HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
OPINION
20 MARCH 2020

atezolizumab
TECENTRIQ 840 mg concentrate for solution for infusion

First assessment

Key points

Unfavourable opinion for reimbursement in three indications:

- in combination with nab-paclitaxel for the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease,
- as monotherapy for the treatment of 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%,
- as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC with ALK gene rearrangement (ALK+), after prior chemotherapy.

Favourable opinion for reimbursement in an indication within a restricted scope: in the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy, with patients with activating EGFR mutation also having to have received a prior targeted therapy.

What therapeutic improvement?

No clinical added value compared to the presentation already listed (TECENTRIQ 1,200 mg) in the treatment of locally advanced or metastatic NSCLC after prior chemotherapy, with patients with activating EGFR mutation also having to have received a prior targeted therapy.

In the other indications: not applicable.

Role in the care pathway?

- *Triple-negative breast cancer*

In the absence of a treatment having specifically demonstrated its benefit with an optimal level of evidence in triple-negative breast cancer, patients are currently treated in accordance with the guidelines for the treatment of HER2-negative breast cancer. At an advanced stage, treatment is mainly based on sequential mono-chemotherapy with, as first-line treatment, anthracyclines and taxanes (docetaxel or paclitaxel) for patients not previously treated with these treatments. The use of platinum salts recommended in the treatment of advanced-stage triple-negative breast cancer following treatment with a taxane or an anthracycline may be discussed as a first-line treatment for metastatic disease, particularly in the event of BRCA gene mutation.

Role of TECENTRIQ (atezolizumab) in combination with nab-paclitaxel in the care pathway for triple-negative breast cancer:

Given the impossibility of determining the clinical benefit of combination of TECENTRIQ (atezolizumab) with nab-paclitaxel in view of the current treatment in France in the absence of a relevant comparison, the role of this combination in the care pathway cannot be determined. Consequently, the Committee considers that TECENTRIQ (atezolizumab) in combination with nab-paclitaxel has no role in the treatment of patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease.

- *Urothelial carcinoma*

The first-line treatment of metastatic urothelial cancers is based on multi-agent chemotherapy containing platinum salts with, in particular, for cisplatin eligible patients, GC (gemcitabine, cisplatin) or MVAC-HD [MVAC (methotrexate, vinblastine, adriamycin and cisplatin) combined with G-CSF] protocols, or MVAC or PCG (paclitaxel, cisplatin, gemcitabine) protocols. For cisplatin ineligible patients, the first-line treatment of metastatic disease depends on the patient's characteristics (in particular, renal function and ECOG status). Carboplatin-based chemotherapy is recommended (in particular, the protocol combining carboplatin and gemcitabine). In the event of cancer with PD-L1 expression, pembrolizumab (KEYTRUDA) and atezolizumab (TECENTRIQ) have an MA but are not reimbursed in France (in the absence of an application for reimbursement submitted by the pharmaceutical companies[3,24]). Other treatment options are the paclitaxel and gemcitabine combination or single-agent chemotherapies based on taxanes or gemcitabine.

As second-line therapy following treatment with platinum salts, immunotherapies such as pembrolizumab (KEYTRUDA), atezolizumab (TECENTRIQ) and nivolumab (OPDIVO) have an MA. However, only pembrolizumab (KEYTRUDA) is reimbursed at present. For patients for whom immunotherapy cannot be envisaged, chemotherapy is recommended. Vinflunine (JAVLOR) has an MA at this stage of the disease in the event of urothelial carcinoma with transitional cells, and other chemotherapies may be used off-label (paclitaxel, docetaxel, gemcitabine).

Role of TECENTRIQ (atezolizumab) in the care pathway for urothelial carcinoma:

As the dossier currently stands and considering:
- non-significant results for overall survival compared to chemotherapy as second-line treatment following the failure of chemotherapy in a phase 3 study,
- the absence of comparative data versus clinically relevant comparators, despite this comparison being possible, in the first-line treatment of patients who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%,
the Committee considers that TECENTRIQ (atezolizumab) has no role in the care pathway for the treatment of locally advanced or metastatic urothelial carcinoma.

- *NSCLC*

Refer to the Transparency Committee opinion of 30 May 2018 relative to the proprietary medicinal product TECENTRIQ 1,200 mg.

01 COMMITTEE'S CONCLUSIONS

01.1 Clinical benefit

1.1.1 Triple-negative breast cancer

◗ Triple-negative breast cancer, at the unresectable locally advanced or metastatic stage, is a serious, life-threatening disease.
◗ This is a specific curative treatment for triple-negative breast cancer.
◗ The efficacy/adverse effects ratio of TECENTRIQ (atezolizumab) in combination with nab-paclitaxel has not been adequately established on the basis of currently available data based on a comparison with nab-paclitaxel alone, whereas this taxane has no MA for the first-line treatment of advanced breast cancer and is not considered to be a clinically relevant comparator in view of current management in France in this treatment line (see Section 05 of this opinion). Consequently, the clinical benefit of TECENTRIQ (atezolizumab) in combination with nab-paclitaxel in the current care pathway in France cannot be determined from the comparative data derived from the IMpassion130 trial in which a modest increase in median progression-free survival was demonstrated (+2.50 months compared to nab-paclitaxel alone in the PD-L1 ≥ 1% subpopulation retained by the MA) and without any demonstrated impact to date on overall survival (in ITT and in the PD-L1 ≥ 1% subpopulation).
◗ There are therapeutic alternatives in the first-line treatment of advanced breast cancer although these do not have an MA specifically for the case of triple-negative cancer (RH-/HER2-)
◗ TECENTRIQ (atezolizumab) in combination with nab-paclitaxel has no role in the care pathway for patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumours have PD-L1 expression ≥ 1% and who have not received prior chemotherapy for metastatic disease (see 08.1 Role in the care pathway).

◗ **Public health impact**

Considering:
- the seriousness of triple-negative breast cancer at the unresectable locally advanced or metastatic stage, and its incidence,
- the poorly covered medical need,
- the lack of response to the identified need (no impact demonstrated to date on mortality or quality of life of patients),
- the lack of elements supporting the absence of a deterioration in the care and/or life pathway in the absence of robust quality of life data,

TECENTRIQ (atezolizumab) in combination with nab-paclitaxel is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of TECENTRIQ (atezolizumab) in combination with nab-paclitaxel is insufficient to justify its funding by the French national health insurance system, pending data compared to current treatment in France (in particular comparative data versus paclitaxel).

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication(s) and dosages.

1.1.2 Urothelial carcinoma

◗ Urothelial carcinoma is a serious disease that is life-threatening.
◗ This is a curative treatment.
◗ The efficacy/adverse effects ratio of TECENTRIQ (atezolizumab) as monotherapy is:

- not adequately established in second-line treatment following platinum-based chemotherapy due to the inconclusive nature of the phase 3 trial (IMvigor211) versus chemotherapy for the primary endpoint, overall survival (see 07.6.2 Summary & discussion);
- not adequately established in first-line treatment in patients who are cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5% in the absence of comparative data versus a clinically relevant comparator.

◗ There are medicinal alternatives for the first-line treatment of patients ineligible for cisplatin-based therapy and for second-line treatment after the failure of prior platinum-based chemotherapy.

◗ As the dossier currently stands, TECENTRIQ (atezolizumab) in combination with nab-paclitaxel has no role in the care pathway (see 08.2 Role in the care pathway).

◗ **Public health impact**

Considering:
- the seriousness of urothelial cancer, particularly at the unresectable locally advanced or metastatic stage,
- the low incidence of the disease,
- the partially met medical need in the first-line treatment of patients considered cisplatin ineligible and as second-line treatment after the failure of prior platinum-based chemotherapy,
- the absence of any expected additional impact on morbidity and mortality, in view of the absence of comparative data versus clinically relevant comparators, in the first-line treatment of patients who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%, and demonstration of the absence of a benefit in terms of overall survival compared to chemotherapy as second-line treatment following the failure of platinum-based chemotherapy in a phase 3 trial (IMvigor211),
- the absence of quality of life data in first-line treatment and the impossibility of drawing any conclusions due to the open-label character of the pivotal study in second-line treatment,
- the lack of expected impact on the organisation of care,

TECENTRIQ (atezolizumab) is unlikely to have an additional impact on public health.

Considering all these elements, as the dossier currently stands, the Committee deems that the clinical benefit of TECENTRIQ (atezolizumab) is insufficient to justify its funding by the French national health insurance system.

The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication(s) and dosages.

1.1.3 NSCLC

In accordance with the opinion issued on 30 May 2018 for the proprietary medicinal product TECENTRIQ 1,200 mg in this same indication[Erreur ! Signet non défini.], the Committee considers that the clinical benefit of TECENTRIQ 840 mg is:
- **substantial in the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy, with patients with activating EGFR mutation also having to have received a prior targeted therapy;**
- **insufficient to justify its funding by the French national health insurance system in the treatment of patients with locally advanced or metastatic NSCLC with ALK gene rearrangement (ALK+), after prior chemotherapy.**

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication: "for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy, with patients with activating EGFR mutation also having to have received a prior targeted therapy" and at the MA dosages.
The Committee issues an unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication: "for the

treatment of patients with locally advanced or metastatic NSCLC with ALK gene rearrangement (ALK+), after prior chemotherapy".

01.2 Clinical Added Value

1.2.1 Triple-negative breast cancer

Not applicable

1.2.2 Urothelial carcinoma

Not applicable

1.2.3 NSCLC

- **In the MA indication with the exception of advanced NSCLC with ALK gene rearrangement (ALK+)**

The medicinal product TECENTRIQ 840 mg concentrate for solution for infusion provides no clinical added value (CAV V) compared to the proprietary medicinal product TECENTRIQ 1,200 mg already listed.

- **In advanced NSCLC with ALK gene rearrangement (ALK+)**

Not applicable