Accelerated Approval for Oncology Drug Products: Regulatory Overview

Oncologic Drugs Advisory Committee Meeting
Atezolizumab 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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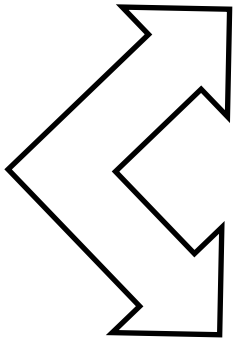
U.S. Approval of Drugs and Biologics



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- 10 (6%)+ withdrawn indications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- AA indications may be withdrawn by the FDA if: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: Atezolizumab Metastatic Urothelial Carcinoma Cisplatin-ineligible

- Treatment landscape changed with OS benefit from alternative checkpoint inhibitor in maintenance setting
- Benefit not yet verified in confirmatory trial in same disease setting
- Other urothelial carcinoma trials (adjuvant and 2nd line) did not meet endpoints

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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Atezolizumab
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 (AA)
  - Confirmatory Study
  - Confirmatory trial has not verified benefit
  - Other Trials in urothelial carcinoma
  - Lack of Clinical Benefit of atezolizumab in urothelial carcinoma
  - Treatment landscape is evolving
- Voting Question for ODAC
  - Should the indication for atezolizumab for the first-line treatment of cisplatin-ineligible patients with advanced/metastatic urothelial carcinoma be maintained pending final OS results from IMvigor130?

Key FDA Concerns

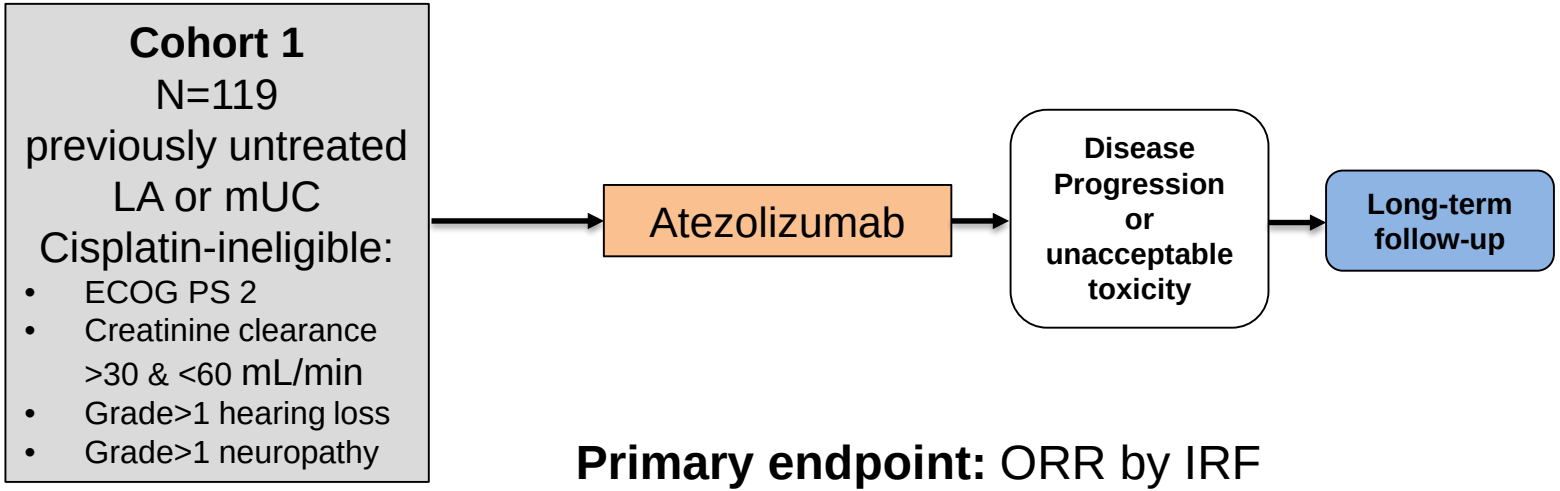
1. Confirmatory trial has not verified benefit
2. Clinical benefit unconfirmed in other settings
3. Treatment landscape is evolving
   - Avelumab maintenance

Atezolizumab Regulatory History
1st line indication

April 2017	•	1st line accelerated approval, based on ORR and DOR IMvigor210 (Cohort 1)
June 2018	•	eDMC Finding & Restriction of 1st-line indication
August 2019	•	Confirmatory randomized trial IMvigor130 in 1st line, PFS results reported, final OS pending

ORR: Overall Response Rate, DOR: Duration of Response, eDMC: external Data Monitoring Committee, OS: overall survival, PFS: progression free survival

IMvigor210 Trial



Primary endpoint: ORR by IRF

IRF: independent radiology facility, LA: Locally advanced, mUC: metastatic urothelial carcinoma, N: Number, ORR: Overall response rate, ITT: Intention to treat

IMvigor210 Trial (Cohort 1) Efficacy Results

Endpoint	**ITT N=119**	**PD-L1-High N=32**
ORR-IRF: CR+PR (95% CI)	23.5% (16.2, 32.2)	28.1% (13.8, 46.8)
DOR, Median in months (range)	NR (3.7, 16.6+)	NR (8.1, 15.6+)

DOR: Duration of Response, IRF: Independent review facility, ITT: Intention to treat, N: Number, NR: not reached, ORR: Objective Response Rate

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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

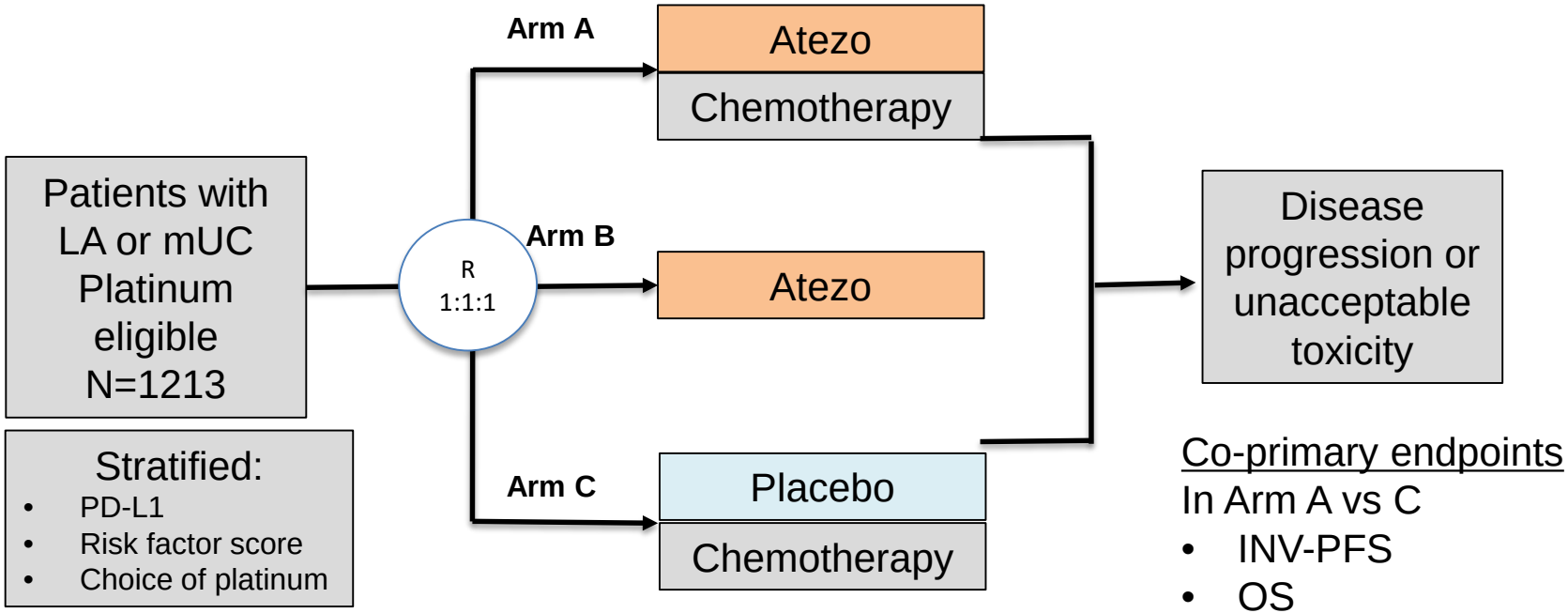
- Durable responses
- Acceptable toxicity profile
- Viable non-chemo option for this older patient population

Risks

- Single arm study
- DOR needs more follow up
- Lack of PFS /OS

Accelerated Approval may require confirmation of benefit

First-Line Confirmatory Trial - IMvigor130



LA: Locally advanced, mUC: metastatic urothelial carcinoma, INV-PFS: investigator-assessed progression-free survival, OS: Overall survival

eDMC Finding KEYNOTE-361 and IMvigor-130

- Two similar 3-arm trials in first-line bladder cancer
  - KN361 for pembrolizumab
  - IMvigor 130 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

- for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC)
  - who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the tumor area), …,
  - or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

IMvigor130 Primary Efficacy Analysis

	Progression-Free Survival		Overall Survival*	
	Atezo+chemo N=451	Placebo+chemo N=400	Atezo+chemo N=451	Placebo+chemo N=400
Median (95% CI), months	8.2 (6.5, 8.3)	6.3 (6.2, 7.0)	16.1 (14.2, 18.8)	13.4 (11.9, 15.2)
HR (95% CI)	0.82 (0.70, 0.96)		0.84 (0.71, 1.00)	
P-value	0.007		Not significant	

Source: Galsky MD et al. 2020
HR: Hazard Ratio, CI: Confidence Interval
*OS at 2nd Interim Analysis with 85% events, final OS results expected 2022

Other Trials in UC (Metastatic)

IMvigor210 (Cohort 2) – Accelerated approval atezolizumab in 2nd line UC

IMvigor211 - Atezolizumab in 2nd or 3rd line UC

- Randomized trial in patients with locally advanced or metastatic UC who have progressed during or following a platinum-containing regimen
  - Atezolizumab vs investigator's choice of chemotherapy
  - Primary endpoint: OS in patients with PD-L1-high tumors

- Failed to meet primary endpoint (HR 0.87, 95% CI: 0.63, 1.21, p=0.41).
  - ➢ 2nd line indication was recently withdrawn

Other Trials in UC (Adjuvant)

Study IMvigor010 - Atezolizumab in Adjuvant setting

- Randomized trial in patients with muscle-invasive urothelial carcinoma
- Atezolizumab monotherapy vs observation
- Primary endpoint: Disease free survival (DFS)
- Failed to meet primary endpoint (HR 0.89, 95% CI: 0.74, 1.08, p=0.24).

Lack of Clinical Benefit of Atezolizumab in UC

- 1st line, cis-ineligible:
  - Study IMvigor210 (cohort 1): Basis of AA
  - IMvigor130: PFS results not confirmed benefit, final OS pending

- 2nd line setting
  - Study IMvigor210 (cohort 2): Basis of AA
  - Study IMvigor211, Phase 3 trial, primary endpoint OS not met
    => Indication was withdrawn

- Adjuvant setting
  - Study IMvigor010, primary endpoint DFS not met

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

Conclusion

- Atezolizumab received accelerated approval based on durable ORR for 1st line treatment in patients ineligible for cisplatin
- Confirmatory trial has not verified clinical benefit
  - Follow up ongoing for final OS analysis
- Randomized trial in 2nd line treatment did not meet endpoint
  - 2nd line accelerated approval indication withdrawn
- Adjuvant randomized trial did not meet endpoint of DFS
- Available therapy with new options
  - OS benefit with avelumab maintenance for patients with no disease progression in 1st line

Voting Question

Given the following:

1. Benefit not yet verified in confirmatory trial in same disease setting
2. Benefit not verified in 2nd line metastatic setting and indication withdrawn
3. Adjuvant trial did not meet primary endpoint
4. Treatment landscape has changed with demonstrated OS benefit from alternative checkpoint inhibitor in maintenance setting

- **Should the indication for atezolizumab for the first-line treatment of cisplatin-ineligible patients with advanced/metastatic urothelial carcinoma be maintained pending final OS results from IMvigor130?**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