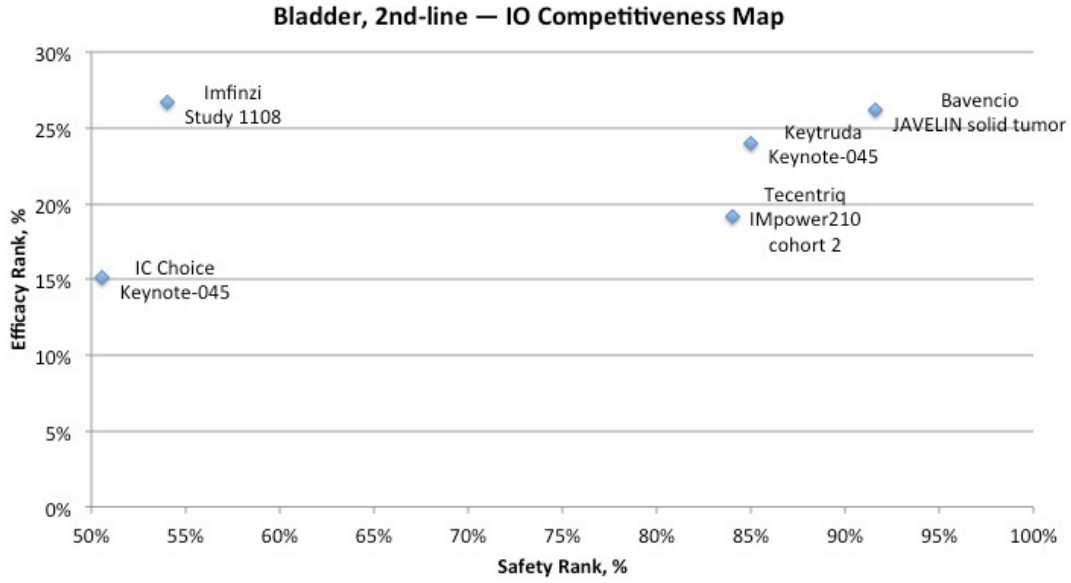
Immuno-Oncology agent competitiveness in treating advanced Bladder Cancer: Does Tecentriq's failure represent a class effect?

Boulder, Colorado, September 15, 2017 – Blomquist & Associates evaluated immuno-oncology agent competitiveness in treating advanced bladder cancer following Roche's 2017-5-10 report of Tecentriq's failure to demonstrate a survival benefit versus chemotherapy in 2nd-line, advanced bladder cancer in the pivotal IMvigor211 study. We set out to answer the following questions for one of our clients:

1. Is there evidence from earlier studies (e.g. phase 2 IMvigor 210) that Tecentriq might fail to demonstrate an efficacy advantage in the phase 3 study (IMvigor211)?
2. Does Tecentriq's failure reflect a class effect for PD-L1 inhibitors?

Method: We conducted a competitive analysis of the immuno-oncology agents approved for 2nd-line use in advanced bladder cancer (advanced or metastatic urothelial cancinoma). Although there have not been any head-to-head comparative studies, we combined the available, pivotal efficacy and safety data for the IO agents approved for 2nd-line bladder cancer to create a competitiveness map. An efficacy rank was created for each agent based on complete response rate (CR%), objective response rate (ORR%), and overall survival rate (OS%). The pivotal clinical data for the efficacy rank ranged from phase 1 through phase 3 clinical studies. Since OS% percent is part of our competitiveness rank, and Opdivo (CheckMater-275) did not report OS%, we excluded it from our analysis.

Results: The efficacy rank for Tecentriq (based on phase 2, IMvigor210) is 19.1% (see graph). Comparatively, the efficacy rank for Keytruda is 24%, versus 15.1% for Investigator's Choice chemotherapy (IC Choice), the active comparator in that study (see graph). Tecentriq's efficacy rank is relatively weak at *only* 4 percentage points higher than IC Choice. Alternatively, the efficacy ranks for the other PD-L1 inhibitors, Bavencio and Imfinzi, were 26.2% and 27.5%, respectively (11.1 and 11.6 percentage points higher than IC Choice, respectively) (see graph).



At the time of writing, Keytruda is the only IO agent that has demonstrated a survival advantage compared to an active comparator in a phase 3 study (Keynote-045). Further, the survival benefit for Keytruda was 10.3 months, significantly better than 7.4 months reported for the IC Choice arm (p=0.002), yet only a net survival benefit of 2.9 months. Keynote-045 was stopped early due to superior overall survival with Keytruda versus chemotherapy (Bellmunt et al., 2017).

Really surprising was that Keytruda missed one of the co-primary endpoints, by failing to improve median PFS (progression-free survival) versus IC Choice arm. The median PFS for Keytruda was 2.2 months, compared to 3.3 months for IC Choice arm, a *negative* PFS benefit of -1.2 months. However, the one-year PFS rate was 16.8 percent with Keytruda, compared to 6.2 percent in the IC Choice arm (Bellmunt et al., 2017).
Conclusions:

1. Tecentriq's low efficacy rank placed it at the bottom of the pack, in 2nd-line advanced bladder cancer and only marginally better than IC Choice. Thus, there is evidence from an earlier study (phase 2 IMvigor210) that Tecentriq might fail to demonstrate an efficacy advantage in the phase 3 study (IMvigor211).

   Our competitive analysis shows that all the IO agents have only modest efficacy in 2nd-line advanced bladder cancer. Our conclusion is supported by Dr. Guru Sonpavde's NEJM editorial, where he stated "…it is important to remember that [Keytruda's efficacy in 2nd-line advanced bladder cancer] remains an incremental advance overall, although the responses were remarkably durable."

2. Tecentriq's failure does not appear to reflect a class effect for PD-L1 inhibitors, based upon our competitive analysis, and given the relatively better efficacy ranks for Bavencio and Imfinzi. Rather, there appears to be somewhat variable efficacy between the different IO agents. This could lead to differentiation based on cancer type and line of treatment, as seen with Imfinzi in maintenance stage 3 non-small cell lung cancer. Additionally, at the time of writing, other IO agents, including Keytruda, have incurred additional clinical trial failures (e.g. Keytruda's failure in HNSCC, Keynote-040 study, and Imfinzi's failure in 1st-line lung, MYSTIC study).

We have employed our approach to create competitiveness maps in a number of other competitive analysis situations involving oncology or other indications over the years. We have found our competitiveness mapping approach has proven effective in assessing overall drug competitiveness, when no head-to-head data are available.

References:

AstraZeneca PR dated 2017-7-27, AstraZeneca reports initial results from the ongoing MYSTIC trial in Stage IV lung cancer. https://www.astrazeneca.com/media-centre/press-releases/2017/astrazeneca-reports-initial-results-from-the-ongoing-mystic-trial-in-stage-iv-lung-cancer-27072017.html

Bellmunt et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017; 376:1015-1026. https://doi.org/10.1056/NEJMoa1613683

Merck PR dated 2017-7-24, Merck Provides Update on Phase 3 Study of KEYTRUDA® (pembrolizumab) Monotherapy in Patients with Previously Treated Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC). http://investors.merck.com/news/press-release-details/2017/Merck-Provides-Update-on-Phase-3-Study-of-KEYTRUDA-pembrolizumab-Monotherapy-in-Patients-with-Previously-Treated-Recurrent-or-Metastatic-Head-and-Neck-Squamous-Cell-Carcinoma-HNSCC/default.aspx

Roche PR dated 2017-5-10, Roche provides update on phase III study of TECENTRIQ® (atezolizumab) in people with previously treated advanced bladder cancer. https://www.roche.com/investors/updates/inv-update-2017-05-10.htm

Sonpavde, G. PD-1 and PD-L1 Inhibitors as Salvage Therapy for Urothelial Carcinoma. N Engl J Med 2017; 376:1073-1074. https://doi.org/10.1056/NEJMe1701182