Press release

Swissmedic grants approval for pembrolizumab (KEYTRUDA®) in combination with axitinib (Inlyta®) for first-line therapy of advanced renal cell carcinoma[1]

- **Swissmedic approval is based on a significant benefit in overall survival with pembrolizumab in combination with axitinib compared to sunitinib in the Phase III study KEYNOTE-426**
- **Pembrolizumab is the first PD-1 inhibitor that has been approved as a part of combination therapy for the treatment of renal cell carcinoma across all IMDC risk groups in Switzerland**

Lucerne, January 23, 2020—MSD (Merck Sharp & Dohme AG) recently announced that Swissmedic has granted approval of pembrolizumab (KEYTRUDA®) for the PD-1 inhibitor in combination with the tyrosine kinase inhibitor axitinib (Inlyta®) for first-line therapy of advanced renal cell carcinoma.

The approval applies to all "International Metastatic Renal Cell Carcinoma Database Consortium" (IMDC) risk groups. It is based on data from the approval-relevant Phase III study KEYNOTE-426.[2] These showed a decrease in mortality risk in patients with advanced renal cell carcinoma receiving combination therapy with pembrolizumab and axitinib compared to sunitinib by 47 % (HR = 0.53 [95 % CI: 0.38-0.74]; p = 0.00005). For the pembrolizumab-axitinib combination, an improvement in progression-free survival (PFS) was demonstrated with a reduction in the progression or mortality risk of 31% compared to sunitinib (HR = 0.69 [95% CI: 0.57-0.84]; p = 0.00012). Furthermore, the objective response rate (objective response rate, ORR) was higher in the patients treated with pembrolizumab in combination with axitinib with 59% (95% CI: 54-64) compared to those in the sunitinib treatment arm with 36% (95% CI) : 31-40) (p <0.0001).[2]

"Advanced renal cell carcinoma is one of the most life-threatening cancers in which the majority of patients died within five years of the initial diagnosis," explained Professor Thomas Powles, Principal Investigator of the KEYNOTE-426 study and Director of the Barts Cancer Centre in London. "It's encouraging that we can now offer patients a combination of pembrolizumab and axitinib as first-line therapy."

"Approval of the combination of pembrolizumab and axitinib for the treatment of advanced renal cell carcinoma is an important milestone in our commitment to patients with this aggressive disease," says Dr. Scot Ebbinghaus, Vice President, Clinical Research, Merck Research Laboratories of Merck & Co., Inc. in Kenilworth, USA (MSD in Switzerland). "The availability of an additional treatment option in first-line therapy is particularly important for patients with advanced renal cell carcinoma and underlines our efforts to continue developing pembrolizumab for areas in obvious need of care."

Approval-relevant data

Swissmedic approval of pembrolizumab in combination with axitinib is based on data from the randomized, multicenter, open-label, active-controlled Phase III study KEYNOTE-426 which has been investigated in patients with advanced renal cell carcinoma with clear cell components

regardless of the PD-L1 tumor expression status and was divided according to IMDC risk group categories.[1,2] The study excluded patients with an autoimmune disease or a disease that required immunosuppression. Randomization was stratified based on risk groups (favorable versus intermediate versus unfavorable) and geographical region (North America versus Western Europe versus the "rest of the world"). Both primary endpoints were overall survival (OS) and PFS.[1] Secondary endpoints were ORR and duration of response (DOR). The study included 861 patients who were randomized (1:1) into one of the following study arms:

- Pembrolizumab 200 mg intravenously every 3 weeks in combination with the oral administration of axitinib 5 mg, twice daily. Patients who tolerated axitinib 5 mg twice daily in two sequential treatment cycles (i.e. 6 weeks) and who had no > grade 2 side effects with axitinib as well as a well-controlled blood pressure of ≤ 150/90 mmHg could increase the dose of axitinib to 7 mg twice daily. Dose escalation of axitinib to 10 mg twice daily was allowed according to the same criteria. Treatment with axitinib could be interrupted or reduced to 3 mg twice daily and then to 2 mg twice daily to manage toxicity.
- Sunitinib 50 mg orally once daily for 4 weeks followed by a two-week rest period.

Treatment with pembrolizumab and axitinib was continued up to a progression of cancer determined according to RECIST v1.1 criteria and either by a blinded independent central review (BICR) or the principal investigator until the occurrence of unacceptable toxicity, or in the case of pembrolizumab, up to a maximum of 24 months.[i]

In combination with axitinib, pembrolizumab showed a statistically significant improvement in OS in KEYNOTE-426 by a 47% decrease in mortality risk compared to sunitinib (HR = 0.53 [95% CI: 0.38-0.74]; p = 0.00005). In patients who received pembrolizumab plus axitinib (n = 432)59 events (14%) were observed compared to 97 events (23%) in patients treated with sunitinib (n = 429). The median OS was not reached in either treatment regimen. An improvement in PFS was demonstrated in the combination of pembrolizumab and axitinib with a decrease in the progression or mortality risk of 31% compared to sunitinib (HR = 0.69 [95% CI: 0.57-0.84]; p = 0.00012). A total of 183 events (42%) were recorded in patients treated with pembrolizumab plus axitinib compared to 213 events (50%) in patients treated with sunitinib. The median PFS was 15.1 months in patients treated with the combination of pembrolizumab and axitinib (95% CI: 12.6-17.7) and 11.0 months (95% CI: 8.7-12.5) in patients treated with sunitinib. In the study, ORR was 59% (95% CI: 54-64) in patients treated with pembrolizumab in combination with axitinib (95% CI: 54-64) compared to 36% in the sunitinib treatment arm (95% CI: 31-40) (p < 0.0001). In patients who received a combination of pembrolizumab and axitinib or sunitinib, the complete response was 6% and 2%, respectively, and the partial response was 53% and 34%, respectively. The median DOR was not reached in the treatment arm with combination therapy (range: 1.4+ to 18.2+); in the sunitinib arm, it was 15.2 months (range: 1.1+ to 15.4+).

The KEYNOTE-426 study also investigated the safety of pembrolizumab in combination with axitinib in patients with previously untreated advanced renal cell carcinoma. After administration

[i] *assessed by a blinded independent central review (BICR) using the response evaluation criteria in solid tumors (RECIST) v1.1*

of pembrolizumab in combination with axitinib, patients with advanced renal cell carcinoma were observed as being more likely to have elevated ALT and AST values (20% and 13%, respectively) in grade 3 and 4 compared to pembrolizumab alone. The most common side effects in this patient population were diarrhea (54%), hypertension (45%), fatigue (38%), hypothyroidism (35%), reduced appetite (30%), palmar-plantar erythrodysesthesia syndrome (28%), nausea (28%), elevated levels of ALT (27%), elevated levels of AST (26%), dysphonia (25%), cough (21%), cough (21%) and constipation (21%). Grade 3–5 side effects occurred in 76% of patients receiving pembrolizumab combination therapy and in 71% of patients receiving sunitinib monotherapy.

Concerning renal cell carcinoma (RCC)

Renal cell carcinoma (RCC) is the most common form of renal cancer and accounts for approximately nine out of ten renal cancers. RCC occurs approximately twice as often in men than women. The risk factors that may be subject to influence include smoking, being overweight, coming into contact with certain carcinogens in the workplace and having high blood pressure. Almost 1,000 people contract kidney cancer annually in Switzerland. Some 300 patients died annually as a result of this disease.[3]

References

1) Prescribing information on pembrolizumab (KEYTRUDA®) , www.swissmedicinfo.ch
2) Rini BI, Plimack ER, Stus V, et al.; for the KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1116 – 1127.
3) Federal Statistical Office. Cancer, new diseases and mortalities: Figures, rates, median age and risk per cancer localization. Data from 2011-2015. https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/gesundheitszustand/krankheiten/krebs/spezifische.assetdetail.6466409.html

Pembrolizumab (KEYTRUDA®)

Pembrolizumab is a PD-1 (programmed cell death 1 protein)-inhibitor that potentiates the ability of the immune system to detect and fight tumor cells. Pembrolizumab is a humanized monoclonal antibody that blocks interaction between PD-1 and its ligands PD-L1 and PD-L2 and, therefore, activates T- lymphocytes which can be used to attack both tumor cells and healthy cells.

In Switzerland, pembrolizumab is indicated in the presence of unresectable or metastatic melanoma in adults.
In Switzerland, pembrolizumab is indicated as monotherapy for adjuvant treatment of adults with complete resected stage III melanoma.
In Switzerland, pembrolizumab is indicated as monotherapy for first-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumors express PD-L1 with a tumor proportion score (TPS) ≥50% and who have no genomic tumor aberrations of EGFR or ALK type.
In Switzerland, pembrolizumab is indicated in combination with pemetrexed and platinum chemotherapy for the first-line treatment of metastatic non-squamous NSCLC in adults who do not have genomic tumor aberrations of the EGFR or ALK type.

In Switzerland, pembrolizumab is indicated in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of metastatic squamous NSCLC in adults.
In Switzerland, pembrolizumab is indicated as monotherapy for the treatment of advanced, metastatic NSCLC following previous chemotherapy in adults whose tumors express PD-L1 with a TPS ≥1%. Patients with genomic tumor aberrations of the EGFR or ALK type should also have received therapy approved for these aberrations before they are treated with Keytruda.
In Switzerland, pembrolizumab is indicated for the treatment of refractory or recurrent classical Hodgkin's Lymphoma (rrcHL) in adults with at least 3 pre-treatments.
In Switzerland, pembrolizumab is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have been previously treated with platinum-based chemotherapy.
In Switzerland, pembrolizumab is indicated in combination with axitinib for first-line treatment of advanced renal cell carcinoma (metastatic or recurrent) in adults.

The recommended dose of pembrolizumab as monotherapy is either 200 mg every 3 weeks as an intravenous administration over 30 minutes.
Pembrolizumab must be given as an intravenous infusion over 30 minutes.
Pembrolizumab should not be administered as an intravenous pressure or bolus injection.
When used in combination, the summary of product characteristics of the respective accompanying therapeutic agents must be taken into account.
When using KEYTRUDA® as part of combination therapy with intravenous chemotherapy, KEYTRUDA® should be administered first.

About MSD in Switzerland:
The field of human medicine in Switzerland is responsible for selling drugs and biopharmaceuticals available only on prescription in the therapy areas of oncology, diabetes, cardiovascular, infectious diseases (amongst others, fungus infections, antibiotic resistances, HIV/AIDS and Hepatitis C), immunology, women's health as well as vaccines for children, adolescents and adults. In Switzerland, MSD conducts clinical research and manufactures drugs for worldwide clinical studies. MSD is also involved at its Lucerne location, among other things in the annual specialist event "Trendtage Gesundheit Luzern". In 2019, the Switzerland company received the certification "Top Employer" for the seventh time in a row as well as the award "Top Employer Europe" for the fourth time.

About MSD global:
MSD is a protected name owned by Merck & Co., Inc., Kenilworth, New Jersey, U.S.A. MSD is a leading global biopharmaceutical company that has been conducting research for life for over a century and develops drugs and vaccines to combat challenging diseases all over the world, including cancer, cardiovascular, Alzheimer's as well as infectious diseases including HIV and Ebola.

Find out more here: www.msd.ch. Follow us on Twitter, LinkedIn and YouTube.

This information is intended exclusively for media professionals. MSD presents the advertising law provisions of pharmaceutical law, in particular to the ban on public advertising for prescription medicinal products.

Media department MSD Switzerland
media.switzerland@merck.com | Tel. +41 58 618 30 30
Jean-Blaise Defago (Policy & Communications Director)