A milestone in oncology has been reached in recent years with the advent of immune checkpoint inhibitors (ICIs) which target programmed cell death protein 1 (PD-1) or its ligand, PD-L1, and cytotoxic T-lymphocyte-associated protein 4 (CTLA4). ICIs were first approved by the Food and Drug Administration (FDA) for melanoma in 2011 and subsequently in several other tumor types. In contrast to more immunogenic solid tumor types, breast cancer (BC) is typically not characterized by a high tumor mutation burden which is known as one of the predictive biomarkers of response to ICI (well described in melanoma and lung cancer), and so it has been considered potentially less immunogenic.

However, data from large clinical trials demonstrated that subsets of early BC contain tumor-infiltrating lymphocytes (TILS), mainly represented by T lymphocytes, especially in triple-negative (TN) subtypes (i.e., the absence of expression of the estrogen and progesterone receptors and a lack of amplification of the HER2 gene) (1,2). Indeed, among BC, the TN subtype is characterized by greater tumor immune infiltrate (intratumoral and stromal TILs), which is another predictive marker for responses to immunotherapy (3,4). Recently, a large pooled individual patient analysis demonstrated that stromal TILs had a strong prognostic role in patients with early-stage triple negative breast cancer (TNBC) who received adjuvant chemotherapy (5). In this study, each 10% increment in stromal TILS corresponded to a significant improvement in survival outcomes. Fewer data are available for metastatic TNBC (mTNBC), but a correlation between TIL quantification and PD-L1 expression has also been described (6). Moreover, metastatic sites seem to have a lower percentage of TILs compared to primary tumors, suggesting the role of immune escape in tumor progression. Since PD-L1 expression and TILs have been associated with increased activity of ICIs in lung, bladder and renal cancers, they also appear to be promising therapeutic targets in TNBC.

Here, we discuss the results published by Adams et al. from the phase II multicohort, single-arm study KEYNOTE-086. Two cohorts of patients with mTNBC were included: cohort A included patients that progressed on at least one systemic therapy regardless of PD-L1 expression (7) while cohort B (results of which will be discussed here) included previously untreated, PD-L1-positive, metastatic triple-negative breast cancer: cohort B of the phase II KEYNOTE-086 study. Ann Oncol 2019;30:405-11.
of patients. The primary endpoint was safety. As expected with previous studies with pembrolizumab, it demonstrated an acceptable safety profile, including mainly grade 1–2 (90.5%) [asthenia (26.2%), nausea (13.1%), and diarrhea (11.9%)]. Only one patient (1.2%) stopped pembrolizumab treatment because of treatment–related adverse events (AEs). Immune-mediated AEs, which are now well known, were hypo (9.5%) or hyperthyroidism (4.8%). Secondary endpoints were efficacy outcomes. After a median follow-up of 12.3 months, the objective response rate (ORR) was 21.4% (range, 13.9–31.4%), with 4/84 patients having a complete response (CR) and 14/84 patients having a partial response (PR), according to RECIST v1.1 criteria. Interestingly, 8 of the 18 responses (44.4%) were ongoing at the time of data cutoff. Disease control rate, defined as the proportion of patients with CR, PR, or stable disease (SD) for ≥24 weeks, was 23.8% (range, 15.9–34.0%). The median duration of response was 10.4 months (4.2 to 19.2+ months), and the estimated rate of response duration longer than 12 months was 49.4%.

Other previous phase I/II trials demonstrated a signal of activity with an anti-PD-L1 used as a single agent in mTNBC. Importantly, PD-L1 expression and earlier administration of the ICI (first line vs. second line or more) were associated with a higher promise of response. The first study to evaluate pembrolizumab in advanced, pre-treated, PD-L1-positive mTNBC was the phase Ib KEYNOTE-012 trial (9). Of the 27 patients evaluable for efficacy, the ORR was 18.5% (95% CI: 6.3–38.1). A total of 116 mTNBC patients were included in the expansion cohort of a phase I trial that evaluated atezolizumab, an anti-PD-L1 (10). The ORR was 24% (5/21) in first-line patients, which was higher than in pre-treated patients (6%, 6/94 patients). Patients with PD-L1 expression (defined as ≥1% tumor-infiltrating immune cells) had higher ORRs than those <1% (12% vs. 0%). After a median follow-up of 25.3 months, median duration of response was 21 months, which is very rare with cytotoxic agents in mTNBC but is often reported with ICIs in other solid tumors (11).

In the cohort A of the phase II KEYNOTE-086 trial, 170 heavily pre-treated mTNBC patients (43.5% of patients had received three prior lines of chemotherapy in the advanced setting) were included, regardless of PD-L1 expression (7). Most patients were PD-L1 positive (61.8%). ORR was only 5.3% in the total and 5.7% in the PD-L1-positive population, but median duration of response was not reached either in the total (range, 1.2+ to 21.5+) or the PD-L1-positive (range, 6.3 to 21.5+) populations.

A third ICI, avelumab, an anti-PD-L1, was investigated in the phase Ib JAVELIN trial, which included all subtypes of pre-treated metastatic BC (n=168 in the overall cohort, 58 TNBC) (12). ORR was 3.0% in the overall cohort, with a trend toward a higher ORR in PD-L1-positive tumors, especially in mTNBC patients (22.2% [2/9] vs. 2.6% [1/39]). In this study, PD-L1 expression was assessed in tumor cells with a cut-off of 1%, 5%, or 25%, with tumor-associated immune cells having a cut-off of 10%.

As demonstrated by all these early-phase trials, although the prospect of selecting a subgroup of mTNBC patients with a durable response appears especially promising with an anti-PD(L)1 as single agent, these results support further evaluations of ICI alone in these patients. Consequently, the randomized phase III KEYNOTE-119 study (NCT02555657) was designed to compare the efficacy and safety of pembrolizumab monotherapy with chemotherapy in pre-treated mTNBC patients (2nd-line or 3rd-line). This study is now closed to inclusions and we are waiting for the results. Interestingly, while the proportion of long-term responders was substantial among patients treated with ICI alone, the median progression-free survival (PFS) and overall survival (OS) were not improved. Long-lasting clinical responses reflect the activation of a potent, tumor-specific memory T-cell response that mediates long-term cancer control, finally improving OS in a subset of patients. It shows that, unlike cytotoxic agents, ICI could potentially change the natural history of mTNBC due to their impact on the tumor micro-environment and systemic immunity.

Further research needs to be done urgently to find robust biomarkers to identify patients likely to have a durable response with ICI alone. Indeed, methods for analyzing PD-L1 expression differ between studies and there is still no standardized method to quantify it. For example, PD-L1 positivity has been defined with different PD-L1 antibodies and assays. In addition, cut-off values differ, so comparison between studies may be erroneous.

Although anti-PD(L)-1 as a single agent has demonstrated durable clinical activity in less than 20% of mTNBC patients, it is important to remember that most patients do not respond. The use of ICI alone is too often insufficient, so the aim is to identify strategies that render the tumor micro-environment (TME) more sensitive to anti-PD(L)1 agent. Therefore, combining ICI with other therapies (targeted therapies, chemotherapy, novel immunotherapies, or radiotherapy) might enhance the development of immunogenic tumors through both the inhibition of immune checkpoints and the generation and amplification of...
T-cell response. While chemotherapy is generally thought to suppress the immune system, cytotoxic chemotherapy can result in the release of tumor antigens that may elicit antitumor immunity, enhance the antigenicity of cancer cells by increasing the expression of the major histocompatibility complex, increase PD-L1 expression on tumor cells, and increase CD8+ TILs (13). Last year and for the first time in mTNBC, a phase III trial suggested a significant benefit on OS with the combination of IC and a cytotoxic as first line in a subset of PD-L1-positive patients. Atezolizumab or placebo was combined with nab-paclitaxel in 902 locally advanced or mTNBC patients (14). PFS and OS were defined as co-primary endpoints in the overall population and in the PD-L1-positive population. PD-L1 expression was used for stratification (40.9% of the patients in the total population had PD-L1-positive disease). ORR in the PD-L1 positive population was 59% in the combination arm, vs. 43% with nab-paclitaxel alone. After a median follow-up of 12.9 months, median PFS [5.5 to 7.2 months; hazard ratio (HR) 0.80 (95% CI: 0.69–0.92); P=0.0025] and OS [17.6 to 21.3 months; HR 0.84 (95% CI: 0.69–1.02); P=0.0840] were significantly improved in the combination arm for the overall population. In the PD-L1-positive subgroup, while median PFS was slightly but significantly improved [5.0 to 7.5 months; HR 0.62 (95% CI: 0.49–0.78); P<0.001], the data concerning the OS, although immature, were very promising with a 9.5-month increase from 15.5 to 25 months [HR 0.62 (95% CI: 0.45–0.86)].

This IMpassion130 study was preceded by a far smaller phase Ib study involving 33 mTNBC patients that now have a longer follow-up of 25 months. Median OS was numerically but not statistically longer in patients with tumors positive for PD-L1 expression vs. those with negative expression: 21.9 vs. 11.9 months, respectively, which is in the same range as the IMpassion130 study. Several patients experienced durables responses: 5 received single-agent atezolizumab for more than 1 year or completely discontinued all study treatments (15). This suggests that by obtaining a good response with the combination therapy, chemotherapy could be stopped. However, the study failed to identify any tumor-based biomarkers associated with responses or survival. Another phase Ib/II trial was designed to combine pembrolizumab with eribulin mesylate (16). The ORR in the combination arm was 33.3% (95% CI: 19.5–48.1) at the interim analysis, and included 39 patients. The ORR for patients who had untreated mTNBC increased to 41.2% (95% CI: 19.3–62.8, n=17). No differences were observed between patients who had PD-L1-positive tumors and those who had PD-L1-negative ones (ORR 29.4% and 33.3%; 17 and 18 patients respectively).

The effect of various cytotoxics on the TME must be studied in order to establish the best partner for anti-PD(L)1. Results on mTNBC are anticipated from several other phase III trials combining immunotherapy and chemotherapy. KEYNOTE-355 (NCT02819518) was designed to compare the efficacy of pembrolizumab or placebo plus one of three chemotherapy regimen (nab-paclitaxel or paclitaxel or carboplatin + gemcitabine) in patients with previously untreated mTNBC. This study should be completed by the beginning of the 2020 after the inclusion of more than 800 patients. IMpassion 131 (NCT03125902) and 132 (NCT03371017) will respectively evaluate atezolizumab plus paclitaxel vs. placebo plus paclitaxel or atezolizumab plus carboplatin, and gemcitabine vs. placebo plus carboplatin and gemcitabine in patients with previously untreated mTNBC. Stratification will be performed in these trials according to PD-L1 status. Results from these trials are eagerly being awaited upon to determine whether those results obtained in the IMpassion130 study can be confirmed.

Another strategy for mTNBC patients consists in demonstrating that the TME could be modulated by a short treatment; i.e., induction treatment, with either irradiation or chemotherapy to improve the response rate to an anti-PD(L)1 alone. This promising strategy has been tested in the adaptive phase II non-randomized and non-comparative trial TONIC that was presented at ASCO 2018, but which has not yet been published.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

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