Accelerated Approval for Oncology Drug Products: Regulatory Overview

Oncologic Drugs Advisory Committee Meeting
Pembrolizumab Metastatic Gastric/Gastroesophageal Junction Cancer
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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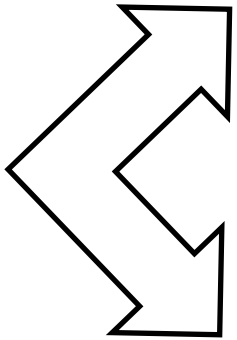
U.S. Approval of Drugs and Biologics



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- 10 (6%)+ withdrawn indications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- AA indications may be withdrawn by the FDA if: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 Metastatic Gastric/ Gastroesophageal Junction Cancer

- Two trials did not confirm benefit (one in same disease setting)
- Treatment landscape changed with OS benefit from alternative checkpoint inhibitor in 1st Line
- 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
Gastric/Gastroesophageal Junction (GEJ) Adenocarcinoma (PD-L1 CPS ≥ 1)

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)

Key Issues

1. Low response rate in microsatellite stable disease
2. Two trials did not confirm benefit
   - KEYNOTE-061
   - KEYNOTE-062
3. Evolving treatment landscape
   - CHECKMATE-649 (nivolumab)
4. Is there a role for monotherapy?

Treatment Landscape

	First-line	Second-line	Third-line (plus)
All Patients	FOLFOX or CAPEOX nivolumab	Paclitaxel +/ - ramucirumab	Trifluridine / tipiracil
	5FU / cisplatin	Ramucirumab	
	Doublet, triplet, or monotherapy cytotoxic	Monotherapy, doublet cytotoxic	Other
Subgroups			
HER-2 positive	Add trastuzumab	Fam-trastuzumab deruxtecan-nxki	
MSI-H or TMB-H		Pembrolizumab (AAs)	
CPS ≥ 1			Pembrolizumab (AA)

AA=accelerated approval; MSI-H=microsatellite instability-high; TMB-H=tumor mutation burden-high; CPS=combined positive score

Trial KEYNOTE-059

- Multicohort trial
  - Cohort 1: Disease progression after 2 or more regimens
- Single arm, multi-national study
- Primary end-point: Objective response rate (ORR) per central review

Third-Line(+) Monotherapy (CPS ≥1) KEYNOTE-059

- Accelerated approval 2017
- ORR 13.3% (95% CI: 8.2, 20) (n=143) microsatellite stable (MSS) or undetermined
- Median duration of response (DOR)
  - range 2.8+ to 19.4+ months
  - 58% ≥ 6 months
  - 26% ≥ 12 months

Microsatellite Instability (or dMMR)

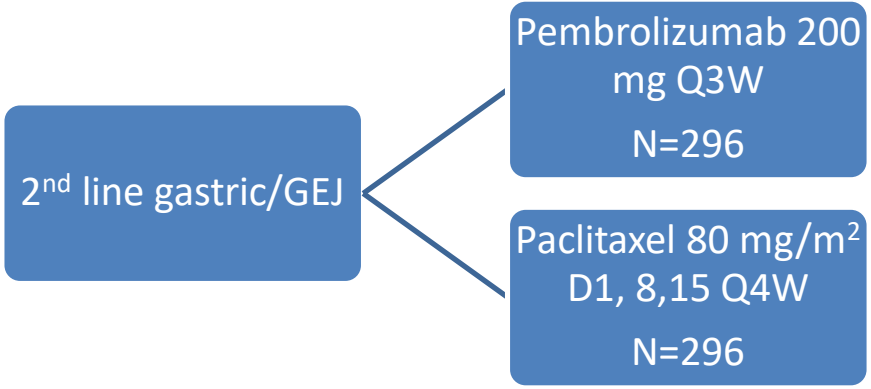
- ORR in known MSS/pMMR and CPS ≥ 1 (n=100): 11% (CI 5.6, 18.8) in *KEYNOTE-059*
- In MSI-H tumors, ORR (*external trials*)
  - 40% (CI 32, 48) in 149 patients overall
  - 56% (CI 21, 86) in 9 patients with gastric/GEJ

Confirmatory Trials

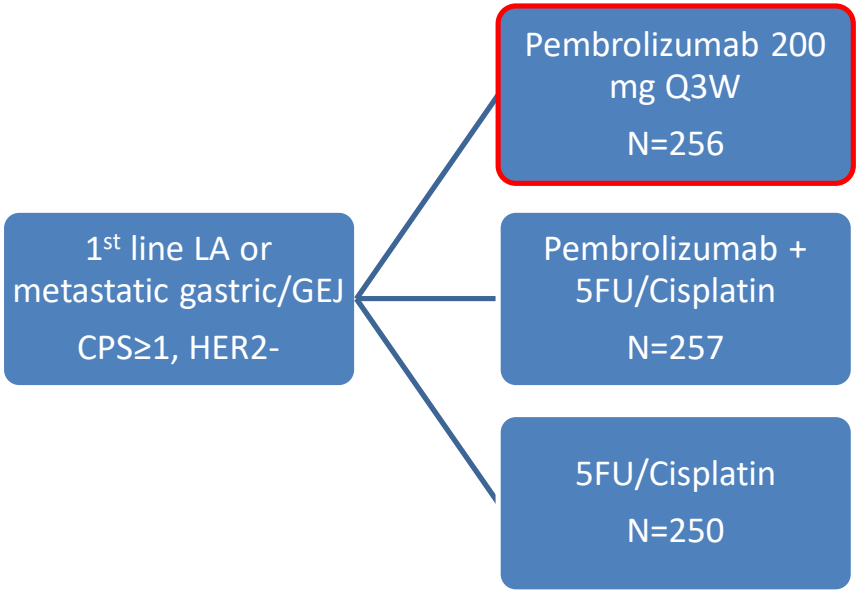
- KEYNOTE-061
  - Second-line
- KEYNOTE-062
  - First-line

Pembrolizumab Randomized Trials

KEYNOTE-061



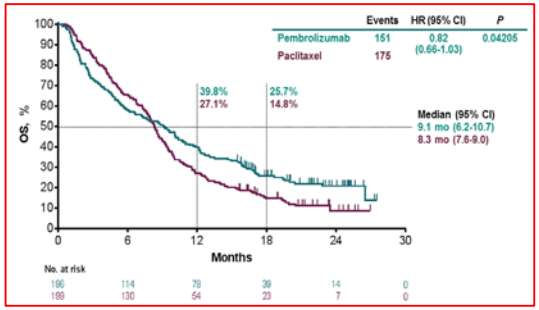
KEYNOTE-062



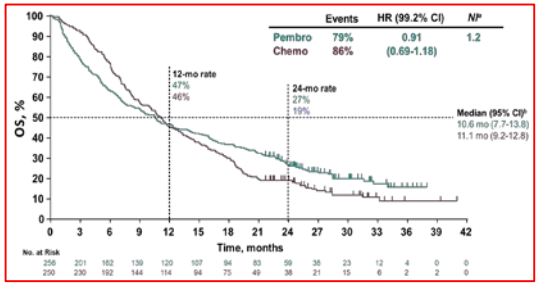
Results KEYNOTE-061 and KEYNOTE-062

(CPS ≥1 Analyses)

KEYNOTE-061 (2nd line)



KEYNOTE-062 (1st line)



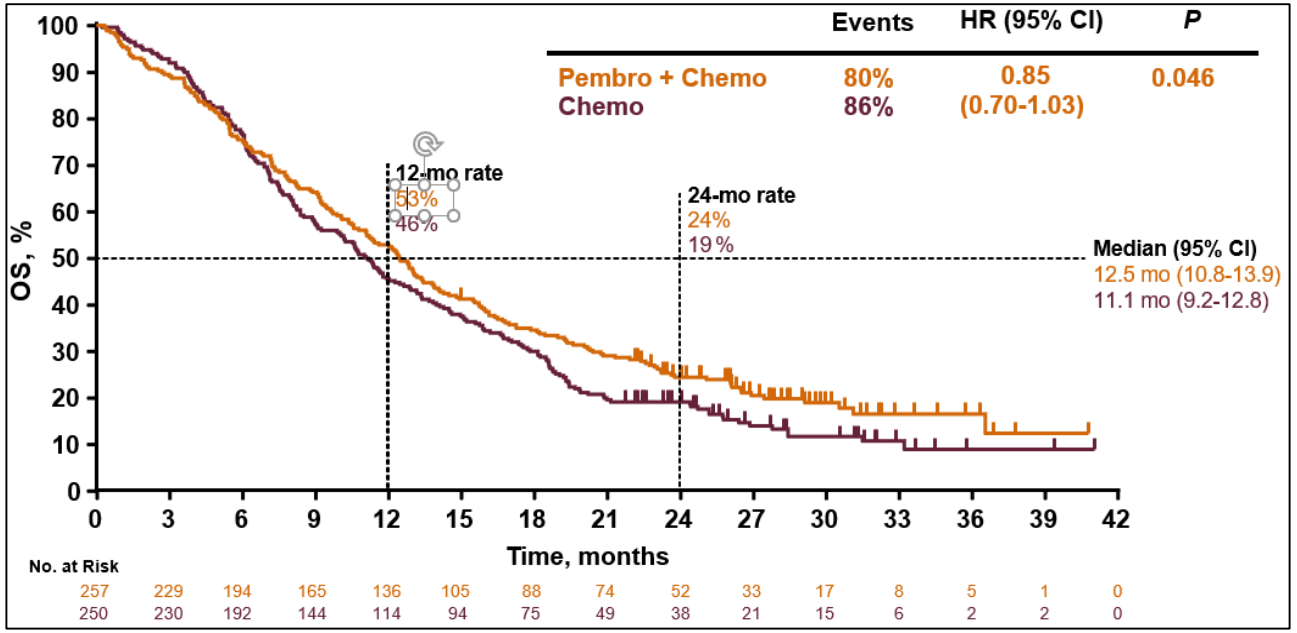
KM curves from Merck's briefing document

	KEYNOTE-61: Pembro vs paclitaxel	KEYNOTE-62: Pembro vs 5FU/cis
OS HR (CI)	0.82 (0.66, 1.03)	0.91 (0.69, 1.18)*
PFS HR (CI)	1.27 (1.03, 1.57)	1.64 (1.36, 1.98)

OS=overall survival; PFS=progression free survival

*99.2% CI

KEYNOTE-062 (PD-L1 CPS ≥1) Pembrolizumab + Chemo vs. Chemo



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Subgroups			
HER-2 positive	Add trastuzumab	Fam-trastuzumab deruxtecan-nxki	
MSI-H or TMB-H		Pembrolizumab (AAs)	
CPS ≥ 1			Pembrolizumab (AA)

AA=accelerated approval

Changing Landscape:
April 16, 2021, FDA Approved Nivolumab

CHECKMATE-649

	Nivolumab + FOLFOX or CAPEOX N=789	FOLFOX or CAPEOX N=792
Median OS, mo	13.8	11.6
HR	0.80 (95% CI: 0.71, 0.94)	
P value	0.002	

Ongoing Pembrolizumab Trials

	KN-859	KN-811	KN-585	LEAP-015
N	1542	692	1000	790
Intervention	PC vs. C	PTC vs. TC	PC vs. C	LPC v C
Population	1st-line G/GEJ	1st-line G/GEJ	Perioperative G/GEJ	1st-line G/GEJ
HER2	Negative	Positive	Either	Not known positive
Enrollment	Complete	91% complete	87% complete	Safety run-in ongoing
Completion	Q3 2024	Q1 2024	Q2 2024	Q4 2024
Key Endpoints	OS, PFS	OS, PFS	EFS, OS, pCR	OS, PFS

P=pembrolizumab; C=chemotherapy; T=trastuzumab; L=lenvatinib; EFS=Event-free survival; pCR=pathological complete response

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

Uncertainties

Two trials did not confirm benefit in CPS ≥1 group

	KEYNOTE-61: Pembro vs paclitaxel	KEYNOTE-62: Pembro vs 5FU/cis
OS HR (CI)	0.82 (0.66, 1.03)	0.91 (0.69, 1.18)*
PFS HR (CI)	1.27 (1.03, 1.57)	1.64 (1.36, 1.98)

*99.2% CI

Uncertainties

- Patient selection
  - Microsatellite instability-high
  - PD-L1 combined positive score
  - Tumor mutation burden-high

Pembrolizumab Risk/Benefit

- ORR 13.3% (11% known MSS)
  - Unclear relationship to clinical benefit
- Immune-related adverse events

Summary

- Unclear risk/benefit
  - Low response rate
  - Immune related adverse events
  - Negative trials
- Changing landscape
  - First-line approval of nivolumab

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

CHECKMATE-649

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Key Endpoints	OS, PFS	OS, PFS	EFS, OS, pCR	OS, PFS

*P=pembrolizumab; C=chemotherapy; T=trastuzumab; L=lenvatinib

Voting Question

Given the following:

1. Low response rate in third-line setting [13% (11% in known MSS)]
2. Treatment landscape has changed with nivolumab approval in the first-line setting based on improvement in OS
3. Two trials with monotherapy comparisons in the first- and second-line settings did not confirm benefit
4. Ongoing trials will not assess the monotherapy effect

Should the indication for the monotherapy use of pembrolizumab in PD-L1 CPS ≥ 1 gastric/GEJ adenocarcinoma (third-line or greater) be maintained pending conduct or completion of additional trials?

– **If your answer is "yes", please discuss after the vote what ongoing or alternative trials may serve to confirm clinical benefit.**


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