31 May 2018
EMA/387407/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tecentriq

International non-proprietary name: atezolizumab

Procedure No. EMEA/H/C/004143/II/0010

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 24 May 2018 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I

Update of sections 4.1, 4.2 and 5.1 of the SmPC of Tecentriq in order to restrict the indication 'for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are considered cisplatin ineligible' to those patients 'whose tumours have a PDL-1 expression ≥ 5% (see section 5.1). This restriction is based on the review of interim analysis data by the independent data monitoring committee (IDMC) from study IMvigor 130 (WO30070). This is a Phase III, multicentre, randomized, placebo-controlled study of atezolizumab administered as monotherapy or in combination with platinum-based chemotherapy compared with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma enrolling patients in the first line setting who are both cisplatin eligible and cisplatin ineligible currently listed as a post authorisation efficacy study (PAES) in the Annex II. The MAH is proposing to distribute a DHPC.

The requested variation proposed amendments to the Summary of Product Characteristics.

2. Introduction

The CHMP has been informed by the MAH for Tecentriq (Atezolizumab) that on 19 March 2018, the IDMC for Study IMvigor130 met for an ad-hoc closed session scheduled at their request. Based on the review of data from a snapshot dated 12 March 2018, and meeting discussion, the IDMC recommended the following to the Sponsor Data Review Board (DRB):

"Based on review of survival data in all patients randomized to date, the DMC recommends closure of Arm B (Atezo alone) to further accrual for all patients whose tumours are IC0 or IC1 for PD-L1. Patients who have tumours that are IC2/3 can continue to be randomized to Arms A, B or C. Arms A and C should remain unchanged (open to all eligible patients irrespective of their PD-L1 status)."

This recommendation was accepted by the Sponsor's DRB on 26 March 2018. After further follow up (5 April 2018), IDMC provided additional clarification on two points: 1) to implement their recommendation using a mechanism that minimises the number of patients with IC0 or IC1 tumours randomized to Arm B (atezolizumab monotherapy); and 2) they do not recommend a change of therapy for patients already randomized on study.

The Sponsor remains blinded to all IMvigor130 data reviewed by the IDMC and has only been provided the IDMC recommendations.

The IMvigor130 study is stated in the EC decision as an Annex II condition under section D "Obligation to conduct post-authorisation measures" which defines study IMvigor130 as a PAES.

Considering the above, the MAH submitted a variation to restrict the indication for the Tecentriq monotherapy of adult patients with locally advanced or metastatic urothelial carcinoma (UC).

3. Clinical Efficacy aspects

3.1. Introduction

The proposed change follows the review of survival data by the independent Data Monitoring Committee (iDMC) of study IMvigor130 in an ad-hoc meeting on 19th March 2018. IMvigor130 (WO30070) is a Phase III, multicenter, randomized, placebo-controlled study of atezolizumab administered as monotherapy or in combination with platinum-based chemotherapy compared with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma enrolling patients in the first line setting who are both cisplatin eligible and cisplatin ineligible:

- Arm A [atezolizumab in combination with platinum-based chemotherapy (cisplatin or carboplatin) and gemcitabine],
- Arm B (atezolizumab monotherapy) or
- Arm C [placebo in combination with platinum-based chemotherapy (cisplatin or carboplatin) and gemcitabine]

The IMvigor130 study is included as an Annex II condition under section D "Obligation to conduct post-authorisation measures" which defines study IMvigor130 as a PAES in order to evaluate the efficacy of atezolizumab in terms of PFS and OS. The MAH was asked to conduct IMvigor 130, comparing atezolizumab monotherapy versus atezolizumab and carboplatin/gemcitabine or cisplatin/gemcitabine in untreated patients (cisplatin-ineligible and –eligible patients) as at the time of the initial approval of Tecentriq in 1L cisplatin-ineligible patients the overall response rate of atezolizumab compared less favourably to the best historical comparator of CarboGem (22.7% vs. 36.1%), responses were ongoing in 70% of patients with a median follow-up of 17.2 months (compared to 5.3 months for Carbo/Gem). In the 2L+ patients response rates in the same range as for chemotherapy were demonstrated consistently in 767 2L UC patients across IMvigor 210 and IMvigor 211. Duration of responses was substantially longer for treatment with atezolizumab (median DOR 21.7 vs. 7.4 months in the atezolizumab vs. control arm). OS data for atezolizumab were numerically superior to SOC for the overall study population and across all IC subgroups. The Kaplan-Meier OS curves showed a separation after approximately 7 months in favour of the atezolizumab monotherapy arm, and it was maintained thereafter suggesting a non-negligible clinical benefit for those patients that achieved a response.

3.2. Discussion - review of interim results of IMvigor130

At the time of the initial approval of Tecentriq in the 1L cisplatin-ineligible the overall response rates of atezolizumab compared less favourably to the best historical comparator of CarboGem (22.7% vs. 36.1%), responses were ongoing in 70% of patients with a median follow-up of 17.2 months (compared to 5.3 months for Carbo/Gem). The MAH was requested to conduct a PAES in order to evaluate the efficacy of atezolizumab in terms of PFS and OS. The MAH was asked to submit the results of study IMvigor 130, a phase 3 randomised study comparing atezolizumab monotherapy or atezolizumab and carboplatin/gemcitabine with cisplatin/gemcitabine in untreated patients (cisplatin-ineligible and –eligible patients).

On 19 March 2018, the IDMC for Study IMvigor130 met for an ad-hoc closed session scheduled at their request. Based on the review of data from a snapshot dated 12 March 2018, and meeting discussion, the IDMC recommended the following to the Sponsor Data Review Board (DRB):

"Based on review of survival data in all patients randomized to date, the DMC recommends closure of Arm B (Atezo alone) to further accrual for all patients whose tumors are IC0 or IC1 for PD-L1. Patients who have tumors that are IC2/3 can continue to be randomized to Arms A, B or C. Arms A and C should remain unchanged (open to all eligible patients irrespective of their PD-L1 status)."

The Sponsor, through a firewalled internal team that has been unblinded to the IMvigor130 data, has reviewed the results of the interim analysis on which the IMvigor130 iDMC based their recommendation. In the subgroup of patients whose tumours express low levels of PD-L1 (less than 5% of immune cells staining for PD-L1), decreased overall survival was observed for the patients treated with atezolizumab monotherapy (Arm B) compared to the patients treated with the control treatment of platinum-based chemotherapy (Arm C). In the subgroup of patients whose tumours express high levels of PD-L1 (5% or greater immune cells staining positive for PD-L1 by immunohistochemistry) the interim results do not impact the current label.

The MAH has appropriately distributed a Dear Investigator Letter (DIL) to all study sites and local health authorities. The DIL clearly describe the decision made by IDMC and the consequences it has.

Overall, data show a lower OS in patients whose tumours have a PD-L1 expression < 5% . The lower efficacy cannot be attributed to higher rates of AE, SAEs or withdrawals, as the safety of atezolizumab in the monotherapy is as expected. Nor can the differences be attributed to differences in baseline characteristics. Tecentriq was approved in 1L cisplatin-ineligible patients based on single arm data. However, study IMvigor130 now provides comparative data that show a lower efficacy in patients that are either PD-L1 negative (IC0) or low expressers (IC1). Thus, a restriction of the indication to patients with PD-L1 expression ≥ 5% is warranted.

Following the review of the data provided by the iDMC and the MAH, the CHMP agreed with the changes of section 4.1, 4.2 and 5.1 of the SmPC to restrict the indication as follows:

- **Section 4.1 'Therapeutic indications'**

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC):

- after prior platinum-containing chemotherapy, or
- who are considered cisplatin ineligible**, and whose tumours have a PD-L1 expression ≥ 5% (see section 5.1).**
- **Section 4.2 'Posology and method of administration'**

<u>PD-L1 testing for patients with UC</u>

Patients with previously untreated UC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

- **Section 5.1 'Pharmacodynamic properties'**

IMvigor130 (WO30070): Phase III multi-center, randomized, placebo-controlled study of atezolizumab as monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma

Based on an independent Data Monitoring Committee (iDMC) recommendation following an early review of survival data, accrual of patients on the atezolizumab monotherapy treatment arm whose tumours have a low PD-L1 expression (less than 5% of immune cells staining positive for PD-L1 by immunohistochemistry) was stopped after observing decreased overall survival for this subgroup. The iDMC did not recommend any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm.

The Package Leaflet has also been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

In addition, a Direct Healthcare Professional Communication (DHPC) is considered necessary in order to communicate on the restriction of indication after agreement of the translations local specificities of the DHPC with national competent authorities.

The DHPC should be sent by 9 July 2018 to Prescribing Oncologists/Oncology clinics/Oncology departments/Pharmacists as per country-specific distribution channels. The DHPC and the communication plan are provided as attachments to this report.

3.3. Conclusion

Based on the data provided by the iDMC and the MAH, the CHMP agreed with the SmPC changes to restrict the 1st line indication in urothelial carcinoma based on the preliminary data from an ongoing clinical trial (IMvigor130) which showed reduced survival with Tecentriq monotherapy compared to standard chemotherapy when used as first-line treatment for patients with locally advanced or metastatic urothelial carcinoma whose tumours have low expression of PD-L1.

A DHPC will be sent by 9th July to Prescribing Oncologists/Oncology clinics/Oncology departments/Pharmacists as per country-specific distribution channels.

4. Clinical Safety aspects

The safety of atezolizumab monotherapy is as expected. There was no increase in frequency of all grade AEs, severe (Grade 3-4) AEs or AEs leading to treatment discontinuations observed for patients in the atezolizumab monotherapy arm of IMvigor130 study and the adverse event profile to date is consistent with the known safety profile for atezolizumab.

5. Risk management plan

The MAH should update the RMP accordingly within an upcoming regulatory procedure affecting the RMP.

6. Overall conclusion and impact on the benefit/risk balance

At the time of the initial approval of Tecentriq in the 1st line cisplatin-ineligible indication, the overall response rates of atezolizumab compared less favourably to the best historical comparator of carboplatine/gemcitabine (Carbo/Gem) (22.7% versus 36.1%), responses were ongoing in 70% of patients with a median follow-up of 17.2 months (compared to 5.3 months for Carbo/Gem). In order to

evaluate the efficacy of atezolizumab in terms of PFS and OS, the MAH was requested to submit the results of study IMvigor 130, a phase 3 randomised study comparing atezolizumab monotherapy or atezolizumab and carboplatin/gemcitabine with cisplatin/gemcitabine in untreated patients (cisplatin-ineligible and –eligible patients).

On 19 March 2018, the independent data monitoring committee (IDMC) for study IMvigor130 met for an ad-hoc closed session scheduled at their request. Based on the review of data from a snapshot dated 12 March 2018, and meeting discussion, the IDMC recommended the following to the Sponsor Data Review Board (DRB):

"Based on review of survival data in all patients randomized to date, the DMC recommends closure of Arm B (Atezo alone) to further accrual for all patients whose tumors are IC0 or IC1 for PD-L1. Patients who have tumors that are IC2/3 can continue to be randomized to Arms A, B or C. Arms A and C should remain unchanged (open to all eligible patients irrespective of their PD-L1 status)."

The MAH has appropriately distributed a Dear Investigator Letter (DIL) to all study sites and local health authorities. The DIL clearly describes the decision made by IDMC and the consequences it has.

Overall, data show a lower OS in patients whose tumours have a PD-L1 expression < 5%. The lower efficacy cannot be attributed to higher rates of AE, SAEs or withdrawals, as the safety of atezolizumab in the monotherapy is as expected. Nor can the differences be attributed to differences in baseline characteristics. Tecentriq was approved in 1L cisplatin-ineligible patients based on single arm data. However, study IMvigor 130 now provides comparative data that show a lower efficacy in patients that are either PD-L1 negative (IC0) or low expressers (IC1).

Thus, a restriction of the indication is warranted.

The MAH applied for a variation to update section 4.1 and 5.1.

The CHMP agreed with the update of Sections 4.1, 4.2 and 5.1 of the SmPC.

A Direct Healthcare Professional Communication (DHPC) was considered necessary to communicate on the restricted indication.

The benefit-risk balance of Tecentriq remains positive in the NSCLC indication and 2nd line urothelial carcinoma indications. As for the 1st line urothelial indication, the benefit risk remains positive in patients whose tumours have a PDL-1 expression ≥ 5%.

7. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.1, 4.2 and 5.1 of the SmPC in order to restrict the 'treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are considered cipsplatin ineligible' indication by including 'and whose tumours have a PDL-1 expression ≥ 5%', based on the review of interim analysis data by the independent data monitoring committee (IDMC) from study IMvigor 130

(WO30070) listed as a PAES in the Annex II; this is a Phase III, multicentre, randomized, placebo-controlled study of atezolizumab administered as monotherapy or in combination with platinum-based chemotherapy compared with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma enrolling patients in the first line setting who are both cisplatin eligible and cisplatin ineligible. The Package Leaflet is updated accordingly. A DHPC was considered necessary to communicate on the restricted indication.

☒ is recommended for approval by consensus.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.