Editorial

Tackling the challenge of brain involvement in driver-negative non-small cell lung cancer

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Despite recent therapeutic advances, brain metastases (BM) remain a major problem in non-small cell lung cancer (NSCLC). For oncogene-driven disease, like EGFR- or ALK-mutated tumors, the presence of BM at initial diagnosis remains the harbinger of shorter progression-free survival (PFS) and overall survival (OS) even with newer tyrosine kinase inhibitors (TKI), like osimertinib and next generation ALK drugs, which show improved brain response rates of approximately 80% and intracranial progression rates <10% per year (1-4). However, for the majority of patients with advanced disease, who lack actionable alterations and receive immune checkpoint inhibitor (ICI)-based treatment, the unmet need regarding BM is much more pressing, since benefit from novel therapies has been modest and prognosis remains consistent with the graded prognostic assessment (GPA) from the era of chemotherapy (5).

In a recent article of *Translational Lung Cancer Research*, Chen *et al.* show how use of available immunotherapeutic options could be optimized in order to help in this difficult situation (6). Through a comprehensive search using PubMed, Embase, the Cochrane Library and other databases, the authors could show considerably higher intracranial overall response rates (icORR) for the combination of ICI with radiotherapy (RT) at 81% *vs.* 34–56% for ICI monotherapy, chemotherapy, chemoimmunotherapy, or various other combinations. At the same time, despite this impressive icORR in the range observed with next-generation EGFR/ALK inhibitors, the duration of responses in driver-negative tumors remain limited with a median intracranial PFS (iPFS) of 7.0 months only. Chen *et al.* provide a possible solution to this problem as well, by showing that the durability of intracranial responses under ICI in NSCLC can be improved by the combined use of checkpoint blockade with dual programmed death 1 (PD-1) cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibition and chemotherapy, which confers an impressive median icPFS of 13.5 *vs.* 2.3–7.0 months only for other options (6). These results are of great importance for clinical practice. Taken together, they suggest the administration of double ICI-based chemoimmunotherapy and additional inductive brain RT as the *bona fide* optimal strategy to maximize outcomes for patients diagnosed with non-driver-dependent NSCLC and baseline BM. Of course, such an aggressive strategy may also be associated with more side-effects, therefore prospective validation will be necessary before it

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Table 1 Combined PD-1/CTLA-4 blockade *vs.* standard chemoimmunotherapy for non-small cell lung cancer with BM

Variables	Checkmate-9LA	Keynote-189/407/21	Atezo-Brain (single-arm)
Treatment	Anti-PD-1/anti-CTLA-4/doublet CT	Anti-PD-1/doublet CT	Anti-PD-L1/doublet CT
All BM patients[a], n (%)	43/8 (84%/16%)	75/30 (71%/29%)	40/0 (100%/0)
ORR	43%	39%	45%
PFS HR (95% CI)	0.40 (0.25–0.64)	0.44 (0.31–0.62)	–
2-y PFS	19%	15%	17%
mPFS	10.6 mo	6.9 mo	8.9 mo
icPFS HR (95% CI)	0.36 (0.22–0.60)	–	–
m-icPFS	13.5 mo	–	6.9 mo
1-y icPFS	51%	–	27%
OS HR (95% CI)	0.43 (0.27–0.67)	0.48 (0.32–0.70)	–
2-y OS	35%	42%	27%
mOS	19.3 mo	18.8 mo	11.8 mo
PD-L1^{neg} BM patients[a], n (%)	17/6 (73%/27%)[b]	–	18/0 (100%/0)
ORR	–	–	–
PFS HR (95% CI)	0.17 (0.06–0.45)	0.42 (0.24–0.73)	–
2-y PFS	7%	–	–
mPFS	10.6 mo	–	–
icPFS HR (95% CI)	–	–	–
m-icPFS	–	–	–
1-y icPFS	–	–	–
OS HR (95% CI)	0.28 (0.13–0.61)	0.41 (0.22–0.74)	–
2-y OS	35%	–	–
mOS	20.6 mo	–	10.4 mo

Data for the subset of patients with BM from pertinent phase 2/3 clinical trials are shown. The experimental arms were: for Checkmate-9LA nivolumab/ipilimumab with 2 cycles of platinum-based doublet CT (8,9); for Keynote-189/407/21 pembrolizumab with platinum-based doublet CT (10); for Atezo-Brain atezolizumab with platinum-based doublet CT (11). The control arm in the Checkmate-9LA and the Keynote trials was standard doublet CT for 4 cycles, followed by pemetrexed maintenance if this drug was used initially, while Atezo-Brain was a single-arm trial. We acknowledge that cross-trial comparisons have important inherent limitations and should be considered with caution. [a], number of patients analyzed, non-squamous/squamous histology (%/%). [b], the total number of patients with BM was 23, but their distribution between non-squamous and squamous histology is not provided, therefore here the published distribution of different histologies among all PD-L1-negative cases (n=131) is given, instead. PD-1, programmed death 1; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; BM, brain metastases; CT, chemotherapy; ORR, overall response rate; ic, intracranial; PFS, progression-free survival; OS, overall survival; neg, negative; m, median; mo, months; y, years; HR, hazard ratio; CI, confidence interval; –, not reported.

can be widely recommended. Nonetheless, this concept is certainly plausible and, besides the current meta-analysis by Chen *et al.* (6), additionally supported by at least two further important arguments: first, a similar strategy combining ipilimumab/nivolumab with upfront brain RT is the treatment of choice for patients with BM from melanoma, another tumor characterized by high tumor mutational burden (TMB) and particular sensitivity to immunotherapy, like NSCLC (7); second, the Checkmate-9LA trial has shown better efficacy for the combined nivolumab/ipilimumab-based chemoimmunotherapy compared to standard triplet chemoimmunotherapies for NSCLC in the cross-trial comparison with other phase 2 and 3 studies (*Table 1*) (8-11). Whether the alternative anti-PD-L1/

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CTLA-4-based chemoimmunotherapy of the POSEIDON study may be equally able to prolong the duration of intracranial responses as the Checkmate 9LA regime, remains unclear at present. However, the fact that the OS hazard ratio (HR) for patients with *vs.* without BM was higher in the POSEIDON (0.81 *vs.* 0.72) (12), but lower in the Checkmate-9LA study (0.43 *vs.* 0.79) casts doubts, and root of the problem may be that POSEIDON limited the administration of the CTLA-4 inhibitor tremelimumab to 5 courses only, while ipilimumab was offered continuously until disease progression in the Checkmate-9LA study.

Thus, continued CTLA-4 blockade appears to be important for the durability of intracranial responses in NSCLC, whereas RT improves their depth, as suggested by the findings of Chen *et al.* (6). The use of RT to augment ICI efficacy is an area of intense investigation currently: goal is to heat-up the tumor microenvironment (TME) by inducing local inflammation, which may improve priming, trafficking and the effector function of tumor-reactive T cells (13,14). Indeed, randomized phase 2 trials could demonstrate that RT significantly increases the ORR and prolongs patient survival if administrated concomitantly with the PD 1 inhibitor pembrolizumab (15). A similar concept of radioimmunotherapy undergoes clinical testing in early and locally advanced NSCLC, as well, especially for frail patients, who need systemic therapy besides RT, but cannot tolerate chemotherapy (16). Promising in this regard is also the very low frequency of intracranial relapse <10% after durvalumab consolidation in stage III disease (17), which additionally argues for an exquisite immunotherapeutic sensitivity of BM in NSCLC. While the optimal radiotherapy regimen for boosting the efficacy of ICI remains unclear at present, both stereotactic (SRT) and whole brain radiotherapy (WBRT) have similar efficacy in NSCLC, as shown by Chen *et al.* (6,9). The same had also been reported earlier for TKI-treated EGFR/ALK-mutated tumors, however, SRT is generally preferred nowadays due to its lower neurotoxicity (18).

Further evidence for an essential role of the TME in NSCLC BM is also underlined by the prominent association between PD-L1 expression and intracranial ICI efficacy reported by Chen *et al.*: the pooled icORRs under ICI monotherapy across the analyzed studies were 54%, 30% and 2% for tumors with PD-L1 tumor proportion score (TPS) ≥50%, 1–49% and <1% respectively (6). These results highlight patients with BM from PD L1 negative NSCLC as an unfavorable subset that does not derive adequate benefit from current immunotherapies. While pembrolizumab- or atezolizumab-based chemoimmunotherapy is certainly more effective than ICI monotherapy (10,11), the best available option for NSCLC patients with BM lacking PD-L1 expression currently appears to be again the dual PD-1/CTLA-4-inhibitor-based chemoimmunotherapy of Checkmate 9LA, whose patients with BM from PD-L1-negative tumors showed better clinical outcomes than those of the Keynote-189/407/21 and Atezo-Brain studies (*Table 1*). These data further corroborate the outstanding intracranial efficacy of dual checkpoint blockade in NSCLC, as highlighted in the meta-analysis of Chen *et al.* (6). Besides PD-L1 expression, other molecular tumor properties are also essential for the control of BM in NSCLC, as exemplified by the earlier intracranial failure of combined TKI and RT in EGFR/ALK-driven NSCLC with high-risk oncogene variants, i.e., *EGFR* mutations beyond exon 19 deletions, or "short" *EML4-ALK* fusions, like v3 (E6;A20) (18,19). Deeper molecular profiling and multiparametric characterization of the TME are expected to refine the stratification and facilitate more individualized management of BM from NSCLC in the near future (20,21). In oncogene-driven tumors, the unmet therapeutic need for BM increases in later lines, when brain involvement has developed in the majority of patients and targeted therapies are not active any more (22).

Thus, although less spectacular than TKI, modern immunotherapy has facilitated significant progress in the treatment of driver-negative NSCLC with BM during the last few years. This underlines the importance of comprehensive reviews, such as the meta-analysis meticulously conducted by Chen *et al.* (6), in order to systematically filter the rapidly growing literature and uncover principles and patterns that may be less obvious, but of key importance for the optimal use of available options. In anticipation of next-generation immunotherapies, such as multispecific antibodies and autologous or allogeneic cell products, which are rapidly evolving are poised to dominate cancer medicine in the future (23-25), the work by Chen *et al.* opens our eyes to the most effective strategies feasible for NSCLC with BM already today: these—to the best of our knowledge, as further refined by the authors—comprise chemoimmunotherapy with combined PD-1/CTLA-4 blockade alongside upfront radiotherapy.

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