HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
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TRANSPARENCY COMMITTEE OPINION SUMMARY

TECENTRIQ (atezolizumab), anti-PD-L1 antibody

In combination with bevacizumab, paclitaxel and carboplatin, in metastatic non-squamous non-small cell lung cancer (NSCLC):

- **moderate clinical benefit as first-line treatment in patients who do not have EGFR mutant or ALK-positive NSCLC without clinical added value compared to bevacizumab, paclitaxel and carboplatin combination ;**
- **insufficient clinical benefit to justify reimbursement in patients with EGFR mutant or ALK-positive (ALK+) NSCLC, after failure of appropriate targeted therapies, due to a lack of clinical data.**

Key points

- TECENTRIQ has a market authorisation in combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, TECENTRIQ, in combination with bevacizumab and the chemotherapy concerned, is indicated only after failure of appropriate targeted therapies.
- The superiority of TECENTRIQ in combination with bevacizumab, paclitaxel and carboplatin compared to bevacizumab, paclitaxel and carboplatinwas demonstrated in terms of progression-free survival assessed by the investigator in an open-label study in the population without EGFR mutations or ALK rearrangements, with a modest absolute increase (+ 1.5 months) and an absolute increase of + 4.5 months overall survival in this same subpopulation on a second interim analysis scheduled in the protocol, with uncertainties relating to these results and the long-term effect.
- The frequency of adverse events having resulted in treatment discontinuation (34% versus 25%) was higher among patients treated with TECENTRIQ + bevacizumab + chemotherapy than among those receiving the combination of bevacizumab + chemotherapy only.

Pre-existing indications[1]

TECENTRIQ already has a market authorisationas monotherapy in the second-line treatment of locally advanced or metastatic NSCLC and in locally advanced or metastatic urothelial carcinoma (UC) (for more information, see MA).

Care pathway

- In the absence of an activating EGFR or BRAF mutation and ALK or ROS gene rearrangement, the standard first-line treatment in patients with no major comorbidities and with an ECOG performance status of 0 to 2 is based on dual therapy combining platinum-based chemotherapies with one of the following drugs: paclitaxel, docetaxel, gemcitabine, vinorelbine or pemetrexed. The addition of bevacizumab can be considered as first-line therapy in the absence of contraindications. In the event of disease progression, second-line treatment is initiated, using one of the following alternatives: immunotherapies in patients with an ECOG score of 0 or 1 (nivolumab, pembrolizumab in the event of PD-L1 (≥1%), atezolizumab), single-agent chemotherapy (docetaxel, pemetrexed), erlotinib. Pembrolizumab is a first-line treatment for some patients:
  - as monotherapy in patients whose tumours express PD-L1 with a tumour proportion score [TPS] ≥ 50% and not presenting a tumour EGFR mutation or ALK rearrangement

1 This summary does not concern these indications.

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- in combination with pemetrexed + platinum salt chemotherapy in patients with an ECOG status of 0 or 1, irrespective of PD-L1 expression rate, and whose tumours do not present EGFR or ALK mutations

- For patients presenting molecular abnormalities (EGFR mutations or ALK or ROS-1 rearrangements), first-line treatment is based on targeted therapy with a tyrosine kinase inhibitor depending on the abnormality:
  - in the event of EGFR mutation: erlotinib, gefitinib, afatinib, osimertinib
  - in the event of ALK + rearrangement: alectinib, crizotinib, ceritinib
  - in the event of ROS-1 rearrangement: crizotinib

  In the event of failure to respond to TKIs, platinum-based chemotherapy is an alternative.
- In patients with an ECOG score of 3 or 4, supportive care should be considered.
- Atezolizumab (TECENTRIQ) as monotherapy is an alternative to nivolumab or pembrolizumab (only in the event of a tumour with overexpression of PD-L1 ≥ 1%) after the failure of platinum-based chemotherapy. The role of atezolizumab remains to be studied in EGFR mutated patients, whereas it has no role in ALK+ patients, in the absence of clinical data.

- **Role of the medicinal product in the care pathway**

  In patients with metastatic non-squamous NSCLC whose tumours do not present an EGFR mutation or ALK rearrangement, TECENTRIQ, in combination with bevacizumab, paclitaxel and carboplatin is an alternative in first-line treatment. In the absence of robust comparative data on the basis of PD-L1 expression [TPS], the role of TECENTRIQ compared to pembrolizumab, as monotherapy or in combination, is not known.

  In patients whose tumours have an EGFR mutation or ALK rearrangement, TECENTRIQ in combination with bevacizumab and the chemotherapy concerned has no role in the care pathway due to a lack of data.

Clinical data

- A randomised, open-label study with three co-primary endpoints assessed the efficacy of atezolizumab (Atezo) in combination with carboplatin/paclitaxel (CP) with or without bevacizumab (Bev) compared to the bevacizumab + carboplatin/paclitaxel combination in chemotherapy-naive metastatic non-squamous NSCLC patients.

  On the date of the primary analysis of progression-free survival (median follow-up of 15.1 months in the Atezo+Bev+CP group and 15.4 months in the Bev+CP group):
  - the median progression-free survival in the selected ITT-WT population[2] (co-primary efficacy endpoint) was 8.3 months in the Atezo+Bev+CP group versus 6.8 months in the Bev+CP group, i.e., an absolute increase of +1.5 months ($HR_{stratified}$ = 0.62, $CI_{99.4\%}$ [0.46; 0.75], p<0.0001)
  - the median progression-free survival in the Teff-high WT population[3] (co-primary efficacy endpoint) was 11.3 months in the Atezo+Bev+CP group versus 6.8 months in the Bev+CP group, i.e., an absolute increase of + 4.5 months ($HR_{stratified}$ = 0.51, $CI_{99.4\%}$ [0.34; 0.74], p<0.0001)

  On the date of the second interim analysis of overall survival (third co-primary efficacy endpoint), with a median follow-up of 19.7 months, the median overall survival was 19.2 months in the Atezo+Bev+CP group versus 14.7 months in the Bev+CP group, i.e., an absolute increase of +4.5 months (HR = 0.78; $CI_{98.2\%}$ = [0.61; 0.99], p= 0.0164).
- These results are limited by the methodological weaknesses of this study :
  - its open-label design, the primary analysis in a selected subgroup of the population,
  - the overlapping of the survival curves according to the Kaplan Meier analysis and the fact that these curves merge at the end of the follow-up, but with few at-risk patients, meaning that it is not possible to assess long-term maintenance of the survival improvement in a population.
- The frequency of adverse events having resulted in treatment discontinuation (34% versus 25%) was higher among patients treated with Atezo + Bev + CP than among those receiving Bev+CP only.

Specific prescribing conditions

- Medicinal product for hospital use only
- Prescription reserved for oncology specialists or physicians with oncology expertise.

2 including only patients without molecular abnormalities (EGFR mutations/ALK rearrangement)

3 population including only patients without molecular abnormalities (EGFR mutations/ALK rearrangement) and with a “high” Teff (effector T cell) gene signature

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Benefit of the medicinal product

- The clinical benefit* of TECENTRIQ in combination with bevacizumab, paclitaxel and carboplatin in adults with metastatic non-squamous NSCLC is:
    - moderate as first-line treatment in patients who do not have EGFR mutant or ALK-positive NSCLC;
    - insufficient to justify its funding by the French national health insurance system in patients with EGFR mutant or ALK-positive (ALK+) NSCLC, after failure of appropriate targeted therapies.
- In the indication in which the clinical benefit is moderate, TECENTRIQ in combination with bevacizumab, paclitaxel and carboplatin provides no clinical added value* (CAV V) compared to the bevacizumab, paclitaxel and carboplatin combination.
- Favourable opinion for hospital reimbursement in the indication in which the clinical benefit is moderate.
- Unfavourable opinion for hospital reimbursement in the indication in which the clinical benefit is insufficient.

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This document was drafted on the basis of the Transparency Committee opinion dated 09 October 2019 (CT-17655) available at **www.has-sante.fr**

* The clinical benefit (CB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the CB, which may be substantial, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The clinical added value (CAV) corresponds to the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the CAV level from I, major, to IV, minor. A level V CAV (equivalent to "no clinical added value") denotes a "lack of clinical improvement".

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