Chemotherapy With or Without Bevacizumab Should Be the Standard of Care for First-Line Unresectable Epithelioid Mesothelioma

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In the 17 years that have elapsed since the first and only approval of the Food and Drug Administration with pemetrexed-cisplatin for frontline therapy of unresectable malignant pleural mesothelioma (MPM),1 ipilimumab and nivolumab (ipi-nivo)2 succeeded in moving the field beyond its therapeutic plateau. The magnitude of this achievement cannot be understated.

In this debate, we will present a counter argument as to why ipi-nivo represents an alternative first-line option, but not a reflex replacement for patients with advanced epithelioid (E)-MPM. In the wake of such a historic approval by the Food and Drug Administration, such a stance may, at first, seem controversial, and so, here, we will underpin the CON side of this debate with the following arguments in turn.

**Efficacy**

**Survival**

Despite the 4-month improvement in survival with ipi-nivo in CheckMate 743 with corresponding 18.1 months (95% confidence limits: 16.8–21.4 mo) compared with 14.1 (12.4–16.2) months for chemotherapy, with hazard ratio (HR) of 0.74 (96.6% confidence limits: 0.60–0.91, p = 0.0020), substantial benefit was observed in the smaller group of patients with the relatively chemoresistant non–E (NE)-MPM. Histology was a stratification factor.

The NE-MPM group constituted a minority of the recruited cohort: 149 versus 456. Overall survival (OS) was 18.1 (12.2–22.8) months for ipi-nivo, that is, not significantly different from the activity observed in patients with E-MPM with a median OS of 18.7 (16.9–22) months. In stark contrast, the survival benefit differed according to the histologic subtype, being 8.8 months in NE-MPM corresponding to an impressive HR of 0.46 (0.31–0.68), whereas it was 16.5 months in E-MPM corresponding to a not significant HR of 0.86 (0.69–1.08). This OS is consistent with the control arm of LUME-Meso, in which the control arm for chemotherapy in an exclusively E-MPM cohort was 16.1 months.3

Taken together, it can be reasonably argued that the OS superiority observed with ipi-nivo in CheckMate 743 was predominantly due to histology-associated heterogeneity with a lower chemotherapeutic efficacy in the NE-MPM cohort. The basis for the differential sensitivity to chemotherapy in NE-MPM versus E-MPM is unknown. Nevertheless, this does not seem to be due to any heightened sensitivity of NE-MPM to ipi-nivo compared with E-MPM.

Chemoresistance was marked in patients with NE-MPM. Recent insights into the strong association of epithelial-mesenchymal transition with NE-MPM4,5 could go some way to help explain this observation. Epithelial-mesenchymal transition is characterized by a highly stem-like, drug-resistant phenotype6 likely to account for the poor efficacy observed with chemotherapy.

**Disease Control**

A proportion of patients receiving ipi-nivo progressed earlier than those receiving chemotherapy with the progression-free survival (PFS) curves crossing after 6 months. Early separation of the PFS curves likely relates to those patients with inherently immunotherapy...
refractory MPM, although data on the histologic composition of this group are not available.

The median PFS was not significantly different between treatment arms in CheckMate 743: 6.8 (5.6–7.4) months for ipi-nivo versus 7.2 (6.9–8.0) for chemotherapy, HR of 1.00 (0.82–1.21). The disease progression rate was higher for ipi-nivo (18%) versus 5% for chemotherapy. Far from being inferior, chemotherapy conferred greater disease control within the first 6 months with a higher partial response rate. Taken together, for patients who are symptomatic from their E-MPM and require the highest likelihood of disease control, chemotherapy may be still considered a reasonable first choice.

The PFS curve crossover observed in CheckMate 743 can be explained by the continued treatment with ipi-nivo beyond six cycles (maintenance). This possibility is supported by evidence from the NAVLT19 (Switch-maintenance gemcitabine after first-line chemotherapy in patients with malignant mesothelioma) randomized trial, in which the use of an active maintenance treatment after chemotherapy has recently been found to markedly improve PFS over active symptom control. In CheckMate 743, ipi-nivo was received, on average for 5.6 months with an interquartile range of 2.0 to 11.4 months compared with 3.5 (interquartile range: 2.7–3.7) months for chemotherapy. Despite this, chemotherapy maintained an equivalent PFS.

CheckMate 743 compared ipi-nivo with chemotherapy alone. Nevertheless, the first ever phase 3 trial to reveal superiority over chemotherapy was MAPS1, in which bevacizumab was added (pemetrexed cisplatin bevacizumab [PCB] regimen). This trial revealed an increase in OS from 16.1 (14.0–17.9) months to 18.8 (15.9–22.6) months in an unselected cohort of patients comprising approximately 20% NE-MPM. Given the equivalence of chemotherapy to ipi-nivo in patients with E-MPM in CheckMate 743, and the superiority of PCB versus chemotherapy alone in respective phase 3 studies in unselected patients, it is not beyond the realms of possibility to suggest that PCB could confer superiority in E-MPM were it to be tested head to head with ipi-nivo. Bevacizumab is not available universally, particularly given the lack of a license; however, where it is, these data may give pause for thought on the choice best suited to the patient.

Toxicity

Assessment of therapeutic risk versus benefit in relation to ipi-nivo versus chemotherapy is especially important given their OS equivalence in patients with E-MPM. In this regard, in CheckMate 743, although not reported by histologic subtype, the rate of any-grade serious adverse events associated with ipi-nivo was more than double compared with chemotherapy (8%). In addition, grade 3 or 4 treatment-related adverse events were found to be more than double that for ipi-nivo (15% compared with 6% for chemotherapy). Furthermore, any-grade adverse event leading to discontinuation of treatment was reported in more patients receiving ipi-nivo (23%) compared with chemotherapy (16%), and this was also reflected in the grade 3 to 4 event rate, which was twice as high for ipi-nivo (15% versus 7%). Although the frequency of treatment-related deaths was low overall, ipi-nivo was associated with a treatment-related death rate (three patients) compared with chemotherapy (one patient owing to myelosuppression). Taken together, these data suggest that chemotherapy remains a relatively safer and equieffective treatment option for patients with E-MPM. During the informed consent process, patients will need to be informed of the relative likelihood of serious toxicity that could be associated with ipi-nivo and the decision to treat will require a balanced judgment of risk versus benefit.

Cost-Effectiveness in the Context of Equivalence

Although health-economic data are not generally available for ipi-nivo in MPM, considerations such as the patent life of pemetrexed and the equivalent efficacy of ipi-nivo compared with chemotherapy may raise questions in some jurisdictions regarding the relative cost-effectiveness. This may be of particular relevance in countries with state-funded health care systems, where rigorous cost-benefit analysis is necessary to sanction the use of treatments for cancer.

A Historical Precedent for Histologic Stratification for Therapy

The use of histology as a stratification factor for selectively treating thoracic cancers is not new. NSCLC lends two examples. In the frontline setting, a pivotal trial comparing pemetrexed-cisplatin versus gemcitabine-cisplatin phase 3 identified nonsquamous histology as a predictive factor for sensitivity to pemetrexed. This led to an approval of pemetrexed with histologic subtype written into the license, despite the trial revealing no overall superiority for any arm. In the second-line treatment setting, the LUME-Lung (BIBF 1120 Plus Docetaxel as Compared to Placebo Plus Docetaxel in 2nd Line Non Small Cell Lung Cancer) trial showed superiority of docetaxel plus nintedanib versus docetaxel alone in patients with lung adenocarcinoma, again, leading to a histology-specific selection in the approved regimen (at least in Europe). In patients with E-MPM therefore, based on the considerations previously outlined, the possibility
of stratifying for PCB or selecting chemotherapy over ipi-nivo could be considered within the scope of normal practice for other cancers.

**Clinical Trials and the Evolution of Frontline Therapy**

There is an ongoing paradigm shift observed with the development of immunotherapy which may forecast the future direction of change for patients with MPM. We may now have entered an era of more rapidly evolving therapy for MPM after a well-trodden path that has secured approvals in NSCLC. This path to date has been defined by the following two key changes: (1) migration of immune checkpoint inhibition from a relapsed to a frontline setting and (2) leveraging synergy through combination of chemoimmunotherapy.

In NSCLC, approved front-chemoimmunotherapy triplets have been based on the results of the KEYNOTE 189,9 KEYNOTE 407 (pembrolizumab + chemotherapy),10 and quadruplets 9LA (ipi-nivo + chemotherapy)11 or IMpower 150 schedule (atezolizumab-bevacizumab + chemotherapy),12 each trial has compared the combination to chemotherapy. The next generation of phase 3 chemo-immunotherapy trials in MPM is ongoing. IND 227 NCT02784171, DREAM3R (DuRvalumab With chEmo-therapy as First Line treAtment in Advanced Pleural Me-thothelioma) NCT04334759 (triplets), and Beat meso NCT03762018 (quadruplet) have all chosen chemotherapy as the control. For patients with E-MPM in these trials, chemotherapy should be considered an acceptable control arm with which to compare novel immunotherapy regimens in common with NSCLC (although ipi-nivo as a control need not be excluded). This way, a path to definitive superiority of a chemoimmunotherapy regimen in E-MPM remains open.

**Sequential Immunotherapy**

There remains no licensed standard of care in the relapsed treatment setting after progression from platinum-based chemotherapy. In the refractory setting, patients may benefit from single-agent immunotherapy as evidenced in the CONFIRM (Checkpoint blockage for Inhibition of Relapsed Mesothelioma) trial (ClinicalTrials.gov identifier NCT03063450), the first phase 3 study to reveal improved OS in this setting. Superiority was revealed in patients with E-MPM. Based on the equivalence of chemotherapy and ipi-nivo in E-MPM, it can be argued that post platinum-doublet immunotherapy could be considered a reasonable treatment option at this time based on phase 3 evidence particularly in settings where bevacizumab and chemotherapy are available in the first-line setting. With the emergence of apparently synergistic immunotherapy combinations in the relapsed setting, an alternative algorithm extending beyond CONFIRM could further improve survival of patients with E-MPM. It is unknown whether previous platinum therapy could prime mesotheliomas to benefit from immunotherapy; however, based on models of Sting-GAS pathway activation involving DNA damaged mediated cytosolic DNA sensing and resulting immune cell tumor infiltration,14 This is plausible, providing an additional rationale for chemotherapy-immunotherapy sequencing.

**Conclusion**

The biological basis for response to ipi-nivo in E-MPM is unknown. Tumor mutation burden, a possible predictor of immunotherapy efficacy, is low (averaging 2 per Mb) and therefore unlikely to matter. The evidence for programmed death-ligand 1 (PD-L1) as a bona fide predictive biomarker is highly equivocal, if not absent. In CONFIRM, PD-L1 did not predict the efficacy of nivolumab, whereas in CheckMate 743, PD-L1 expression greater than 1% was associated with shorter OS in the chemotherapy arm, keeping with previous reports of PD-L1 as a negative prognostic factor. Future identification of a robust predictor of sensitivity to ipi-nivo is needed and could lead to future routine stratification of the relatively larger E-MPM subgroup of patients, enabling physicians to confidently allocate chemotherapy or immunotherapy only to those patients most likely to benefit.

In summary, ipi-nivo in E-MPM is not only equivalent to chemotherapy in terms of disease control (higher risk of disease progression within the first 3 mo) but also carries a higher risk of serious adverse events. Chemotherapy (or chemotherapy and bevacizumab) is presently the backbone for all current chemoimmunotherapy phase 3 trials that could define the next generation of therapy. One cannot rule out the possible superiority of chemotherapy + bevacizumab versus ipi-nivo in E-MPM, although a major caveat is the lack of head-to-head comparative data. Although the future of immunotherapy in MPM is likely to be frontline and combinations, for now, phase 3 evidence in the relapsed setting (CONFIRM) associated with longer OS in patients with E-MPM suggests that sequencing may offer an opportunity to extend survival after chemotherapy in this E-MPM group. Based on these arguments, it can reasonably be argued that chemotherapy with or without bevacizumab should continue to be considered an optimal first-line option in patients with E-MPM.

**CRediT Authorship Contribution Statement**

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References