Accelerated Approval for Oncology Drug Products: Regulatory Overview

Oncologic Drugs Advisory Committee Meeting
Pembrolizumab Hepatocellular Carcinoma
April 29, 2021

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Deputy Director (acting), Office of Oncologic Diseases, FDA

Outline

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

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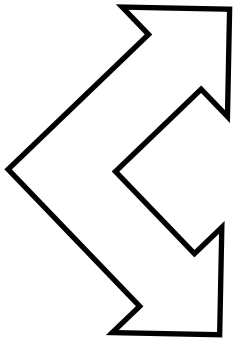
U.S. Approval of Drugs and Biologics



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

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- 10 (6%)+ withdrawn indications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- AA indications may be withdrawn by the FDA if: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

- Treatment landscape changed with OS benefit from alternative checkpoint inhibitor combination in 1st line
- Benefit not verified in confirmatory trial in same disease setting
- Low response rate

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
Hepatocellular Carcinoma (HCC)

April 29, 2021
Oncologic Drugs Advisory Committee Meeting

Steven Lemery, MD, MHS
Director, Division of Oncology 3,
Office of Oncologic Diseases, FDA

Accelerated Approval

1. Serious and-life threatening disease
2. Substantial evidence of safety/efficacy with meaningful therapeutic benefit over available therapy, and
3. Endpoint reasonably likely to predict benefit
4. Confirmatory trial(s)

Current Indication Statement

Treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Key Issues

1. Low response rate
   - KEYNOTE-224
2. KEYNOTE-240 did not confirm benefit
3. Treatment landscape evolving
   - IMbrave150
4. Is there a role for monotherapy?
5. Alternative studies to confirm benefit?

Approvals in Advanced HCC

First-line	Post-sorafenib
Sorafenib (2007)	Regorafenib (2017)
Lenvatinib (2018)	Nivolumab (AA – 2017)
Atezolizumab / bevacizumab (2020)	Pembrolizumab (AA - 2018)
	Cabozantinib (2019)
	Ramucirumab (AFP ≥ 400 ng/mL) (2019)
	Nivolumab + Ipilimumab (AA - 2020)

AA=accelerated approval; AFP=alpha fetoprotein

HCC Treatment is Complex

- HCC burden
- Hepatic function (e.g., Child-Pugh)
- Other sequalae of cirrhosis
  - Varices
- Other patient factors, e.g.,
  - Vascular invasion

KEYNOTE-224 Design

- Single arm, multinational trial
- Patients progressed on or were intolerant to sorafenib
- Important eligibility
  - Child-Pugh A
  - Excluded
    - hepatic encephalopathy,
    - clinically evident ascities,
    - esophageal/gastric bleeding within the past 6 months.
- Primary endpoint: Objective response rate (ORR) per central review

KEYNOTE-224 Patient Characteristics

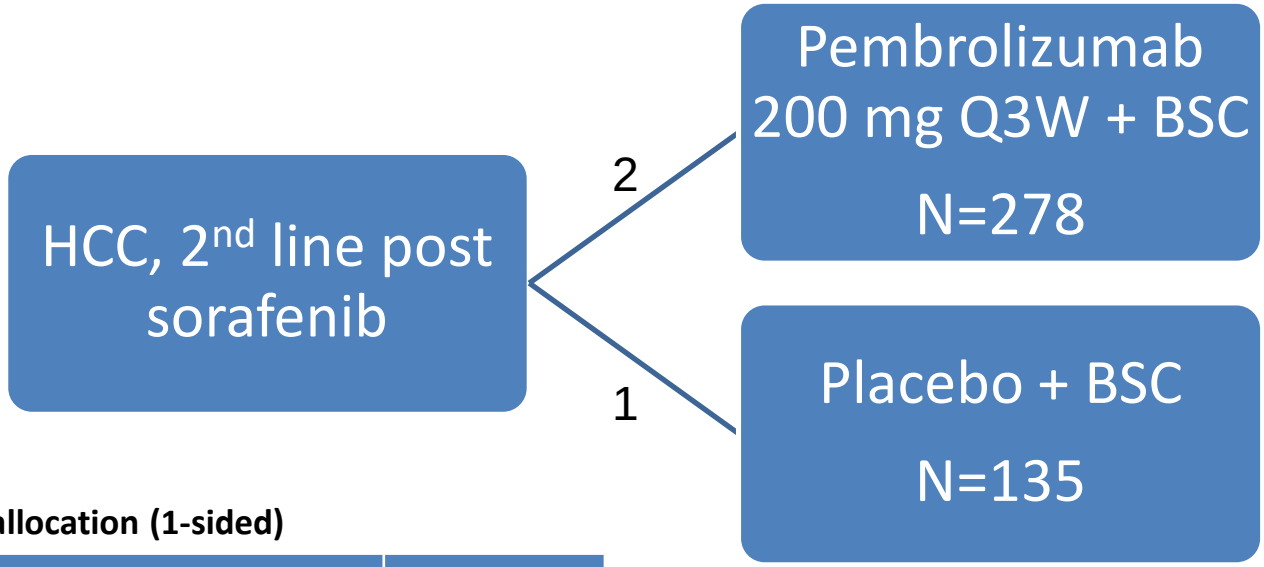
Parameter	% N=104
Hepatitis B virus (HBV) seropositive	21
Hepatitis C virus (HCV) seropositive	25
HBV and HCV seropositive	9
Child-Pugh (CP) A5	72
Child-Pugh (CP) A6	22
Vascular invasion	17
Extrahepatic disease	64
AFP ≥ 400	38

KEYNOTE-224 Results

Parameter	RESULTS
Study	KEYNOTE-224
N	104
ORR (RECIST)	17% (11,26)
responses ≥ 6 mo	89%
responses ≥ 12 mo	56%
ORR (mRECIST)	15% (9,24)*

*Zhu et al., Lancet Oncology, 2018

Confirmatory Trial: KEYNOTE-240



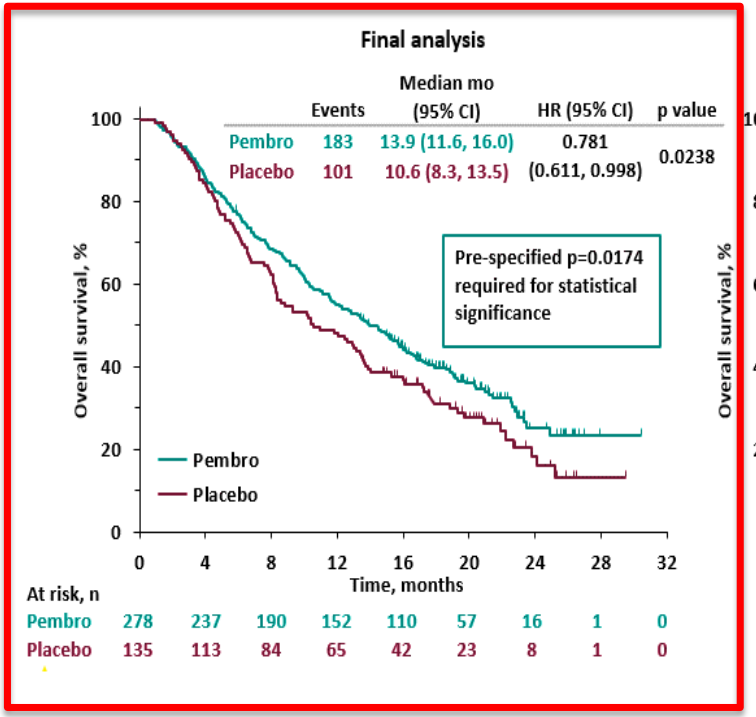
Alpha allocation (1-sided)

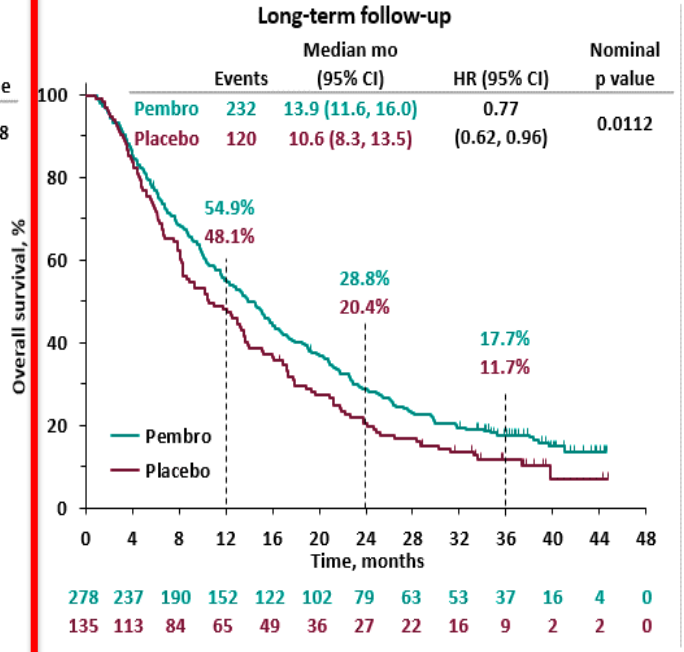
Progression free survival (PFS)	**0.002**
Overall survival (OS)	0.023

KEYNOTE-240 Patient Characteristics

Parameter	Pembro % N=278	Placebo % N=135
Male	81	83
>65 yrs	61	53
HBV	26	22
HCV	16	16
Microvascular invasion	13	12
AFP ≥ 200	46	43
CP A5	63	64
CP A6	36	35

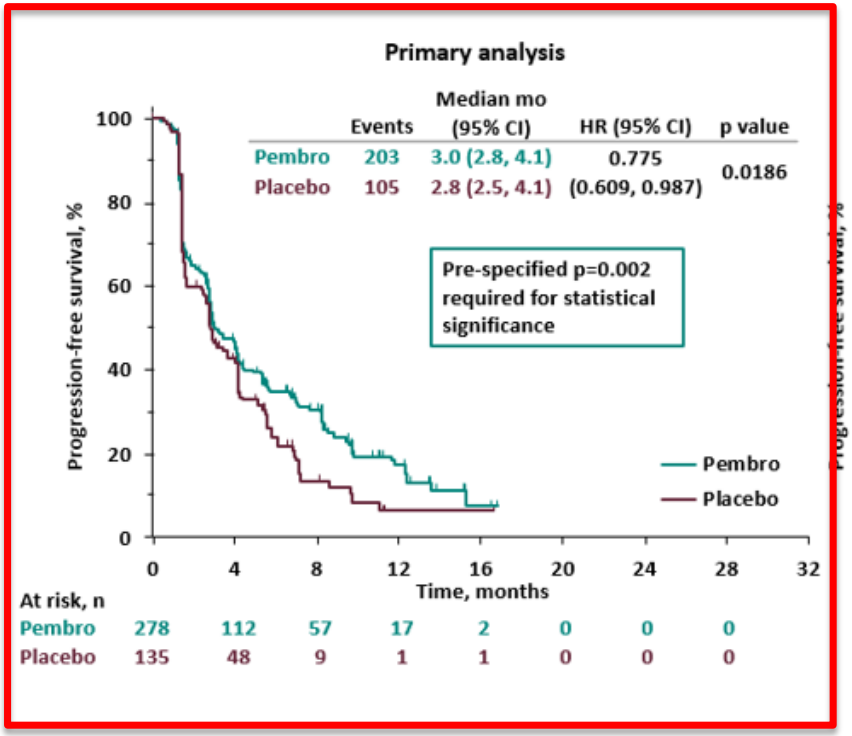
KEYNOTE-240 Results: OS

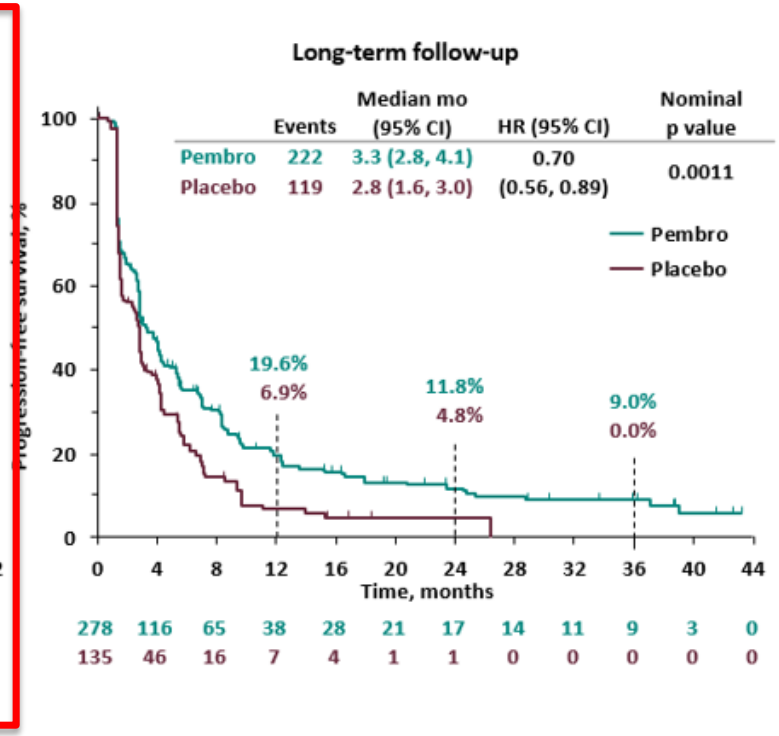




KM curves from Merck's briefing document

KEYNOTE-240 Results: PFS





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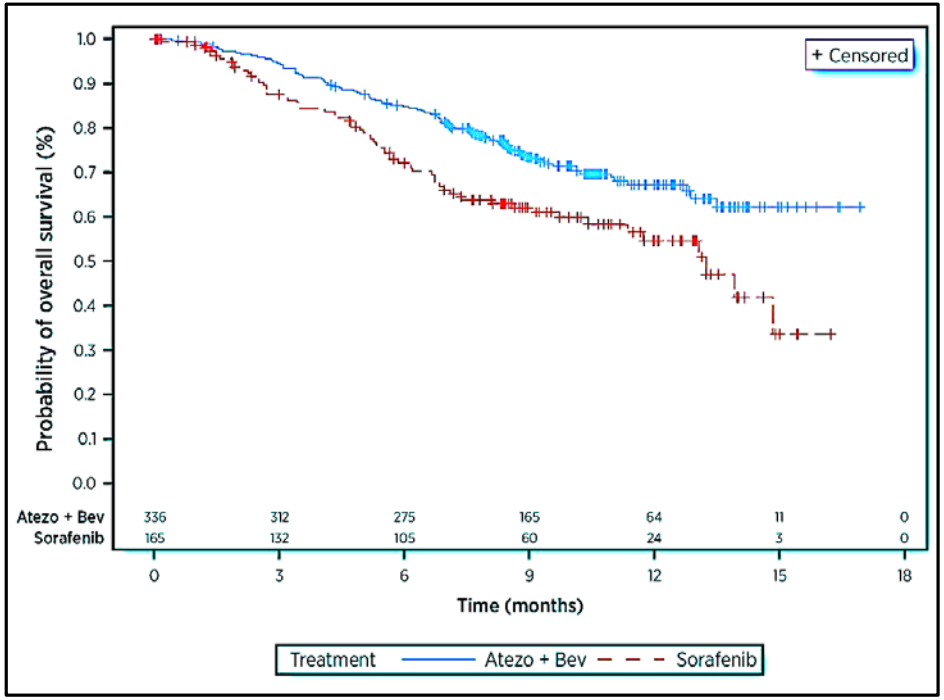
The Treatment Landscape is Changing

Atezolizumab/bevacizumab



From FDA Approval Summary (Casak et al., CCR, 2021)

- Excluded
  - Variceal bleeding within 6 mo
  - Untreated varices with bleeding
  - High risk of bleeding
- Required EGD within 6 mo

The Treatment Landscape is Changing

Parameter	Nivolumab (1 mg/kg) and Ipilimumab (3 mg/kg)
Study	CHECKMATE-040
N	49
ORR (RECIST)	33% (20,48)
responses ≥ 6 mo	88%
responses ≥ 12 mo	56%
ORR (mRECIST)	35% (22,50)

Ongoing Pembrolizumab Trials

	KEYNOTE-394	LEAP-002
N	453	692
Intervention	P+BSC vs. placebo+BSC	PL vs. L
HCC-line of tx	2nd-line HCC (East Asia)	1st-line HCC
Population	BCLC B or C; CPA	BCLC B or C; CPA
Enrollment	Complete	Complete
Completion	June 2021	2022
Key Endpoints	OS	PFS, OS

P=pembrolizumab; L=lenvatinib; BSC=best supportive care; BCLC=Barcelona-Clinic Liver Cancer staging; CPA=Child Pugh A

Monotherapy Benefit/Risk Assessment

Benefits

- Low chance of responding / long duration of response
- Different mechanism of action

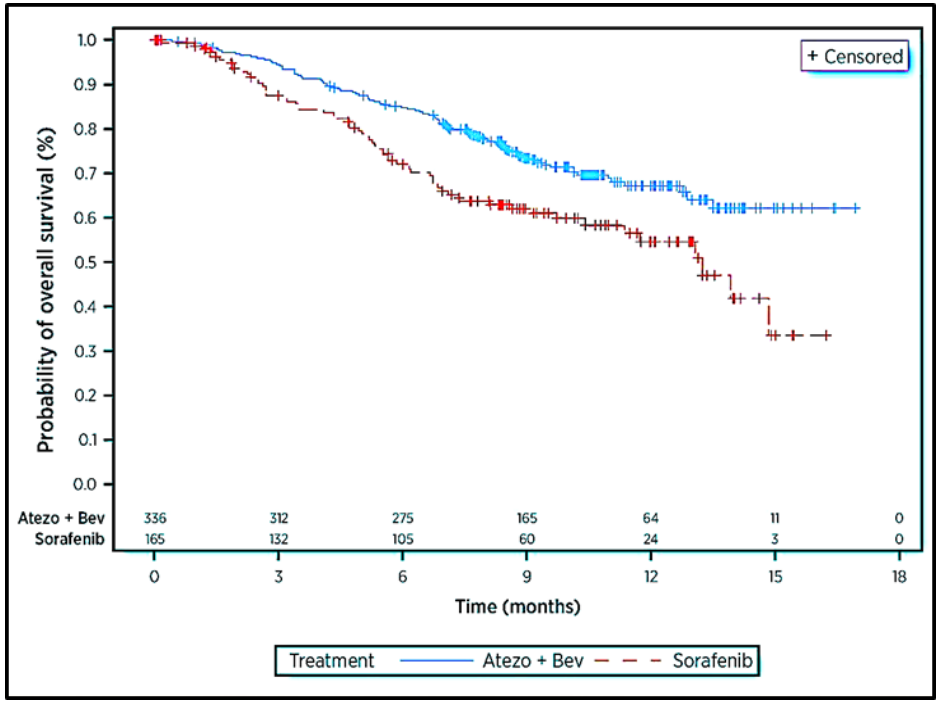
Risks

- Immune-related adverse events
- Most patients do not benefit / randomized trial negative

Uncertainties

- Drug effect in patients with high bleeding risk

How Would a New Application in the Second-Line Setting be Viewed?



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Key Endpoints	OS	PFS, OS

*P=pembrolizumab; L=lenvatinib; BSC=best supportive care

Voting Question

Given the following:

1. Low response rate of monotherapy in post-sorafenib setting
2. Treatment landscape changed with OS benefit of alternative checkpoint inhibitor (atezolizumab) in combination with bevacizumab in the first-line setting
3. Benefit not confirmed in the same (post-sorafenib) setting in KEYNOTE-240

Should the indication for the monotherapy use of pembrolizumab in patients previously treated with sorafenib be maintained pending conduct or completion of additional trials?

– **If your answer is "yes", please discuss after the vote what ongoing or alternative trials, including whether KEYNOTE-394 in the same setting, may serve to confirm clinical benefit.**


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