Accelerated Approval for Oncology Drug Products: Regulatory Overview

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

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Outline

- Regulatory Background
- Accelerated Approval Experience
- Oncologic Drugs Advisory Committee Agenda
- Conclusions

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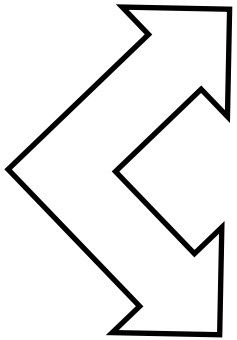
U.S. Approval of Drugs and Biologics



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

21 CFR Part 314, Subpart H; 21 CFR Part 601, Subpart E

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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- 10 (6%)+ withdrawn indications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- AA indications may be withdrawn by the FDA if: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

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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	Day 2: April 28, 2021	Day 3: April 29, 2021
Metastatic Triple Negative Breast Cancer 1. Atezolizumab	**Metastatic Urothelial Carcinoma Cisplatin-ineligible** 2. Pembrolizumab 3. Atezolizumab	**Metastatic Gastric/ Gastroesophageal Junction Cancer** 4. Pembrolizumab **Hepatocellular Carcinoma** 5. Pembrolizumab 6. 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 2nd line setting

OS: Overall Survival

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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


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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)

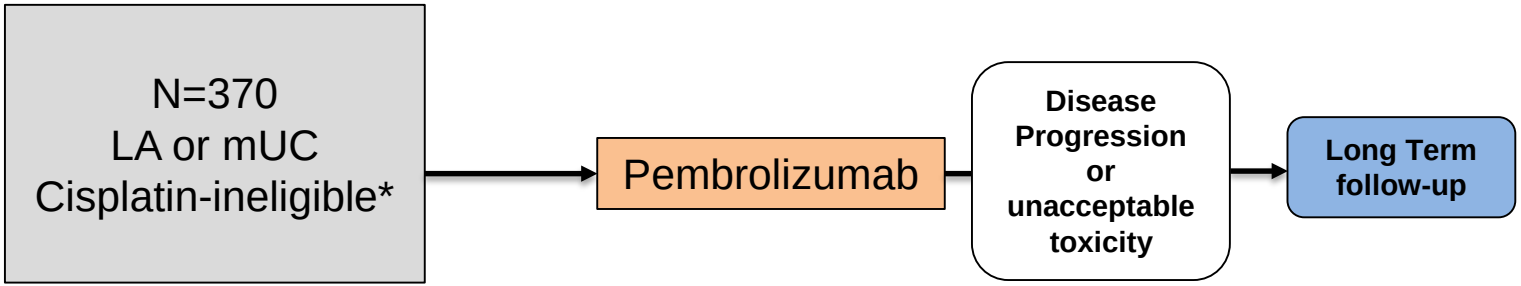
3. Issues with alternative trials to confirm pembrolizumab’ s benefit

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

KEYNOTE-052 Trial



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

BICR: Blinded Independent Central Review, ECOG PS: Eastern Cooperative Oncology Group Performance Status, ITT: Intention to treat, LA: Locally advanced, mUC: metastatic urothelial carcinoma, ORR: Overall response rate, NYHA: New York Heart Association

KEYNOTE-052 Efficacy Results

	Initial Results March 2017		Updated Results* Sept 2018	
Endpoint	ITT N=370	PD-L1-High N=110	ITT N=370	PD-L1-High N=110
BICR-ORR : CR+PR (95% CI)	29% (24, 34)	47% (38, 57)	29% (24, 34)	47% (38, 57)
DOR, Median in months (range)	NR (1.4+, 17.8+)	NR (1.4+, 17.8+)	30 (1.4+, 35.9+)	NR (1.4+, 35.4+)

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

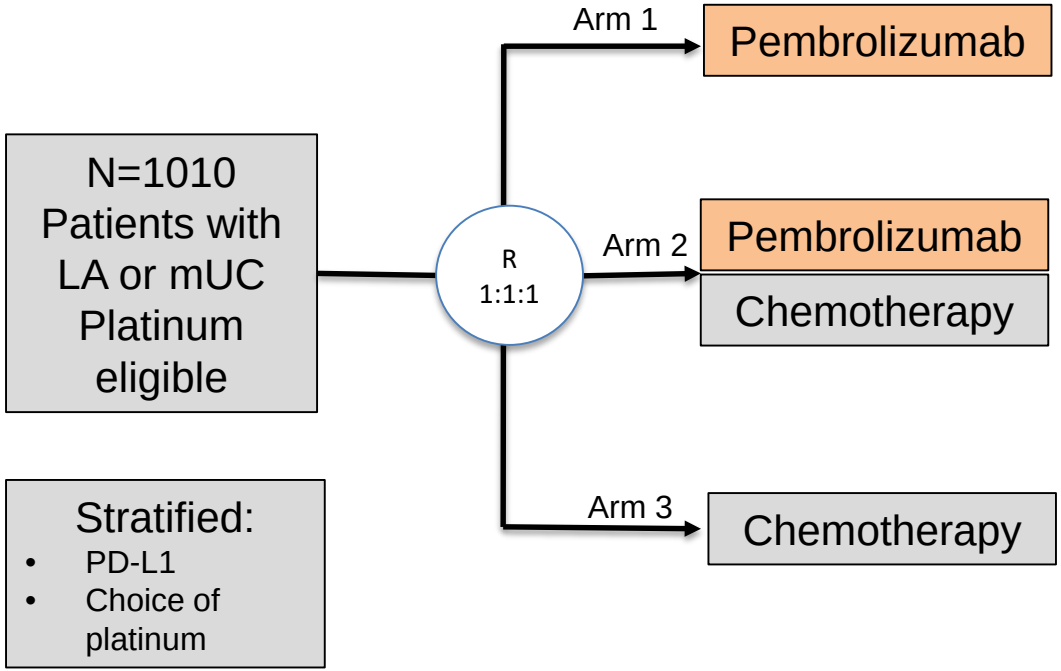
- Durable responses
- Acceptable toxicity profile
- Viable non-chemo option for this older patient population

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

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

	Pembro+Chemo N=351	Chemo N=352
PFS-BICR		
Median (95% CI), months	8.3 (7.5, 8.5)	7.1 (6.4, 7.9)
HR (95% CI)	0.78 (0.65, 0.93)	
p-value	Not significant	
OS		
Median (95% CI), months	17.0 (14.5, 19.5)	14.3 (12.3, 16.7)
HR (95% CI)	0.86 (0.72, 1.02)	
p-value	Not significant	

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)

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

KN-361 results based on Applicant analysis conducted retrospectively

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.

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21 CFR Part 314, Subpart H; 21 CFR Part 601, Subpart E

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 2nd 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**


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