Media Release

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Roche receives EU approval of TECENTRIQ® (atezolizumab) in a specific type of metastatic lung cancer and two types of metastatic bladder cancer

- TECENTRIQ provides a new treatment option for people with previously treated locally advanced or metastatic non-small cell cancer (NSCLC)
- TECENTRIQ is a new treatment option for people with metastatic urothelial carcinoma (mUC) who have been previously treated with a platinum-based chemotherapy and for people who are ineligible to receive cisplatin chemotherapy

Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the European Commission (EC) has granted a marketing authorisation for TECENTRIQ (atezolizumab) as a monotherapy for the treatment of people with locally advanced or metastatic non-small cell lung cancer (NSCLC) after they have been previously treated with chemotherapy regardless of PD-L1 status. People with EGFR-activating mutations or ALK-positive tumour mutations should also have received targeted therapy before receiving TECENTRIQ. This approval is based on results from the large randomised Phase III OAK study and the randomised Phase II POPLAR study.[1, 2] The Phase III OAKstudy showed that TECENTRIQ helped people in the overall study population live a median of 13.8 months–4.2 months longer than those treated with docetaxel chemotherapy (median OS: 13.8 vs 9.6 months; hazard ratio [HR] = 0.73, 95% confidence interval [CI]: 0.62, 0.87).[1]

The EC has also granted marketing authorisation for TECENTRIQ as a monotherapy for the treatment of people with locally advanced or metastatic urothelial carcinoma (mUC) who have been previously treated with a platinum-containing chemotherapy or who are considered ineligible for cisplatin chemotherapy, regardless of PD-L1 status. This approval is based on results from the randomised Phase III IMvigor211 study and cohorts 1 and 2 from the single-arm Phase II IMvigor210 study. The Phase III IMvigor211 study did not meet its primary endpoint of OS, compared with chemotherapy. However, the study showed that the median duration of response (mDOR), a secondary endpoint, for those receiving TECENTRIQ was 21.7 months (95% CI: 13.0, 21.7) in the overall study population, compared with 7.4 months (95% CI: 6.1, 10.3) for those receiving chemotherapy.[3]

At the time of data cutoff, the majority (63%) of people who responded to treatment with TECENTRIQ continued to respond, compared with 21% of people treated with chemotherapy.[3] Results from cohort 1 of the Phase II IMvigor210 study showed that TECENTRIQ achieved a median OS of 15.9 months (10.4, NE) in the overall study population.[4]

"We are delighted that the European Commission has approved TECENTRIQ, the first anti-PD-L1 cancer immunotherapy approved in the EU, as a monotherapy in both advanced bladder and advanced lung cancer", said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "The totality of the data for TECENTRIQ across all indications including long-term responses in advanced bladder cancer and the overall survival advantage observed in our phase III advanced lung cancer study means that we are able to extend the benefits of TECENTRIQ to people living with these types of cancer regardless of their levels of PD-L1 expression."

TECENTRIQ is already approved in the USA and in several other countries for people with metastatic NSCLC – and for people with locally advanced or mUC who are not eligible for cisplatin chemotherapy, or who have had disease progression during or following platinum-containing therapy.

About the OAK study

OAK is a global, multicentre, open-label, randomised, controlled Phase III study that evaluated the efficacy and safety of TECENTRIQ compared with docetaxel. It enrolled 1,225 patients with both squamous and non-squamous disease, regardless of the programmed death-ligand 1 (PD-L1) status of their tumours, and randomised them (1:1) to receive either TECENTRIQ administered intravenously at 1,200 mg every 3 weeks until loss of clinical benefit, or docetaxel administered intravenously at 75 mg/m^2 every 3 weeks.
The co-primary endpoints were overall survival (OS) in the first 850 randomised patients (intention-to-treat population) and in a PD-L1-selected subgroup of this primary analysis population.

Summary of efficacy in the primary analysis population (OAK) ***Primary efficacy endpoint: overall survival (OS)***		
Efficacy endpoint	**TECENTRIQ**	**Docetaxel**
All comers (ITT)*	n=425	n=425
No. of deaths (%)	271 (64%)	298 (70%)
Median time to events (months)	13.8	9.6
95% CI	(11.8, 15.7)	(8.6, 11.2)
Stratified‡ hazard ratio (95% CI)	0.73 (0.62, 0.87)	
p value**	0.0003	
12-month OS (%)*	218 (55%)	151 (41%)
18-month OS (%)*	157 (40%)	98 (27%)
Secondary endpoints		
Investigator-assessed PFS (RECIST v1.1)		
All comers*	n=425	n=425
No. of events (%)	380 (89%)	375 (88%)
Median duration of PFS (months)	2.8	4.0
95% CI	(2.6, 3.0)	(3.3, 4.2)
Stratified hazard ratio (95% CI)	0.95 (0.82, 1.10)	
Investigator-assessed ORR (RECIST v1.1)		
All comers (ITT)	n=425	n=425
No. of responders (%)	58 (14%)	57 (13%)
95% CI	(10.5, 17.3)	(10.3, 17.0)
Investigator-assessed DOR (RECIST v1.1)		
All comers	n=58	n=57
Median (months)	16.3	6.2
95% CI	(10.0, NE)	(4.9, 7.6)

CI=confidence interval; DOR=duration of response; ITT=intention-to-treat population; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours

*'All comers' refers to the primary analysis population consisting of the first 850 randomised patients

‡Stratified by PD-L1 expression in tumour-infiltrating immune cells, the number of prior chemotherapy regimens, and histology

** Based on the stratified log–rank test

About the POPLAR study

The Phase II, multicentre, international, randomised, open-label, controlled study, POPLAR, was conducted in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression. The primary efficacy outcome was OS. A total of 287 patients were randomised 1:1 to receive either TECENTRIQ (1,200 mg by intravenous infusion every 3 weeks until loss of clinical benefit) or docetaxel (75 mg/m^2 by intravenous infusion on Day 1 of each 3-week cycle until disease progression). Randomisation was stratified by PD-L1 expression status on tumour-infiltrating immune cells (IC), by the number of prior chemotherapy regimens and by histology.

An updated analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with TECENTRIQ vs 9.7 months in patients treated with docetaxel (HR 0.69, 95% CI: 0.52, 0.92). Objective response rate (ORR) was 15.3% vs 14.7% and median duration of response (DOR) was 18.6 months vs 7.2 months for TECENTRIQ vs docetaxel, respectively.

About non-small cell lung cancer

Lung cancer is the leading cause of cancer death globally.[5] Each year 1.59 million people die as a result of the disease; this translates into more than 4,350 deaths worldwide every day.[5] Lung cancer can be broadly divided into two major types: NSCLC and small cell lung cancer. NSCLC is the most prevalent type, accounting for around 85% of all cases.[6]

About the IMvigor211 study

IMvigor211 is a Phase III study of TECENTRIQ in comparison with chemotherapy in people with advanced bladder cancer who were previously treated with a platinum-based chemotherapy. The study evaluated the efficacy and safety of TECENTRIQ compared with physician's choice of chemotherapy (vinflunine, paclitaxel or docetaxel) administered every 3 weeks in 931 people with previously treated mUC,who had progressed during or following a platinum-based regimen. The primary efficacy endpoint was OS and key secondary endpoints include ORR, progression-free survival, DOR and safety. The IMvigor211 study did not meet its primary endpoint of OS, compared with chemotherapy. These data were presented in full at EACR-AACR-SIC.

The primary efficacy endpoint, OS, was to be tested in a successive fashion (hierarchical testing) in study populations defined by PD-L1 expression. Statistical significance needed to be achieved for the study populations in the following order: IC2/3 (≥5%), IC1/2/3 (≥1%), and ITT group. However, because such significance was not achieved for OS in the IC2/3 population, results could not be evaluated for statistical significance in the IC1/2/3 and ITT populations, and these analyses are considered descriptive in nature.

The first population tested comprised people with the highest levels of PD-L1 expression (IC2/3), followed by those with any observable level of PD-L1 expression (IC1/2/3), and followed by the overall study population (intention-to-treat: ITT). Per the pre-specified hierarchical testing order, the IC2/3 (≥5%) population was tested first, with an OS HR of 0.87 (95% CI: 0.63, 1.21; median OS (mOS) of 11.1 vs 10.6 months for TECENTRIQ and chemotherapy respectively). In the overall study population (ITT), people treated with TECENTRIQ achieved a mOS of 8.6 months (CI: 95%; 7.8, 9.6), compared with 8.0 months (CI: 95%; 7.2, 8.6) with chemotherapy (HR 0.85, 95% CI 0.73–0.99).

Overall response rates were similar to those previously reported in the Phase II IMvigor210 study and similar between the two study arms. The median duration of response (mDOR), a secondary endpoint, for those receiving TECENTRIQ was 21.7 months (95% CI: 13.0, 21.7) in the overall study population, compared with 7.4 months (95% CI: 6.1, 10.3) for those receiving chemotherapy. At the time of data cutoff, the majority (63%) of people who responded to treatment with TECENTRIQ continued to respond, compared with 21% of people treated with chemotherapy.

About the IMvigor210 study (Cohort 2)

In Cohort 2, the co-primary efficacy endpoints were confirmed ORR, as assessed by an IRF using RECIST (Response Evaluation Criteria in Solid Tumours) v1.1 and investigator-assessed ORR according to Modified RECIST (mRECIST) criteria. There were 310 patients treated with TECENTRIQ 1,200 mg by intravenous infusion every 3 weeks until loss of clinical benefit. The study met its co-primary endpoints in Cohort 2, ORRs per IRF-assessed RECIST v1.1 and investigator-assessed mRECIST, compared with a prespecified historical control response rate of 10%.

The confirmed ORR for all comers per IRF-RECIST v1.1 were 15.8% (95% CI: 11.9, 20.4). The confirmed ORR for all comers per investigator-assessed imRECIST were 19.7% (95% CI: 15.4, 24.6). The rate of complete response per IRF-RECIST v1.1 in the all-comer population was 6.1% (95% CI: 3.7, 9.4). For Cohort 2, median DOR per IRF-RECIST v1.1 was not reached in any PD-L1-expression subgroup or in all comers, but was reached in patients with PD-L1 expression <1% (13.3 months; 95% CI 4.2, NE). An analysis was also performed with a median duration of survival follow-up of 21.1 months for Cohort 2, the OS rate at 12 months was 37% in all comers.

About the IMvigor210 study (Cohort 1)

The approval for patients who are ineligible for cisplatin-based chemotherapy is based on results from Cohort 1, which consisted of 119 people with locally advanced or mUC who were ineligible for cisplatin-containing chemotherapy and were either previously untreated or had disease progression at least 12 months after neoadjuvant (before surgery) or adjuvant (after surgery) chemotherapy. Clinically relevant IRF-assessed ORRs per RECIST v1.1 were shown; however, when compared to a pre-specified historical control response rate of 10%, statistical significance was not reached for the primary endpoint. The median OS results for all comers were 15.9 (10.4, NE).

Summary of efficacy data from Cohort 1, IMvigor210 study			
Efficacy endpoint	**PD-L1 expression of ≥5% in IC**	**PD-L1 expression of ≥1% in IC**	**All comers**
ORR (IRF-assessed; RECIST v1.1)	n = 32	n = 80	n = 119
No. of responders (%) 95% CI	9 (28.1%) 13.8, 46.8	19 (23.8%) 15.0, 34.6	27 (22.7%) 15.5, 31.3
No. of complete response (%) 95% CI	4 (12.5%) (3.5, 29.0)	8 (10.0%) (4.4, 18.8)	11 (9.2%) (4.7, 15.9)
No. of partial response (%) 95% CI	5 (15.6%) (5.3, 32.8)	11 (13.8%) (7.1, 23.3)	16 (13.4%) (7.9, 20.9)
DOR (IRF-assessed; RECIST v1.1)	n = 9	n = 19	n = 27
Patients with event (%)	3 (33.3%)	5 (26.3%)	8 (29.6%)
Median (months) (95% CI)	NE (11.1, NE)	NE (NE)	NE (14.1, NE)
PFS (IRF-assessed; RECIST v1.1)	n = 32	n = 80	n = 119
Patients with event (%)	24 (75.0%)	59 (73.8%)	88 (73.9%)
Median (months) (95% CI)	4.1 (2.3, 11.8)	2.9 (2.1, 5.4)	2.7 (2.1, 4.2)
OS	n = 32	n = 80	n = 119
Patients with event (%)	18 (56.3%)	42 (52.5%)	59 (49.6%)
Median (months) (95% CI)	12.3 (6.0, NE)	14.1 (9.2, NE)	15.9 (10.4, NE)
1-year OS rate (%)	52.4%	54.8%	57.2%

CI=confidence interval; DOR=duration of response; IC= tumour-infiltrating immune cells; IRF= independent review facility; NE=not estimable; ORR=objective response rate; OS=overall survival; PD-L1=programmed death-ligand 1; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours

Pooled safety profile

The safety of TECENTRIQ is based on pooled data in 2,160 patients with mUC and NSCLC. The most common adverse all-grade reactions were fatigue (35.4%), decreased appetite (25.5%), nausea (22.9%), dyspnoea (21.8%), diarrhoea (18.6%), pyrexia (18.3%), rash (18.6%), vomiting (15.0%), arthralgia (14.2%), asthenia (13.8%) and pruritus (11.3%).

About urothelial carcinoma

Metastatic urothelial carcinoma (mUC) is associated with a poor prognosis and limited treatment options. Until recently this disease had not seen any major advances for more than 30 years.[7] UC is the ninth most common cancer worldwide, with 430,000 new cases diagnosed in 2012, and it results in approximately – 165,000 deaths globally each year.[5] Men are three times more likely to suffer from UC than women[8], and the disease is three times more common in developed countries than in less developed countries.[9]

About TECENTRIQ (atezolizumab)

TECENTRIQ is a monoclonal antibody designed to bind with a protein called PD-L1. TECENTRIQ is designed to bind to PD-L1 expressed on tumour cells and tumour-infiltrating immune cells, blocking its interactions with both PD-1 and B7.1 receptors. By inhibiting PD-L1, TECENTRIQ may enable the activation of T cells. TECENTRIQ has the potential to be used as a foundational combination partner with cancer immunotherapies, targeted medicines and various chemotherapies across a broad range of cancers

About Roche in cancer immunotherapy

For more than 50 years, Roche has been developing medicines with the goal to redefine treatment in oncology. Today, we're investing more than ever in our effort to bring innovative treatment options that help a person's own immune system fight cancer.

By applying our seminal research in immune tumour profiling within the framework of the Roche-devised cancer immunity cycle, we are accelerating and expanding the transformative benefits with TECENTRIQ to a greater number of people living with cancer. Our cancer immunotherapy development programme takes a comprehensive approach in pursuing the goal of restoring cancer immunity to improve outcomes for patients.

To learn more about the Roche approach to cancer immunotherapy please follow this link: http://www.roche.com/research_and_development/what_we_are_working_on/oncology/cancer-immunotherapy.htm

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics under one roof have made Roche the leader in personalised healthcare – a strategy that aims to fit the right treatment to each patient in the best way possible.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. Thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Roche has been recognised as the Group Leader in sustainability within the Pharmaceuticals, Biotechnology & Life Sciences Industry nine years in a row by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2016 employed more than 94,000 people worldwide. In 2016, Roche invested CHF 9.9 billion in R&D and posted sales of CHF 50.6 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit www.roche.com.

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