Accelerated Approval for Oncology Drug Products:
Regulatory Overview

Oncologic Drugs Advisory Committee Meeting
Pembrolizumab Metastatic Cisplatin-ineligible Urothelial Carcinoma
April 28, 2021

Julia Beaver, MD
Chief of Medical Oncology, Oncology Center of Excellence, FDA
Deputy Director (acting), Office of Oncologic Diseases, FDA
Outline

• Regulatory Background
• Accelerated Approval Experience
• Oncologic Drugs Advisory Committee Agenda
• Conclusions
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U.S. Approval of Drugs and Biologics

Accelerated approval pathway

Regular (or traditional) approval pathway
Accelerated Approval Requirements

- Serious and life-threatening disease
- Substantial evidence of Efficacy and Safety
- Endpoint reasonably likely to predict clinical benefit
- Meaningful therapeutic benefit over available therapy
- Confirmatory trial

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Oncology Accelerated Approval Experience

- 151* Oncology Accelerated Approvals
  - 35* Accelerated Approvals for anti-PD-(L)1 antibodies
- 74 (49%)* converted to regular approval (median 3 years)
- 10 (6%)+ withdrawn indications

* to January 1, 2021
+ to April 2021

PD-(L)1: programmed death-(ligand) 1
Accelerated Approval (AA) Withdrawal

• AA indications may be withdrawn by the FDA if:
  – Postmarketing trial(s) fails to confirm a benefit
  – Failure to perform postmarketing trial with due diligence

• Voluntary Withdrawal or FDA initiated withdrawal proceedings
Outline

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Accelerated Approvals

• 76* Total indications for anti-PD-(L)1 antibodies
  – 35* Accelerated Approvals

• Communication with companies
  – Withdrawal or advisory committee discussion

* to January 1, 2021
+ to April 2021

PD-(L)1: programmed death-(ligand) 1
Voluntary Withdrawals

- 3rd line metastatic small cell lung cancer
  - Nivolumab
  - Pembrolizumab
- 2nd line advanced/metastatic urothelial carcinoma
  - Durvalumab
  - Atezolizumab
### Oncologic Drugs Advisory Committee Meeting

**Day 1: April 27, 2021**

**Metastatic Triple Negative Breast Cancer**
1. Atezolizumab

**Day 2: April 28, 2021**

**Metastatic Urothelial Carcinoma Cisplatin-ineligible**
2. Pembrolizumab
3. Atezolizumab

**Day 3: April 29, 2021**

**Metastatic Gastric/Gastroesophageal Junction Cancer**
4. Pembrolizumab
5. Atezolizumab

Hepatocellular Carcinoma
6. Pembrolizumab
7. Nivolumab
Key Issues: Pembrolizumab Metastatic Urothelial Carcinoma Cisplatin-ineligible

- Treatment landscape changed with OS benefit from alternative checkpoint inhibitor in maintenance setting
- Benefit not verified in confirmatory trial in same disease setting
- OS benefit and regular approval in 2^{nd} line setting
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Accelerated Approval Conclusions

• Tradeoff: earlier marketing of promising drugs with increased uncertainty

• Accelerated approval has successfully allowed for approval of transformative oncology drugs years earlier

• Re-evaluation necessary when results change the risk/benefit

Oncologic Drugs Advisory Committee Discussion

• Should the indication be maintained while additional trial(s) are conducted or completed
Pembrolizumab
1st-line Treatment of Cisplatin Ineligible Patients with Urothelial Cancer (UC)

April 28, 2021
Oncologic Drugs Advisory Committee Meeting

Laleh Amiri-Kordestani, MD
Division Director, Division of Oncology 1,
Office of Oncologic Diseases, FDA
Outline

• Key FDA Concerns

• Regulatory Background
  – Initial Accelerated Approval
  – Confirmatory Study
  – Treatment landscape of 1st line UC is changing
  – Confirmatory trial has not verified benefit
  – effectiveness of pembrolizumab in urothelial carcinoma
  – Can additional trials confirm the benefit?

• Voting Question for ODAC
  – Should the indication for pembrolizumab for the first-line treatment of cisplatin-ineligible and carboplatin-ineligible patients with advanced/metastatic urothelial carcinoma be maintained pending conduct or completion of additional trial(s)?
    • If your answer is “yes”, please discuss after the vote, what trials may serve to confirm clinical benefit including KN-045
Key FDA Concerns

1. Benefit not verified in confirmatory trial KN-361

2. Treatment landscape is changed with overall survival (OS) benefit from alternative checkpoint inhibitor in maintenance setting (avelumab)

3. Issues with alternative trials to confirm pembrolizumab’s benefit
Pembrolizumab Regulatory History in UC

May 2017  •  Regular approval in 2nd line, based on OS in KN-045
            •  Accelerated approval in 1st line, based on ORR and DOR in single arm trial KN-052

June 2018  •  eDMC Finding & Restriction of 1st-line indication

April 2020  •  Confirmatory randomized trial KN-361 in 1st line did not confirm clinical benefit

ORR: Overall Response Rate, DOR: Duration of Response, eDMC: external Data Monitoring Committee

www.fda.gov
KEYNOTE-052 Trial

N=370
LA or mUC
Cisplatin-ineligible*

Pembrolizumab

Disease Progression or unacceptable toxicity

Long Term follow-up

Primary endpoint: BICR-ORR in ITT and PD-L1-high

*Cisplatin-ineligibility criteria
- ECOG PS 2,
- Creatinine clearance >30 & <60 mL/min,
- Grade>1 hearing loss,
- Grade>1 neuropathy,
- NYHA Class III heart failure


www.fda.gov
## KEYNOTE-052 Efficacy Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Initial Results</th>
<th></th>
<th>Updated Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>March 2017</td>
<td>Sept 2018</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ITT N=370</td>
<td>ITT N=370</td>
<td>PD-L1-High N=110</td>
</tr>
<tr>
<td>BICR-ORR: CR+PR (95% CI)</td>
<td>29% (24, 34)</td>
<td>47% (38, 57)</td>
<td>29% (24, 34)</td>
</tr>
<tr>
<td>DOR, Median in months (range)</td>
<td>NR (1.4+, 17.8+)</td>
<td>NR (1.4+, 17.8+)</td>
<td>30 (1.4+, 35.9+)</td>
</tr>
</tbody>
</table>

BICR: Blinded Independent Central Review, CR: Complete response, DOR: Duration of Response, ITT: Intention to treat, N: Number, NR: not reached, ORR: Objective Response Rate, PR: Partial response

*updated results based on Applicant analysis
Available Therapies at Initial Approval

Available options, but with limited efficacy in small studies

• Combination therapy
  – Gemcitabine + carboplatin
    ORR: 30-45%  DOR= 5-8 mo
  – Gemcitabine + paclitaxel
    ORR=37% DOR=7.6 mo

• Single agent chemo

ORR: Objective Response Rate
DOR: Duration of Response
Initial Benefit/Risk Assessment

Benefits
• Durable responses
• Acceptable toxicity profile
• Viable non-chemo option for this older patient population

Risks
• Single arm study
• DOR needs more follow up
• Lack of survival

Accelerated Approval may require confirmation of benefit
Confirmatory Trial KEYNOTE-361

- Co-primary endpoints:
  - Arm 2 vs Arm 3, ITT
  - BICR-PFS
  - OS

- Chemotherapy: cisplatin or carboplatin + gemcitabine

- N=1010 Patients with LA or mUC Platinum eligible
- Stratified: PD-L1, Choice of platinum
eDMC Finding KEYNOTE-361 and IMvigor-130

• Two similar 3-arm trials in first-line bladder cancer
  – KN361 for pembrolizumab
  – IMvigor130 for atezolizumab

• Decreased OS in both trials in PD-L1- low populations; single agent immunotherapy vs chemotherapy in both trials

• Enrollment stopped in patients with tumors with low PD-L1 expression on monotherapy arms in both trials
Restricted Accelerated Approval Indication

• June 2018
  – for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC)
    • who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥10)...
    • or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
KEYNOTE-361 (Confirmatory Trial)
Primary Efficacy Results – ITT population

<table>
<thead>
<tr>
<th></th>
<th>Pembro+Chemo N=351</th>
<th>Chemo N=352</th>
</tr>
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<tbody>
<tr>
<td><strong>PFS-BICR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td>8.3 (7.5, 8.5)</td>
<td>7.1 (6.4, 7.9)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.65, 0.93)</td>
<td></td>
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<tr>
<td>p-value</td>
<td>Not significant</td>
<td></td>
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<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (95% CI), months</td>
<td>17.0 (14.5, 19.5)</td>
<td>14.3 (12.3, 16.7)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.86 (0.72, 1.02)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>Not significant</td>
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KN-361 results based on Applicant analysis, HR: hazard ratio, PFS-BICR: Progression-free survival by blinded independent central review, OS: Overall survival
### KEYNOTE-361 in Sub-Population Corresponding to KEYNOTE-052 (Exploratory Analysis)

<table>
<thead>
<tr>
<th>Population</th>
<th>KEYNOTE-052</th>
<th>KEYNOTE-361</th>
<th>KEYNOTE-361</th>
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<tbody>
<tr>
<td></td>
<td>PD-L1-High</td>
<td>PD-L1-High</td>
<td>PD-L1-High</td>
</tr>
<tr>
<td></td>
<td>N=110</td>
<td>N=71</td>
<td>N=82</td>
</tr>
<tr>
<td>Treatment</td>
<td>Pembrolizumab</td>
<td>Pembrolizumab</td>
<td>Carboplatin + Gemcitabine</td>
</tr>
<tr>
<td>Duration of Follow-up, months (range)</td>
<td>29.4 (7.8, 41.2)</td>
<td>25.5 (5.4, 40.5)</td>
<td>25.5 (5.4, 40.5)</td>
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<tr>
<td>ORR-BICR : CR+PR (95% CI)</td>
<td>47% (38, 57)</td>
<td>25% (16, 37)</td>
<td>48% (36, 59)</td>
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<td>DOR, Median in months (range)</td>
<td>NR (1.4+, 35.4+)</td>
<td>NR (4.0+, 36.1+)</td>
<td>6.4 (2.1+, 33.8+)</td>
</tr>
</tbody>
</table>

KN-361 results based on Applicant analysis conducted retrospectively

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Proposed Trials to Confirm Benefit

- **LEAP-011**: Phase 3 study of pembrolizumab + lenvatinib versus pembrolizumab + placebo for previously untreated locally advanced or metastatic urothelial carcinoma in cisplatin-ineligible participants whose tumors express PD-L1, and in participants ineligible for any platinum-containing chemotherapy regardless of PD-L1 expression.
  - Enrollment began JUN-2019 and anticipated completion date is OCT-2023.
  - Does not isolate the effect of pembrolizumab

- **KEYNOTE-866**: Phase 3 study of perioperative pembrolizumab + neoadjuvant chemotherapy versus perioperative placebo + neoadjuvant chemotherapy for cisplatin-eligible participants with muscle invasive bladder cancer (MIBC).
  - Enrollment began JUL-2019 and anticipated completion date is JUN-2025.
  - Evaluates a cisplatin-eligible population

- **KEYNOTE-905**: Phase 3 study of cystectomy plus perioperative pembrolizumab +/- enfortumab vedotin versus cystectomy alone in cisplatin-ineligible participants with MIBC.
  - Enrollment began in AUG-2019 and anticipated completion date is May-2027.
Accelerated Approval Requirements

• Serious and life-threatening disease
• Substantial evidence of Efficacy and Safety
• Endpoint reasonable likely to predict clinical benefit
• Meaningful therapeutic benefit over available therapy
• Confirmatory trial

Treatment Landscape Evolving

• Maintenance with Avelumab
  – Regular approval for patients with no disease progression following 1st line platinum-containing chemotherapy
  – OS improvement, HR 0.69 (95% CI: 0.56, 0.86)
  – Majority of cis-ineligible patients are eligible for avelumab
Effectiveness of Pembrolizumab in UC

• First line:
  – KEYNOTE-052: Single arm, cisplatin-ineligible, under accelerated approval
  – KEYNOTE-361: Confirmatory randomized, did not confirm clinical benefit

• Second-Line
  – KEYNOTE-045: Randomized trial, OS benefit led to regular approval

• Non-muscle-invasive bladder cancer, KEYNOTE-057: regular approval
Voting Question

Given the following:

1. Benefit not verified in confirmatory trial in same disease setting
2. OS benefit and regular approval in 2\textsuperscript{nd} line setting for pembrolizumab (KN-045)
3. Treatment landscape is changed with OS benefit from alternative checkpoint inhibitor in maintenance setting (avelumab)
4. Alternative/ongoing trials in different disease setting or population, or design does isolate the effect

• Should the indication for pembrolizumab for the first-line treatment of cisplatin-ineligible and carboplatin-ineligible patients with advanced/metastatic urothelial carcinoma be maintained pending conduct or completion of additional trial(s)?
  – If your answer is “yes”, please discuss after the vote, what trials may serve to confirm clinical benefit including KN-045