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Editorial Open Access

Bladder Cancer Enters the Targeted Immunotherapy Age

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Editorial

While other cancers have seen great improvements in outcomes due to new therapies and treatment paradigms over the last decades, advanced bladder cancer has been one of the few solid tumors for which no new major breakthrough have been seen in thirty years. However, all that changed a few weeks ago with the US Food and Drug Administration (FDA) accelerated approval of atezolizumab (Tecentriq, Genentech, Inc), for the treatment of advanced urothelial carcinoma, the most common type of bladder cancer.

Atezolizumab is a targeted immunotherapy that acts as a programmed cell death ligand inhibitor (PD-L1), and is the third agent approved in cancer that targets the PD-1/PD-L1, PD-L2 checkpoint pathway (with nivolumab and pembrolizumab being the other two). It is now approved for patients who had progression on or after a cisplatin-based chemotherapy regimen or patients with disease recurrence less than 12 months after a neoadjuvant or adjuvant cisplatin-based regimen.

The approval of atezolizumab was based on the results of the IMvigor 210 trial, an open-label, multicenter, phase II study that evaluated the safety and efficacy of atezolizumab in patients with locally advanced or metastatic urothelial carcinoma, regardless of PD-L1 expression. In the trial, 310 patients all received 1200 mg of atezolizumab IV every 21 days until unacceptable toxicity or either radiographic or clinical progression occurred. The primary endpoint of the study was objective response rate (ORR); the median follow-up was 14.4 months. The ORR was 26% for the subgroup with the highest positivity for PD-L1, 18% for the subgroup with lower positivity, and 15% for all patients.

Eleven percent of patients in highest-PD-L1 subgroup achieved a complete radiographic response, while 5% of all patients in the study achieved this remarkable outcome. Responses were durable, as is commonly seen in other immunotherapy trials. In fact, the median duration of response for entire study population and those in the higher PD-L1 group was not reached by the time the study was reported at the Genitourinary Symposium earlier this year. Even for those in the lower-positivity group, the median duration of response was over a year.

Median progression-free survival was a modest 2.1 months for all patients, but this may represent the fact the pseudo-progression is common with targeted immunotherapy agents and most current measures of progression (i.e., RECIST, etc) do not take into account this phenonmenon. Median overall survival was 7.9 months for all patients. Overall survival was 11.4 months for those patients in the highest-positivity subgroup, and 6.7 months for those in the lowest-positivity subgroup. Twelve-month overall survival was 36% for all patients and 48% for the high PD-L1 group.

These results are impressive. They further confirm that the immunotherapy era has fully arrived, and it is extremely likely that many more approvals of drugs targeting the PD-1/PD-L1, PD-L2 checkpoint pathway will be forthcoming. The approval of a new agent in advanced bladder cancer, especially in the second-line setting, will be a godsend for many patients. After years of stagnation this approval will provide an efficacious agent with modest toxicities (especially compared to standard chemotherapy), and may be useful for the many patients who have borderline performance statuses and comorbidities, especially kidney dysfunction after surgery and nephrotoxic chemotherapy.

To say that this approval is a game-changer would be an understatement. The first major breakthrough in bladder cancer in decades brings hope for further advancements in this rather stagnant corner of oncology. Many questions remain. It's clear that PD-L1 positivity is predictive of response, but even those who have no PD-L1 staining seem to garner some benefit from the drug. Therefore, how to properly use and interpret PD-L1 testing in a clinical setting will be an evolving challenge. The use of atezolizumab beyond its indication is being and will be studied in future trials. Pressing questions remain: Is the agent appropriate in the first-line setting for advanced bladder cancer? Can it be combined with chemotherapy or other immunotherapies for better efficacy? How does it compare to first-line standard chemotherapy? Is it appropriate in the neoadjuvant or adjuvant setting? Would it be useful in earlier stage bladder cancer? What about histological varients and rare forms of bladder cancer? We may only be scratching the surface with this approval and the full utility and limits of targeted immunotherapy in bladder cancer may not be fully elucidated for many years.

Until then let us breathe a sigh of relief and celebrate this victory--our long wait for a major breakthrough for advanced bladder cancer patients is finally over.