)	28 (15.0)	
2020	155 (12.6)	133 (85.8)	22 (14.2)	
2021	61 (5.0)	51 (83.6)	10 (16.4)	

Abbreviation: ECOG = Eastern Cooperative Oncology Group.
*P values were calculated using χ^2 test or Fisher's exact test.

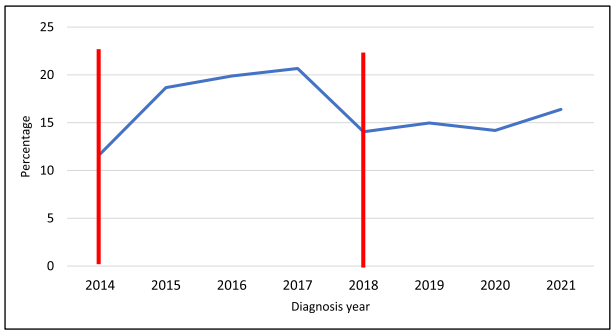

Figure 1 Proportion of patients who received consolidative thoracic radiation therapy by calendar year of diagnosis.

receive cTRT, including age, sex, race, ECOG performance status, geographic region, insurance type, treatment groups, or year of diagnosis. We further analyzed baseline characteristics of patients who did or did not receive cTRT by patient sex and found no significant differences (Table E1). This pattern persisted in the bivariable and multivariable logistic regression models, with no statistically significant associations between patient factors and receipt of cTRT (Table E2).

Survival analysis

Women experienced superior OS (Fig. 2A) and PFS (Fig. 2B) compared with men (log-rank $P < .001$ for both outcomes). Among women, cTRT was associated with superior OS (unweighted hazard ratio [HR], 0.67; 95% CI, 0.52-0.87; $P = .002$) and PFS (unweighted HR, 0.63; 95% CI, 0.49-0.82; $P < .001$; Fig. 3, Tables E3 and E4). However, cTRT was not associated with improved survival in men, in terms of OS (unweighted HR, 1.03; 95% CI, 0.80-1.31; $P = .84$) and PFS (unweighted HR, 1.12; 95% CI, 0.85-1.47; $P = .44$; Fig. 3). Systemic therapy type did not moderate the association between cTRT on OS or PFS for either men (OS, cTRT*systemic therapy interaction, $P = .33$; PFS, $P = .85$) or women (OS, $P = .56$; PFS, $P = .77$). Therefore, we did not further stratify models by systemic therapy type, but we included systemic therapy for covariate adjustment. After weighting by the inverse probability of treatment, we achieved adequate balance in baseline covariates among women and men (Figs. E2 and E3). The findings from the weighted analysis were consistent with the findings from the unweighted survival models (Fig. 3).

Discussion

In this analysis of patients with ES-SCLC receiving systemic therapy with or without cTRT, 2 important findings emerged. First, we found that the receipt of cTRT increased between 2014 and 2017, but then decreased after 2017. This

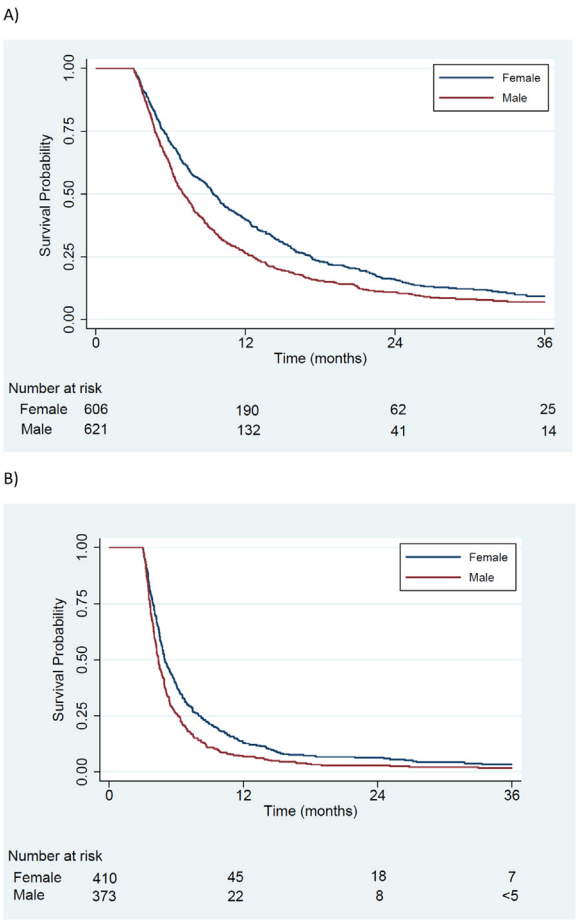

Figure 2 Kaplan-Meier estimator of (A) overall survival and (B) progression-free survival stratified by sex.

pattern roughly mirrored the timing of publications of the CREST trial (September 2014) and IMpower133 (September 2018). Second, we demonstrated a differential response to cTRT based on sex that was not affected by systemic therapy type. Female patients receiving cTRT had an improvement in OS and PFS, while their male counterparts

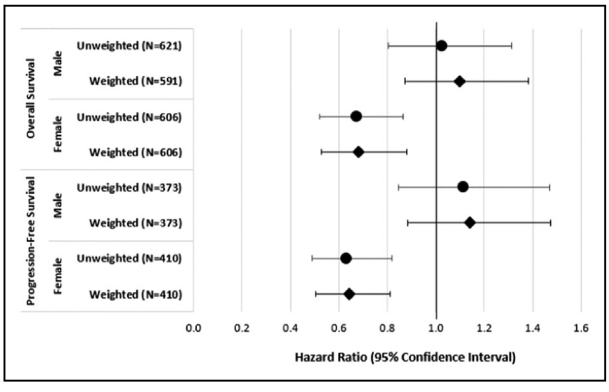

Figure 3 Association between consolidative thoracic radiation therapy and overall survival and progression-free survival in unweighted and weighted analyses.

did not benefit from cTRT. These findings were remarkably consistent with subgroup analyses of the CREST trial, demonstrating similar trends and effect sizes for overall survival. Additional exploration is needed to determine intrinsic sex-specific biologic or confounding environmental factors that may account for these differences.

There has been limited data exploring patterns of cTRT in patients with ES-SCLC. A survey of academic thoracic radiation oncologists in 2017 showed that all respondents offered cTRT, although there was significant variation in contexts and scenarios in which cTRT was offered.[22] A survey of Canadian radiation oncologists found that 88% of respondents would offer cTRT to eligible patients.[23] In our study of predominantly community oncology centers, we showed that only a small minority of patients who survived for at least 90 days after systemic therapy received cTRT since the CREST trial publication (<21% of eligible patients in each year).

One explanation for the decrease in utilization of cTRT after 2017 is the publication of the IMpower133[8] and CASPIAN[9] trials that established first-line chemoimmunotherapy as the new standard of care for ES-SCLC. Notably, both trials excluded cTRT given safety concerns with combining immunotherapy and thoracic radiation. Perhaps the most anticipated adverse thoracic toxicities from combined treatment include pneumonitis, esophagitis, and cardiac toxicity. However, multiple studies published since then have demonstrated the safety of combined immunotherapy and thoracic radiation therapy,[14,15,24-27] although there may be a higher risk for radiation pneumonitis in patients with prior immune-related adverse events.[28] In addition to safety, there is a question of whether cTRT is still efficacious after chemoimmunotherapy or if any potential benefit is abrogated by the addition of immunotherapy. Our findings suggest a benefit of cTRT among female patients receiving chemoimmunotherapy. This idea is being prospectively evaluated by the currently accruing NRG LU007 RAPTOR trial, which is studying the safety and efficacy of cTRT to up to 5 sites (both intrathoracic and extrathoracic) concurrent with maintenance atezolizumab after chemoimmunotherapy.[29]

Our other notable finding was that any potential benefit for cTRT appears to have been restricted to women rather than men among patients receiving either chemotherapy alone or chemoimmunotherapy. Sex has been previously shown to be an independent prognostic factor of survival in SCLC and NSCLC favoring women, although its role as a predictive response to treatment has been scarcely examined.[30-32] Notably, our findings were consistent with subgroup analyses of the CREST trial, which showed a nonstatistically significant trend toward improved OS with cTRT in women after upfront chemotherapy (HR, 0.68; 95% CI, 0.46-1.00; P = .06), with no signal of benefit from cTRT in men (HR, 1.01; 95% CI, 0.72-1.41).[4] The hazard ratios for both OS and PFS for women and men in the chemotherapy cohort in our study closely mirror those of the subgroup analyses of the CREST trial. We hypothesize that the CREST study may not have been powered for this subgroup analysis. Moreover, our study is the first to suggest a potential benefit of cTRT in female patients receiving chemoimmunotherapy, given that systemic therapy type did not modify the effect of cTRT on survival among women and men.

Our finding of a survival benefit from cTRT only among women does not mean that cTRT should only be offered to women, but rather that stratification by sex should be considered for clinical trials studying cTRT in ES-SCLC. Potential avenues for exploration of the etiologies behind these sex-based differences include biologic and environmental influences as well as unmeasured confounders. Investigations into sex-specific biologic differences in SCLC are limited, although there is some suggestion of a different mutational profile.[33] In addition, it is known that patients who benefit most from cTRT have a particular disease presentation characterized by residual thoracic disease and limited extrathoracic disease after systemic therapy.[34,35] Previous reports have shown that women with SCLC may have an overall lower disease burden (smaller tumor size, fewer metastases, and lower stages),[36] consistent with a disease presentation which may portend a more favorable response to cTRT in comparison to men. Finally, because women with SCLC tend to live longer than men,[31] they may be more likely to realize the benefit of cTRT. Nevertheless, given that modern-day cTRT can be delivered with low doses and low toxicity even with concurrent maintenance immunotherapy, it may be reasonable to consider this treatment in both male and female patients who had a good response to systemic therapy with residual disease in the thorax and limited extrathoracic disease burden, while strongly encouraging participation in the ongoing NRG LU007 RAPTOR trial.[34,35]

Limitations

The limitations of this study are inherent to those of observational data sets and retrospective analyses. First, this real-world database lacks details on tumor bulk, number and sites of metastases, degree of response to therapy, radiation dose and dosimetry, sites of radiation beyond the thorax, and toxicity outcomes. As mentioned previously, cTRT primarily benefits patients with a specific disease presentation after systemic therapy.[34,37] Without these full details, it is impossible for us to isolate potential unknown confounders to explain the causation underlying the sex-based differential response to cTRT, although IPTW is designed to minimize the effect of these unknown confounders as much as possible. In addition, our study had a limited sample size of patients treated with chemoimmunotherapy given the relative recency of the Impower133 and CASPIAN trials, and it will be critical to reevaluate our findings with real-world data once

more patients have received this treatment. Despite these limitations, this real-world database offers a diverse cohort with greater representation of women, elderly, and nonwhite patients, compared with clinical trials.[3] Furthermore, our study could not currently be addressed with other available large national databases in the chemoimmunotherapy era since Flatiron Health incorporates more recent data than the National Cancer Database or Surveillance, Epidemiology, and End Results database.

Conclusion

Consolidative thoracic radiation therapy has been used in a minority of potentially eligible patients with ES-SCLC nationally, although an increase in utilization coincided with publication of the CREST trial and a subsequent decrease in utilization coincided with the publication of the IMpower133 trial. Most notably, we found the response to cTRT was differentially effected by sex, suggesting a potential benefit for women, but not for men, after either chemotherapy or chemoimmunotherapy. Additional research is needed to identify the etiology of such differences. In the meantime, we would encourage enrollment on the ongoing NRG LU007 RAPTOR trial studying the role of consolidative cTRT in the context of chemoimmunotherapy, as well as consideration of sex-based stratification for future trials with this patient population.

Disclosures

Pamela R. Soulos reported receiving consulting fees from TARGET PharmaSolutions outside of the submitted work. Cary P. Gross reported receiving grants or contracts from Johnson & Johnson, the National Comprehensive Cancer Network, and Genentech, and a leadership role in the American Society of Clinical Oncology (ASCO)-Quality Annual Meeting planning committee, outside of the submitted work. Anne C. Chiang reported receiving research funding from Bristol Myers Squibb, AbbeVie, and Genentech, and is on the advisory board or consultant to Genentech, AstraZeneca, Regeneron, and Daichi, outside the submitted work. Henry S. Park reported receiving research funding from RefleXion and Merck, consulting fees from AstraZeneca and RefleXion, honoraria from Bristol Myers Squibb and G1 Therapeutics, and serving on the advisory board for AstraZeneca and Galera, outside the submitted work. Vikram Jairam, Ben J. Slotman, and K.C. Madhav reported no disclosures.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101413.

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