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Merck & Co's Keytruda Disappoints In Small-Cell Lung Cancer

Triple-Negative Breast Cancer The Next Big Therapeutic Opportunity?

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Executive Summary

In top-line final Phase III results from KEYNOTE-604, Keytruda improves PFS but not OS when combined with chemotherapy for the first-line treatment of small-cell lung cancer.

Source: Shutterstock

Merck & Co. Inc.'s release of somewhat disappointing top-line final Phase III data from the KEYNOTE-604 study of Keytruda (pembrolizumab) in extensive-stage small-cell lung cancer (SCLC) has drawn attention to what may be one of the remaining major untapped markets for the anti-PD-1 immunotherapy.

In KEYNOTE-604, Keytruda was found to significantly improve progression-free survival (PFS) but not overall survival (OS) when combined with chemotherapy for the first-line treatment of SCLC.

“For Merck, front-line SCLC represented one of the largest metastatic market opportunities remaining for Keytruda to penetrate,” noted analysts at SVBLeerink, who pointed to the forthcoming readout of KEYNOTE-355 in first-line triple-negative breast cancer as now becoming an increasingly important event for the anticancer agent.

Other potential topline Phase III readouts for Keytruda in 2020, according to Informa Pharma’s pipeline database, Biomedtracker, include: KEYNOTE-204 in Hodgkin’s lymphoma; KEYNOTE-361, involving first-line use in bladder cancer; KEYNOTE-177 in patients with microsatellite instability-high colorectal cancer; and KEYNOTE-122, second-line use in nasopharyngeal cancer.

Other immunotherapies have fared better in SCLC therapy; Roche’s PD-L1 inhibitor, Tecentriq (atezolizumab), was approved in the EU in September 2019, and in the US in March 2019, for use with chemotherapy for the initial treatment of extensive-stage SCLC, based on the IMpower133 study which showed it improved OS and PFS. However, the UK HTA NICE has more recently questioned its long-term effectiveness. (Also see "NICE Rejects Tecentriq For Small-Cell Lung Cancer In England" - Pink Sheet, 3 Jan, 2020.)

And AstraZeneca PLCs anti-PD-L1 MAb, Imfinzi (durvalumab), was granted priority review in the US in November 2019 for first-line extensive-stage SCLC use, based on the results of the CASPIAN study, with action expected in the first quarter of 2020 (see sidebar).

“The Keytruda miss lends credence to the argument that targeting the PD-L1 side of the PD-1/PD-L1 axis is more effective in settings characterized by low PD-L1 expression and poor patient fitness (like SCLC),” commented the SVBLeerink analysts.

Bristol-Myers Squibb Co.’s PD-1 inhibitor Opdivo (nivolumab) was approved in the US in 2018 as a third-line therapy in patients with metastatic SCLC. (Also see "Bristol's Opdivo Enjoys IO First-Mover Advantage In Small Cell Lung Cancer " - Scrip, 17 Aug, 2018.)

Keytruda is already approved in five lung cancer indications, including being granted an accelerated US approval in June 2019 as a later-line monotherapy for patients with metastatic SCLC. But the keenly awaited results from KEYNOTE-064 appear to compare poorly at first-sight with other immunotherapies.

AstraZeneca Gets Fast Imfinzi Review For SCLC

By Kevin Grogan

29 Nov 2019

The drug major has won a priority review for Imfinzi in small cell lung cancer from the FDA. If approved, the new indication could add $1bn to sales of the checkpoint inhibitor

Read the full article here ›

First-Line Use In SCLC

On the positive side, in KEYNOTE-064, pembrolizumab added to chemotherapy (etoposide plus cisplatin or carboplatin) resulted in a significant improvement in PFS compared with chemotherapy alone (HR=0.75; 95% CI, 0.61-0.91), Merck announced on 6 January.

However, for the second co-primary endpoint, OS, an improvement was seen when pembrolizumab was added to chemotherapy, but this did not achieve significance when compared with chemotherapy alone (HR=0.80; 95% CI, 0.64-0.98).

The study enrolled 453 patients with newly diagnosed extensive-stage SCLC, and secondary endpoints include objective response rate and duration of response.

SCLC is a fast-growing cancer with early metastases, and has usually spread to both sides of the lung at the time of diagnosis. It is therefore classified as extensive-stage disease, notes Datamonitor Healthcare's October 2019 Market Spotlight report on the condition. SCLC accounts for about 10% to 15% of all lung cancer cases, and the five-year survival rate for patients diagnosed in the US with any stage of SCLC is 6%.

Although there are numerous investigational agents in Phase II for SCLC, there are only a handful in Phase III SCLC studies, including AstraZeneca's Imfinzi (durvalumab), PharmaMar SA's Zepsyre (lurbinectedin), and United Therapeutics Corp.'s dinutuximab.

In December 2019, PharmaMar announced it had filed a US NDA for accelerated approval of lurbinectedin in relapsed SCLC, on the basis of the results of a Phase II clinical trial, and United Therapeutics has also previously indicated that its Phase II/III DISTINCT study of dinutuximab in SCLC is fully enrolled.

Merck says it is continuing to evaluate pembrolizumab across 20 company-sponsored clinical trials in lung cancer, involving various clinical settings and stages of disease.