ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

EDITORIAL

Incorporating immunotherapy in the management of early-stage estrogen receptor-positive breast cancer

Immune checkpoint inhibitors (ICI) have been incorporated into standard treatment regimens for patients with early and advanced triple-negative breast cancer (TNBC).[1,2] Unlike in TNBC, the first studies to test the efficacy of ICI in patients with metastatic estrogen receptor-positive (ER+) disease showed limited efficacy, probably reflecting the lower immunogenicity of these tumors compared with TNBC.[3-5] However, building on the knowledge that primary tumors are often less immunosuppressed than pretreated malignancies, and that combining ICI with cytotoxic agents may elicit antitumor immune responses, early studies have explored this strategy in the preoperative setting.[6,7] A pathological complete response (pCR) rate of 16% was observed among 43 patients with Luminal B-like breast cancer treated with neoadjuvant chemotherapy (NACT), followed by nivolumab in combination with endocrine therapy (ET) in the GIADA trial.[8] In the I-SPY2 trial, the addition of pembrolizumab to NACT increased estimated pCR rates from 13% to 30% in 40 patients with ER+/human epidermal growth factor receptor 2 (HER2)-negative (HER2−) MammaPrint-high breast cancer, suggesting that at least a subgroup of patients with ER+ disease could derive benefit from the addition of immune checkpoint blockade.[9]

In this context, the results of two large placebo-controlled, phase III studies evaluating the addition of ICI to NACT in patients with high-risk ER+ early breast cancer were recently reported. The KEYNOTE-756 trial enrolled 1278 patients with T1c-2 ($\geq$2 cm) cN1-2 or T3-4 cN0-2, grade 3, ER+/HER2− invasive ductal carcinoma (invasive lobular carcinoma excluded), randomized 1 : 1 to neoadjuvant pembrolizumab or placebo, both administered with weekly paclitaxel for 12 weeks, followed by four cycles of doxorubicin/epirubicin and cyclophosphamide.[10] After surgery ($\pm$ radiotherapy), patients received pembrolizumab or placebo for nine cycles in combination with ET. The study's co-primary endpoints were pCR and event-free survival (EFS). An increase in pCR rate favoring the pembrolizumab-containing arm was demonstrated (24.3% versus 15.6%, $P = 0.00005$), corresponding to an absolute difference of 8.5% [95% confidence interval (CI) 4.2% to 12.8%] between the arms.[10] EFS results are immature and have not yet been presented. Similarly, the CheckMate 7FL study randomized patients with T1c-2 and N1-2 or T3-4 and N0-2, grades 2-3, ER+/HER2− invasive breast cancer to receive preoperative nivolumab or placebo in combination with anthracycline- and paclitaxel-based NACT, followed by post-operative ET with nivolumab or placebo.[11] Although the study design initially included pCR and EFS as co-primary endpoints, due to changes in the treatment landscape [including introduction of adjuvant cyclin-dependent kinases 4 and 6 (CDK4/6) inhibition] a protocol amendment changed the primary endpoint to be pCR only, with EFS being an exploratory endpoint, and accrual stopped after the randomization of 521 patients.[11] The addition of nivolumab to NACT was associated with an increase in pCR from 13.8% to 24.5% ($P = 0.0021$), corresponding to a delta of 10.5% (95% CI 4.0% to 16.9%).[11] Patients enrolled in the immunotherapy arms experienced higher rates of grade 3-4 adverse events, treatment discontinuations, and immune-related adverse events compared with those in the placebo arms (Table 1).[10,12]

Despite the gains observed in pCR, evaluation of long-term outcomes will ultimately be necessary to guide the incorporation of this strategy into clinical practice. This is especially important because the reliability of pCR as a surrogate endpoint for long-term outcomes has been questioned both in the ER+ population and in immunotherapy trials.[13] In the CheckMate 7FL trial, this may be a particularly relevant limitation, as EFS was shifted from co-primary to an exploratory endpoint.

Considering the risk of immune-related adverse events in patients treated with ICI, the search for predictive biomarkers is of the utmost importance. In both the KEYNOTE-756 and CheckMate 7FL studies, a greater magnitude of pCR benefit was observed in patients with higher programmed death-ligand 1 (PD-L1) expression and lower ER expression, although few patients (<10%) with ER-low disease were included in either study.[12,14] In KEYNOTE-756, the PD-L1 positivity rate was 76% based on the DAKO 22C3 assay using combined positive score criteria, while CheckMate 7FL reported a 35% positivity rate according to the Ventana SP142 assay for immune cell infiltration, with this discrepancy likely due to differences in the scoring methods.[12,14] In the CheckMate 7FL study, median stromal tumor-infiltrating lymphocytes (TILs) was 1% (range 1%-98%) and an incrementally increasing benefit of ICI was also observed in patients with higher TILs.[12] In this trial, lower progesterone receptor (PR) expression (<10%) was also associated with higher pCR rates. In line with observations from other studies, these findings emphasize the significant heterogeneity among patients with ER+ disease and underscore the

Table 1. Efficacy and safety results of KEYNOTE-756 and CheckMate 7FL trials

Arm	KEYNOTE-756		CheckMate 7FL	
	Pembrolizumab	Placebo	Nivolumab	Placebo
Randomly allocated **p**atients	635	643	263	258
pCR **r**ate	24.3%	15.6%	24.5%	13.8%
pCR **r**ate (absolute difference)	8.5%		10.5%	
All AEs (**a**ny **g**rade)	98%	99%	98%	98%
Grade ≥3 AEs	52%	46%	42%	38%
Serious **AE**s	19%	10%	23%	13%
AEs leading **to t**reatment **d**iscontinuation	19%	10%	10%	3%
Grade 5 AEs	1 (0.2%)	0	2 (0.8%)	0
IrAEs	33%	7%	NR	NR
Grade ≥ 3 irAEs	7%	1%	NR	NR
Most **c**ommon AEs	Alopecia (64%) Nausea (48%) Anemia (32%) Fatigue (30%) Diarrhea (27%)	Alopecia (61%) Nausea (50%) Anemia (26%) Fatigue (28%) Diarrhea (20%)	Alopecia (49%) Nausea (45%) Anemia (36%) Fatigue (32%) Diarrhea (22%)	Alopecia (48%) Nausea (37%) Anemia (29%) Fatigue (26%) Diarrhea (23%)

AEs, adverse events; irAEs, immune-related adverse events; NR, not reported; pCR, pathological complete response.

potential for identifying predictive biomarkers. Similarly to what was observed in the CheckMate 7FL trial, lower PR expression was associated with higher pCR rates among patients with ER-positive breast cancer treated with ICI in both the GIADA and I-SPY2 trials.[8,15] In the GIADA trial, which enrolled patients with Luminal B-like breast cancer defined as ER+ with high Ki67 and/or histologic grade 3, PAM50 analysis classified 25% of participants as Luminal A, 56% as Luminal B, and 19% as basal.[8] Notably, the pCR rate was significantly higher in patients with the basal subtype (50%) compared with those with Luminal A (9%) and Luminal B (8%).[8] Initially developed to assess chemotherapy versus ET sensitivity, gene expression profiles have also been shown to predict benefit from ICI. In the I-SPY2 study, patients classified as MammaPrint ultrahigh (MP2) showed a significant response to durvalumab and olaparib, with an estimated pCR rate of 64% compared with 22% in the control group, while no pCR benefit was seen in the MP1 group (9% versus 10%).[15] Similar findings were observed in patients treated with pembrolizumab in I-SPY2, where MP2 status was significantly associated with higher pCR rates.[16] The immune infiltrate also appears to play a critical role in modulating the response to immunotherapy among patients with ER+ disease, with a higher magnitude of pCR benefit observed in those with higher stromal TILs in both the CheckMate 7FL and GIADA trials.[8,12] Interestingly, PD-L1 expression has been shown to be predictive of response to immunotherapy in metastatic, but not in early, TNBC.[17] The reasons why PD-L1 status may predict response to ICI in early ER+ but not in TNBC remain unclear, although previous studies have shown that in patients with ER+ breast cancer, PD-L1 positivity was associated with higher

Table 2. Eligibility criteria in studies evaluating CDK4/6 inhibitors and immunotherapy in early estrogen receptor-positive breast cancer

Stage				Eligibility criteria			
		T	N	MonarchE	NATALEE	KEYNOTE-756[a]	CheckMate 7FL[b]
I	IA	T1	N0	✖	✖	✖	✖
	IB	T0	N1mi	✖	✖	✖	✖
	IB	T1	N1mi	✔[c]	✖	✔[e]	✔[e]
II	IIA	T0	N1	✖	✔	✖	✖
	IIA	T1	N1	✔[c]	✖	✔[e]	✔[e]
	IIA	T2	N0	✖	✔[d]	✖	✖
	IIB	T2	N1	✔[c]	✔	✔	✔
	IIB	T3	N0	✖	✔	✔	✔
III	IIIA	T0	N2	✖	✔	✖	✖
	IIIA	T1	N2	✔	✔	✔[e]	✔[e]
	IIIA	T2	N2	✔	✔	✔	✔
	IIIA	T3	N1	✔	✔	✔	✔
	IIIA	T3	N2	✔	✔	✔	✔
	IIIB	T4	N0	✖	✔	✔	✔
	IIIB	T4	N1	✔	✔	✔	✔
	IIIB	T4	N2	✔	✔	✔	✔
	IIIC	Any T	N3	✔	✔	✖	✖

[a] KEYNOTE-756: histological grade 3 required.
[b] CheckMate 7FL: grade 3 or grade 2 with an estrogen receptor expression between 1% and 10%.
[c] If G3 or Ki67 ≥20%.
[d] If G3, or G2 and Ki67 ≥20%, or high genomic risk.
[e] If tumor size ≥2 cm.

recurrence scores by OncotypeDx and TIL levels.[15,18,19] Taken together, these findings suggest that patients with lower ER/PR signaling, higher immune infiltrates and PD-L1 expression, and elevated MammaPrint/OncotypeDx scores represent a population in which the addition of ICI may significantly improve outcomes. While no single biomarker alone was able to accurately identify patients who would benefit from ICI, their integration could achieve a sufficient level of precision to select the ideal candidates for this strategy. Indeed, the identification of an optimal predictive biomarker will likely require the integration of multiple tumor and microenvironmental characteristics, including immune infiltrates, PD-L1 expression, hormone receptor expression, molecular subtypes, and gene expression profiles.[20]

Another active question is the role of post-operative administration of ICI, particularly as adjuvant abemaciclib is a standard adjuvant treatment option for patients with high-risk node-positive ER+ breast cancer. The significant overlap between the inclusion criteria of studies evaluating ICI and CDK4/6 inhibitors in the early setting (Table 2) is a point of concern given the difficulty of administering these two agents concurrently due to excessive toxicity.[21,22] If the benefit of both classes of drugs is confirmed in an overlapping population, a sequencing strategy could be considered, for example starting a CDK4/6 inhibitor after the completion of adjuvant ICI. While sequencing strategies may be considered, it is crucial to prioritize the identification of biomarkers to determine which patients will benefit most from each approach, as the populations that benefit from each strategy may differ. Importantly, as the patients enrolled in the KEYNOTE-756 and CheckMate 7FL studies did not receive adjuvant CDK4/6 inhibition, the EFS results observed in these studies will not reflect the potential additional benefit from ICI in patients treated with CDK4/6 inhibitors.

Moving forward, refining the selection of patients with ER+ breast cancer who may derive the greatest benefit from preoperative ICI will be an essential next step in this field, and EFS results from the trials detailed above, as well as ongoing studies, will help to better understand the role of ICI in molecularly selected populations. The phase III SWOG S2206 (NCT06058377) trial is testing the addition of durvalumab to NACT in patients with stage II-III ER+, HER2− breast cancer and a MammaPrint ultrahigh score. Other immunotherapy priming strategies being evaluated include the incorporation of radiotherapy into neoadjuvant chemo-immunotherapy regimens in patients with high-risk ER+ disease defined by clinicopathological parameters and high genomic risk [P-RAD (NCT04443348) and Neo-CheckRay (NCT03875573) trials].[23,24] This approach may be particularly promising in less immune-reactive subgroups, as demonstrated by the Neo-CheckRay trial, where the addition of immunotherapy to preoperative chemoradiotherapy led to a 31% increase in pCR rates among patients with PD-L1-negative tumors.[25] While the follow-up of the phase III studies continues, we await the presentation of long-term outcomes and additional biomarker analyses. The identification of subgroups more sensitive to intensified ET with CDK4/6 inhibitors, ICI, or both will allow personalized treatment selection and sequencing strategies to optimize outcomes.

G. Nader-Marta[1,2,3]*, A. G. Waks[1,2,3], S. M. Tolaney[1,2,3] & E. L. Mayer[1,2,3]

[1]*Department of Medical Oncology, Dana-Farber Cancer Institute, Boston;*
[2]*Department of Medical Oncology, Breast Oncology Program, Dana-Farber Brigham Cancer Center, Boston;*
[3]*Department of Medical Oncology, Harvard Medical School, Boston, USA*
(*E-mail: guilherme_nadermarta@dfci.harvard.edu).

Available online xxx

https://doi.org/10.1016/j.esmoop.2024.103977

FUNDING

None declared.

DISCLOSURE

GNM reported travel support from AstraZeneca. AGW reported research support (to institution) from Genentech, Gilead, Macrogenics, and Merck; speakers' fee from AstraZeneca; and consulting or advisory roles for AstraZeneca and AMBRX. SMT reported consulting or advisory roles for Novartis, Pfizer (SeaGen), Merck, Eli Lilly, AstraZeneca, Genentech/Roche, Eisai, Sanofi, Bristol Myers Squibb, CytomX Therapeutics, Daiichi Sankyo, Gilead, Zymeworks, Zentalis, Blueprint Medicines, Reveal Genomics, Sumitovant Biopharma, Umoja Biopharma, Artios Pharma, Menarini/Stemline, Aadi Bio, Bayer, Incyte Corp, Jazz Pharmaceuticals, Natera, Tango Therapeutics, Systimmune, eFFECTOR, Hengrui USA, Cullinan Oncology, Circle Pharma, Arvinas, BioNTech, Johnson&Johnson/Ambrx, Launch Therapeutics, Zuellig Pharma, and Bicycle Therapeutics; research funding from Genentech/Roche, Merck, Exelixis, Pfizer, Lilly, Novartis, Bristol Myers Squibb, Eisai, AstraZeneca, Gilead, NanoString Technologies, Seattle Genetics, OncoPep, Daiichi Sankyo, and Menarini/Stemline; and travel support from Eli Lilly, Sanofi, Gilead, Jazz Pharmaceuticals, Pfizer, and Arvinas. ELM reported consulting for AstraZeneca, Eli Lilly, and Novartis.

REFERENCES

1. Korde LA, Somerfield MR, Hershman DL. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer Guideline Expert Panel. Use of Immune Checkpoint inhibitor pembrolizumab in the treatment of high-risk, early-stage triple-negative breast cancer: ASCO Guideline rapid recommendation update. *J Clin Oncol*. 2022;40(15):1696-1698.
2. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic

breast cancer. *Ann Oncol Off J Eur Soc Med Oncol*. 2021;32(12):1475-1495.
3. Rugo HS, Delord JP, Im SA, et al. Safety and antitumor activity of pembrolizumab in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2018;24(12):2804-2811.
4. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN solid tumor study. *Breast Cancer Res Treat*. 2018;167(3):671-686.
5. Tolaney SM, Barroso-Sousa R, Keenan T, et al. Effect of eribulin with or without pembrolizumab on progression-free survival for patients with hormone receptor-positive, ERBB2-negative metastatic breast cancer: a randomized clinical trial. *JAMA Oncol*. 2020;6(10):1598-1605.
6. Voorwerk L, Slagter M, Horlings HM, et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. *Nat Med*. 2019;25(6):920-928.
7. Szekely B, Bossuyt V, Li X, et al. Immunological differences between primary and metastatic breast cancer. *Ann Oncol Off J Eur Soc Med Oncol*. 2018;29(11):2232-2239.
8. Dieci MV, Guarneri V, Tosi A, et al. Neoadjuvant chemotherapy and immunotherapy in Luminal B-like breast cancer: results of the phase II GIADA trial. *Clin Cancer Res Off J Am Assoc Cancer Res*. 2022;28(2):308-317.
9. Nanda R, Liu MC, Yau C, et al. Effect of pembrolizumab plus neoadjuvant chemotherapy on pathologic complete response in women with early-stage breast cancer: an analysis of the ongoing phase 2 adaptively randomized I-SPY2 trial. *JAMA Oncol*. 2020;6(5):676-684.
10. Cardoso F, McArthur HL, Schmid P, et al. LBA21 KEYNOTE-756: phase III study of neoadjuvant pembrolizumab (pembro) or placebo (pbo) + chemotherapy (chemo), followed by adjuvant pembro or pbo + endocrine therapy (ET) for early-stage high-risk ER+/HER2− breast cancer. *Ann Oncol*. 2023;34:S1260-S1261.
11. Loi S, Curigliano G, Salgado RF, et al. LBA20 A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER+ HER2− primary breast cancer (BC). *Ann Oncol*. 2023;34:S1259-S1260.
12. Loi S, Curigliano G, Salgado R. (GS01-01) Biomarker results in high-risk estrogen receptor positive, human epidermal growth factor receptor 2 negative primary breast cancer following neoadjuvant chemotherapy ± nivolumab: an exploratory analysis of CheckMate 7FL. Paper presented at the San Antonio Breast Cancer Symposium. 2023; San Antonio, Texas.
13. Litton JK, Regan MM, Pusztai L, et al. Standardized definitions for efficacy end points in neoadjuvant breast cancer clinical trials: NeoSTEEP. *J Clin Oncol Off J Am Soc Clin Oncol*. 2023;41:4433-4442.
14. Cardoso F, O'Shaughnessy J, McArthur H. (GS01-02) Phase 3 study of neoadjuvant pembrolizumab or placebo plus chemotherapy, followed by adjuvant pembrolizumab or placebo plus endocrine therapy for early-stage high-risk ER+/HER2− breast cancer: KEYNOTE-756. Paper presented at the San Antonio Breast Cancer Symposium. 2023; San Antonio, Texas.
15. Pusztai L, Yau C, Wolf DM, et al. Durvalumab with olaparib and paclitaxel for high-risk HER2-negative stage II/III breast cancer: results from the adaptively randomized I-SPY2 trial. *Cancer Cell*. 2021;39(7):989-998.e5.
16. Yau C, Wolf D, Brown-Swigart L, et al. Abstract PD6-14: analysis of DNA repair deficiency biomarkers as predictors of response to the PD1 inhibitor pembrolizumab: results from the neoadjuvant I-SPY 2 trial for stage II-III high-risk breast cancer. *Cancer Res*. 2018;78(suppl 4):PD6-PD14.
17. Schmid P, Cortes J, Dent R, et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med*. 2022;386(6):556-567.
18. Rozenblit M, Blenman K, Harigopal M, et al. PD-L1 protein expression in relation to recurrence score values in early-stage ER + breast cancer. *Breast Cancer Res Treat*. 2022;196(1):221-227.
19. Wolf DM, Yau C, Wulfkuhle J, et al. Redefining breast cancer subtypes to guide treatment prioritization and maximize response: predictive biomarkers across 10 cancer therapies. *Cancer Cell*. 2022;40(6):609-623.e6.
20. Zagami P, Cortés J, Carey LA, Curigliano G. Immunotherapy in the treatment landscape of hormone receptor-positive (HR+) early breast cancer: is new data clinical practice changing? *ESMO Open*. 2024;9(9).
21. Rugo HS, Kabos P, Beck JT, et al. Abemaciclib in combination with pembrolizumab for HR+, HER2− metastatic breast cancer: phase 1b study. *NPJ Breast Cancer*. 2022;8(1):118.
22. Jerusalem G, Prat A, Salgado R, et al. Neoadjuvant nivolumab + palbociclib + anastrozole for oestrogen receptor-positive/human epidermal growth factor receptor 2-negative primary breast cancer: results from CheckMate 7A8. *Breast Edinb Scotl*. 2023;72:103580.
23. Connolly JJ, Spring LM, Taghian AG, et al. Abstract OT3-15-01: TBCRC-053: P-RAD: a randomized study of preoperative chemotherapy, pembrolizumab and no, low or high dose RADiation in node-positive, HER2-negative breast cancer. *Cancer Res*. 2023;83(suppl 5):OT3-15-01.
24. De Caluwe A, Romano E, Poortmans P, et al. First-in-human study of SBRT and adenosine pathway blockade to potentiate the benefit of immunochemotherapy in early-stage luminal B breast cancer: results of the safety run-in phase of the Neo-CheckRay trial. *J Immunother Cancer*. 2023;11(12):e007279.
25. De Caluwe A, Desmoulins I, Cao K, Remouchamps V. LBA10 Primary endpoint results of the Neo-CheckRay phase II trial evaluating stereotactic body radiation therapy (SBRT) +/- durvalumab (durva) +/- oleclumab (ole) combined with neo-adjuvant chemotherapy (NACT) for early-stage, high risk ER+/HER2− breast cancer (BC). *Ann Oncol*. 2024;35(suppl 2):1-72.