Investor Update

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CHMP recommends EU approval for Roche's TECENTRIQ (atezolizumab) in a specific type of metastatic lung and two types of metastatic bladder cancer

- **TECENTRIQ as a potential treatment option for people with previously treated locally advanced or metastatic non-small cell lung cancer (NSCLC)**
- **TECENTRIQ as a potential 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 EU Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion for TECENTRIQ® (atezolizumab) as a monotherapy for the treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) after they have been previously treated with chemotherapy. People with EGFR activating mutations or ALK positive tumour mutations should also have received targeted therapy before receiving TECENTRIQ. This positive recommendation is based on results from the large randomised Phase III OAK study and the randomised Phase II POPLAR study. The CHMP has also adopted a positive opinion for the use of TECENTRIQ as a monotherapy for the treatment of adults with locally advanced or metastatic urothelial carcinoma (mUC) who have been previously treated with a platinum based chemotherapy or who are considered ineligible for cisplatin chemotherapy. This positive opinion is based on results from the randomised Phase III IMvigor211 study and cohorts 1 and 2 from the single-arm Phase II IMvigor210 study.

"This positive CHMP opinion represents great news for people living with either advanced lung or bladder cancer because, despite recent developments, long-term survival rates for people with these cancers are inferior to those with other common cancers," said Sandra Horning, MD, Roche's Chief Medical Officer and Head of Global Product Development. "We are encouraged that the CHMP considered the totality of the data for TECENTRIQ including the importance of key clinical endpoints, such as long-term responses."

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Based on this positive CHMP opinion, a final decision from the European Commisssion is expected in the near future. TECENTRIQ is already approved in the US and in a number of other countries for people with metastatic NSCLC; and for people with locally advanced or mUC and who are not eligible for cisplatin chemotherapy, or who have 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 1225 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 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.

The OAK study 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 overall survival [OS]: 13.8 vs. 9.6 months; HR = 0.73, 95% CI: 0.62, 0.87).

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%)

Data table continued on the following page

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 in months	16.3	6.2
95% CI	(10.0, NE)	(4.9, 7.6)

CI=confidence interval; DOR=duration of response; IC=tumour-infiltrating immune cells; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1;

*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

A phase II, multi-centre, 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 overall survival. 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 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 of 0.69, 95% CI: 0.52, 0.92). ORR was 15.3% vs. 14.7% and median 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. Each year 1.59 million people die as a result of the disease; this translates into more than 4,350 deaths worldwide every day. 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.

About the IMvigor211 study

IMvigor211 is a Phase III study of TECENTRIQ compared to 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 to chemotherapy of physician choice (vinflunine, paclitaxel or docetaxel) administered every three weeks in 931 people with previously-treated mUC who progressed during or following a platinum-based regimen. The primary efficacy endpoint was OS and key secondary endpoints include objective response rate, progression-free survival, duration of response and safety. IMvigor211 study did not meet its primary endpoint of overall survival (OS) compared to chemotherapy. These data were presented in full at the EACR-AACR-SIC Special Conference 2017.

The primary efficacy endpoint, overall survival, was to be tested in a successive fashion (hierarchical testing) in study populations defined by PD-L1 expression. The first population tested was 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 of 11.1 vs. 10.6 months for TECENTRIQ and chemotherapy respectively). In the overall study population (intention-to-treat or ITT) people treated with TECENTRIQ achieved a mOS of 8.6 months (CI: 95%; 7.8, 9.6) compared to 8.0 months (CI: 95%; 7.2, 8.6) with chemotherapy (HR 0.85, 95% CI 0.73-0.99).

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 statistical 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 those analyses are considered descriptive in nature.

Overall Response Rates (ORR) 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 to 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 to 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 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, demonstrating statistically significant ORRs per IRF-assessed RECIST v1.1 and investigator-assessed mRECIST compared to a pre-specified historical control response rate of 10%.

An analysis was also performed with a median duration of survival follow-up of 21.1 months for Cohort 2. The confirmed ORRs per IRF-RECIST v1.1 were 28.0% (95% CI: 19.5, 37.9) in patients with PD-L1 expression IC2/3 (≥ 5%), 19.3% (95% CI: 14.2, 25.4) in patients with PD-L1 expression IC1/2/3 (≥ 1%), and 15.8% (95% CI: 11.9, 20.4) in all comers. The confirmed ORR per investigator-assessed mRECIST was 29.0% (95% CI: 20.4, 38.9) in patients with PD-L1 expression ≥ 5%, 23.7% (95% CI: 18.1, 30.1) in patients with PD-L1 expression ≥ 1%, and 19.7% (95% CI: 15.4, 24.6) in all comers. 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, however was reached in patients with PD-L1 expression < 1% (13.3 months; 95% CI 4.2, NE). The OS rate at 12 month was 37% in all comers.

About the IMvigor210 study (Cohort 1)

The positive CHMP opinion 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. The primary endpoint of the study was objective response rate (ORR).

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; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumours v1.1.

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 metastatic urothelial carcinoma

Metastatic urothelial carcinoma (mUC) is associated with a poor prognosis and limited treatment options. It is a disease that has seen no major advances for more than 30 years outside of the US. UC is the ninth most common cancer worldwide, with 430,000 new cases diagnosed in 2012, and it results in approximately

145,000 deaths globally each year. Men are three times more likely to suffer from UC, compared with women, and the disease is three times more common in developed countries than in less developed countries.

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. The Roche cancer immunotherapy research and development programme comprises more than 20 investigational candidates, 12 of which are in clinical trials and target all three tumour phenotypes (profiles).

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 for improving patient access to medical innovations by working with all relevant stakeholders. Twenty-eight 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 eight 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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