Editorial Commentary

Sequence of therapies for advanced BRAFV600E/K melanoma

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The treatment of BRAF-mutant advanced melanoma currently relies on targeted therapy and immunotherapy. Targeted therapy combines a BRAF and a MEK inhibitor (1-3), whereas immunotherapy is based on an anti-programmed death 1 (PD-1) antibody, either alone or combined with an anti-CTLA4 antibody (4). Patients who receive one of these options and have a progression can be treated with the other one.

A long-term debate has been established about the optimal sequence: should patients first receive targeted therapy or immunotherapy? Either modality has pros and cons. Targeted therapy achieves fast and profound responses, with less than 5% of patients refractory to the combination. Its tolerance is excellent, and the toxicity is usually easily manageable. But resistance usually appears after 12–18 months on therapy.

On the other hand, immunotherapy more commonly leads to durable responses, although responses are less common and 40% of patients are refractory to treatment. Moreover, the combination of the anti-PD-1 antibody nivolumab plus the anti CTLA-4 antibody ipilimumab produce high grade toxicities in more than 50% of patients, with some of them potentially fatal if medical management is not adequate (4,5).

Results from the DREAMseq study, a pharmaceutical independent clinical trial led by the ECOG-ACRIN research group, are very relevant for the clinical practice (6). It is the first phase 3 study to test the optimal sequence for advanced BRAFV600E/K mutant melanoma. Half the patients first received induction nivolumab (anti-PD-1) plus ipilimumab (anti-CTLA4), followed by nivolumab maintenance (Arm A); upon progression, patients were treated in arm C with dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor). This sequence was compared with the opposite, arms B and D. The primary end point of the study was the 2-year overall survival rate (OS_{2y}). A total of 265 patients were included. The study demonstrated benefit in terms of OS_{2y} for the arm starting with the combination of ipilimumab plus nivolumab, OS_{2y} 72% *vs.* 51%, P=0.01 (6).

Patient recruitment was slower than expected, and lasted around six years, which reflects the difficulties in the completion of academic studies in a setting where pharmaceutical sponsored trials may be more appealing. This could have contributed to a selection bias favoring the inclusion of cases with less favorable characteristics, who were not candidates for other studies. For instance, 25% of patients in arm B of the DREAMseq trial had BRAFV600K mutated tumors, while the frequency of this BRAF mutation is only 17% of the total BRAF mutations in most series. This could be the in part the reason for the unexpected low response rate observed with dabrafenib plus trametinib as first-line therapy in the DREAMseq study, with an overall response rate (OR) of only 46% (6), while in the pivotal

Table 1 Summary of DREAMseq and SECOMBIT trial design and main results

	DREAMseq	SECOMBIT
Number of patients	265	209
ICI combination	Ipilimumab plus nivolumab	Ipilimumab plus nivolumab
BRAF-MEK inhibitor combination	Dabrafenib plus trametinib	Encorafenib plus binimetinib
Primary endpoint	OS_{2y}	OS_{2y}
Median follow-up (months)	27.7	32.2
OS_{2y}		
ICI as first line	71.8%	73%
BRAF-MEK inh as first line	51.5%	65%
OR 1st line		
ICI	46%	45%
BRAF-MEK inh	43%	87%
OR 2nd line		
ICI	29.6%	25.7%
BRAF-MEK inh	47.8%	57.9%
Rate of cross over		
ICI as first line	48% (21/44)	37% (10/27)
BRAF-MEK inh as first line	55% (39/71)	53% (19/36)
BRAFV600K rate		
ICI as first line	12%	NR
BRAF-MEK inh as first line	25%	NR

ICI, immune checkpoint inhibitor; BRAF-MEK inh, BRAF inhibitor combined with MEK inhibitor drugs; OS, overall survival; OR, overall response rate; NR, not reported.

trials of the combination of dabrafenib plus trametinib the OR is over 70% (1). It is believed that BRAFV600K tumors do not respond to targeted therapy as well as the most common BRAFV600E (7,8).

The DREAMseq study, had particular exclusion criteria, such as having very high LDH levels (when LDH was over 10 times the normal limit) and brain metastases that had not been previously treated with local therapy or brain metastases that had received holocraneal radiotherapy (6). So, its conclusion can not be applied for patients with very high tumor burden.

At the time of progression, the criteria for transferring patients to the second line of treatment were very strict and a minimum of 2 weeks of washout between therapies was required before switching therapies. This was probably the main reason for the low crossover rate in both arms: only 48% of patients treated in arm A were subsequently treated with BRAF-MEK inhibitors in arm C, and only 55% of the patients treated in arm B, were treated with immunotherapy as second line in arm D (*Table 1*) (6).

Despite the issues discussed, the study provides highly relevant information with a clear impact on the clinical practice. The benefit in terms of survival is objective, clinically significant and comes to clarify a highly relevant issue for patients with BRAFV600E/K mutant advanced melanoma.

The conclusions of the DREAMseq study are consistent with the results of a similar investigator-initiated trial conducted in Europe, SECOMBIT (*Table 1*) (9). SECOMBIT is a phase 2 study that compares encorafenib (a BRAF inhibitor) plus binimetinib (a MEK inhibitor) followed upon progression by nivolumab plus ipilimumab (arm A), the opposite sequence (arm B), and a sandwich approach starting with encorafenib plus binimetinib for

8 weeks, then nivolumab plus ipilimumab and, upon progression, back to targeted therapy (arm C). The results favored the strategy of immunotherapy first (arm B) versus the opposite (arm A): OS_{2y} 73% *vs.* 65% and OS_{3y} 64% *vs.* 53%(9). The OR of the immunotherapy combination was lower in second line setting compared to the response of ipilimumab-nivolumab as first line [OR 26% *vs.* 45% in SECOMBIT (9) and 30% *vs.* 46% in DREAMseq (6)] (*Table 1*). Both studies suggest that after progression to BRAF plus MEK inhibitors, the susceptibility of melanoma to the combination of nivolumab plus ipilimumab is reduced. This clinical observation is consistent with preclinical data showing an increase in immunosuppressive microenvironment when tumors become resistant to BRAF-MEK inhibitors (10,11), with a higher percentage of M2 macrophages and a low number of CD103 dendritic cells (12), while tumors responding to BRAF-MEK inhibitors were more susceptible to immunotherapy (13).

Although data from DREAMSeq and SECOMBIT (6,9) show an advantage for starting therapy with immunotherapy, several questions remain open. First, most patients with rapidly progressive disease and high tumor burden were excluded, so it is unclear if this subgroup could have higher benefit if they receive during the first line targeted therapy, well sequentially or in combination with immunotherapy. Second, no studies have used single-agent anti-PD-1 as a comparator, a relevant issue considering that many patients are no suitable for the combination of nivolumab plus ipilimumab, and anti PD-1 antibodies as single agent use to be the comparator arm in most phase 3 trials. Finally, a significant proportion of patients first receiving immunotherapy will have refractory disease: in the DREAMseq study, 34 of the 133 patients starting with immunotherapy had an early progression and did not have the option to switch to targeted therapy, partly due to the strict crossover criteria (6). It is probable that if these persons had been treated with a BRAF inhibitor plus MEK inhibitor as first line therapy, they would have had a rapid response, with clinical improvement lasting months. It is urgent to discover predictive factors of intrinsic resistance to immunotherapy based in immune checkpoint inhibitors (ICI). The subgroup analysis carried out in the DREAMseq study indicate that clinical data were not useful for defining who will be the patients resistant to ICI, as first line treatment with the combination to ipilimumab plus nivolumab was superior to the first line with the combination of BRAF plus MEK inhibitors both for patients with good prognostic clinical factors (normal LDH, ECOG PS0 and stages M1a or M1b) , as well as for patients with poor clinical prognostic factors (6).

Investigating new treatment formulas for this refractory subgroup of patients as the sandwich sequence tested in the third arm of the SECOMBIT trial (9) or triple combination of BRAF-MEK inhibitors with immunotherapy at least during the first months of treatment, followed by ICI as maintenance may be better options for this resistant subgroup.

In summary, the DREAMseq study, supported by the results of the independent study SECOMBIT, defines the combination of ipilimumab plus nivolumab as the preferred option at first line setting versus the combination of BRAF plus MEK inhibitors. Future research is needed to understand why a high percentage of patient do not respond to immunotherapy.

Academical studies are needed to clarify relevant clinical questions that are not the focus of pharmaceutical companies.

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Footnote

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