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Kim, Myung S
Prasad, Vinay

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When we move cancer drugs from the second or third to the first line of treatment: what lessons can we learn from KEYNOTE-177 and JAVELIN-100

Myung S Kim,[1] Vinay Prasad[2,2]

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[1]Department of Medicine, Division of Hematology and Oncology, Oregon Health & Science University, Portland, Oregon, USA
[2]Department of Medicine, University of California San Francisco, San Francisco, California, USA

Correspondence to:
Vinay Prasad, Department of Medicine, University of California San Francisco, San Francisco CA 94158, USA; vinayak.prasad@ucsf.edu

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If the current standard of care is to give a new cancer drug as the second or third treatment option for a patient and there is interest in moving the drug to the front-line setting, how should we design and evaluate the study? Two recent examples can help us make sense of this question.

The recent KEYNOTE-177 Study[1] evaluated pembrolizumab in microsatellite-instability-high (MSI-high) advanced colorectal cancer found that front-line use of pembrolizumab is associated with an improved progression-free survival (PFS), median 16.5 months versus 8.2 months, compared with standard chemotherapy. Similarly, JAVELIN-100[2] found that among patients with metastatic urothelial cancer who achieved at least stable disease after four to six cycles of therapy, the use of maintenance avelumab increased median PFS from 2.0 months to 3.7 months and median overall survival (OS) from 14.3 months to 21.4 months. Both pembrolizumab and avelumab are checkpoint inhibitors that target immune checkpoints that unleash the immune response to cancer cells. These trials join studies such as KEYNOTE-48[3] and KEYNOTE-189,[4] as justification to move a drug previously used in a latter line of therapy to the front-line setting. Moving these drugs to the front line will certainly increase the number of patients in each of these tumour types who receive the medication, growing market share and unfortunately, also, aggregate immune-related adverse events, but the key question is whether patients are better off as a result and how to make that assessment. Here, we discuss sequencing, duration and patient selection. KEYNOTE-177 and JAVELIN-100 have several interesting features that may provide guidance for future trials.

Shape of the Kaplan-Meier curve for progression suggests that not all patients benefit from immunotherapy

The KEYNOTE-177 Study had coprimary endpoints of PFS and OS. The trial found that median PFS was improved, and the HR favoured the pembrolizumab arm, but proportional hazards assumption appears to be violated. In other words, the curves have radically different shapes. Patients in the pembrolizumab arm have a wide variance of outcomes compared with the chemotherapy arm. Approximately 40% of patients experience death or progression in the first 6 months of treatment, while 40% of patients experience a durable response or stable disease for more than 3 years.

The finding that there is a subset of patients getting pembrolizumab with durable response and subset with rapid progression is supported by findings in the provided waterfall plots representing the as-treated population is included in the supplement. Overall, 104 of 138 patients (67.9%) in the pembrolizumab arm experienced any tumour shrinkage as best response compared with 111 of 135 patients (77.6%) in the chemotherapy arm underscoring the higher proportion of patients who initially respond to chemotherapy. The superior percentage of any tumor shrikage with chemotherapy in waterfall plots is likely an underestimate as some patients in the chemotherapy arm did not receive a single dose of chemotherapy. Only 143 of the 154 patients randomised to chemotherapy received at least one dose of chemotherapy (93%) and were thus included in the waterfall plot, while 100% (153/153) assigned to pembrolizumab received at least one dose. High rates of early censoring in the control arm are commonly seen in clinical trials that are not blinded[5] and may represent patient's withdrawing from study due to discontent at random assignment. Such patients are often highly motivated and may be more likely to have superior outcomes.

Putting these findings together and acknowledging that OS results remain immature, we believe the correct interpretation of KEYNOTE-177 is more circumspect. The FDA has approved of pembrolizumab for first-line therapy of MSI-high colorectal cancer. Based on KEYNOTE-177, pembrolizumab is an early treatment option to consider; however, it lacks evidence for pembrolizumab to be designated as the best first-line option for all MSI-high patients. For patients in whom there is concern about the risk of early progression, chemotherapy may be reasonable; as such, it would be incorrect to view KEYNOTE-177 as a trial that shows pembrolizumab first is always best. Finally, biomarkers to identify patients who are more likely to respond are in the early stages of development as evidenced by the variation in outcome even among MSI-high patients and it is yet to be confirmed in prospective studies they are needed.

Moving drugs from subsequent to front line

JAVELIN Bladder 100 is a phase III study of maintenance avelumab in advanced or metastatic urothelial carcinoma in patients with complete response, partial response or stable disease

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following first-line platinum-based chemotherapy. Positivity of PD-L1, considered a predictive marker of response to checkpoint inhibitors, was not a requirement of entry.

Notably, this study is fundamentally concerned not with whether a patient with bladder cancer should get checkpoint inhibition at some point during their cancer journey, but when such a patient should get the drug.[6] Pembrolizumab is effective in urothelial carcinoma in the second-line setting and patients in the control arm who progress after chemotherapy must receive immunotherapy as the standard of care.

Both JAVELIN Bladder 100 and KEYNOTE-177 do not include crossover in trial design. The proportion of patients who receive immunotherapy after progression on chemotherapy in JAVELIN-100 is 153 (43.7%). This is only 70% of the 216 patients (61.7%) who receive subsequent anticancer therapy in the control arm. KEYNOTE-177 has an effective crossover rate of 59% with 56 patients (36%) crossing over to the pembrolizumab arm and 35 patients (23%) receiving immunotherapy off trial.

JAVELIN Bladder 100 found an OS benefit, which is supportive of upfront use of checkpoint inhibitor in the maintenance setting, but is unable to answer whether this truly improves OS over the US standard of care of providing PD1/PDL1 Ab to all patients (not 70%) on progression. It is also concerning that maintenance of avelumab is described as a new standard of care based on comparison of median OS with other strategies.[7] This does not consider that JAVELIN-100 excludes patients with progression on chemotherapy, which leads to selection bias when comparing to other trials. KEYNOTE-177 has not yet resulted in an OS benefit, but if it does, we will have residual uncertainty as to whether it would have in an environment with routine PD1/PDL1 Ab administration on progression. In order to adequately answer the clinical question of optimal use of immunotherapy, crossover is mandatory in trials that seek to advance drugs used in latter lines to the front line.

Conclusion

Immunotherapy is an exciting development in oncology. It represents a novel mechanism of action with durable response seen in selected patients even with aggressive cancers. Current knowledge is limited however in predicting who will have initial response and therefore how and when to give immunotherapy upfront is a complicated question requiring critical appraisal of clinical trials. With difference in dynamics of initial response and duration of response compared with chemotherapy, median PFS is an imperfect outcome and should be interpreted with caution. Future trials should include crossover in the trial design so that there are low barriers for patients to remain on the trial after progression and receive standard second-line treatments. Clinical factors such as disease burden as well as predictive markers of response to immunotherapy must also be explored.

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