Accelerated Approval for Oncology Drug Products: Regulatory Overview

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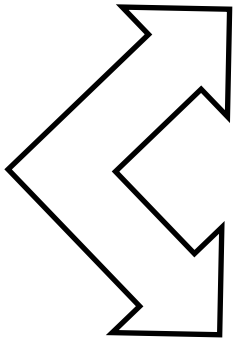
U.S. Approval of Drugs and Biologics



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- 10 (6%)+ withdrawn indications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- AA indications may be withdrawn by the FDA if: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

- Treatment landscape changed with OS benefit from alternative checkpoint inhibitor in 1st line
- Benefit not verified in confirmatory trial in 1st line 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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION

Nivolumab
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 Accelerated Approval Indications

- As a single agent: treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib
- In combination with ipilimumab: treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib

Key Issues

1. Low response rate
   - CheckMate-040
2. CheckMate-459 did not confirm benefit
3. Treatment landscape evolving
   - IMbrave150
   - CheckMate-040 nivolumab and ipilimumab
4. Is there a role for monotherapy?
5. Alternative studies to CheckMate-459?

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

CheckMate-040 Design

- Multicohort, multinational trial
- Patients progressed on or were intolerant to sorafenib
- Important eligibility
  - Child-Pugh A (or B)
  - Excluded
    - Hepatic encephalopathy
    - Clinically significant ascities
- Primary endpoint: Objective response rate (ORR) per central review

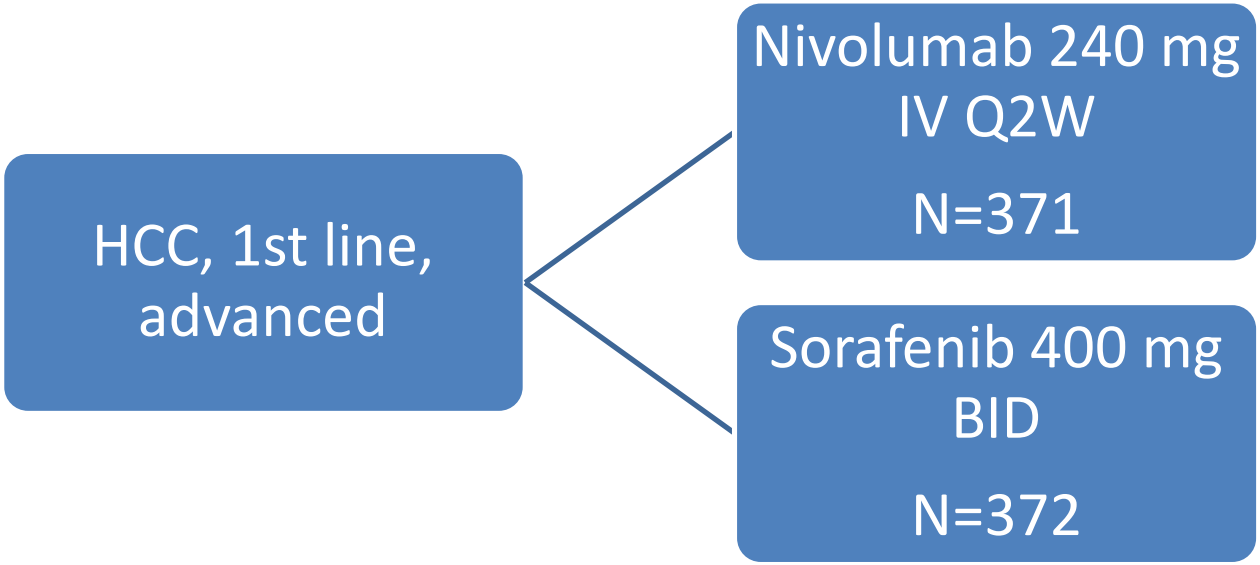
CheckMate-040 Patient Characteristics

Parameter	% N=154
Hepatitis B virus (HBV) seropositive	34
Hepatitis C virus (HCV) seropositive	29
Child-Pugh (CP) A5	68
Child-Pugh (CP) A6	31
Vascular invasion	29
Extrahepatic disease	71
AFP ≥ 400	37

CheckMate-040 Results

Parameter	Results
N	154
ORR (RECIST)	14% (9,21)
responses ≥ 6 mo	91%
responses ≥ 12 mo	55%
ORR (mRECIST)	18% (12,25)

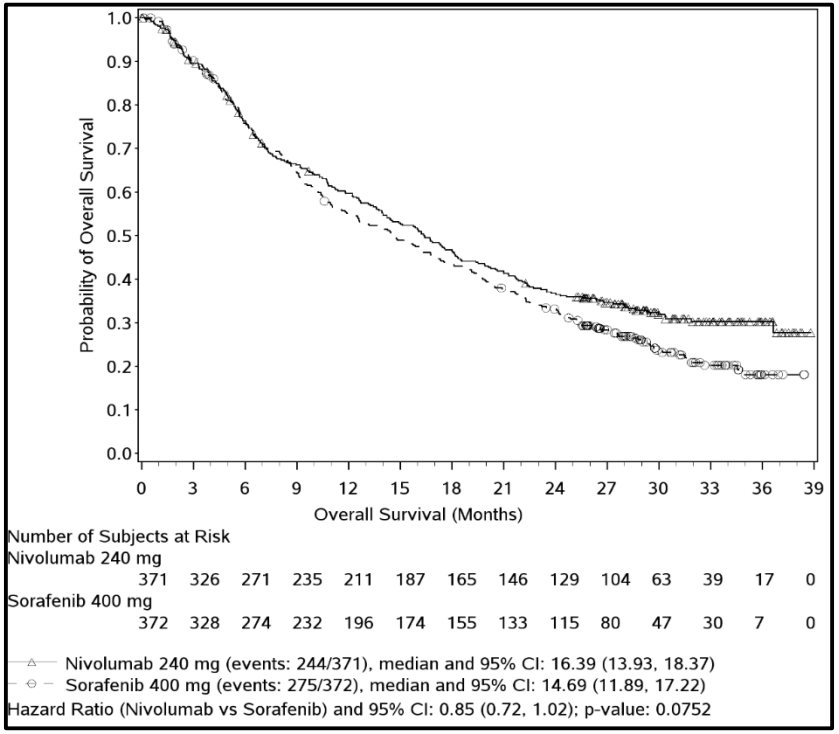
CheckMate-459



Alpha allocation (2-sided)

Overall survival (OS)	**0.05**

CheckMate-459 Results

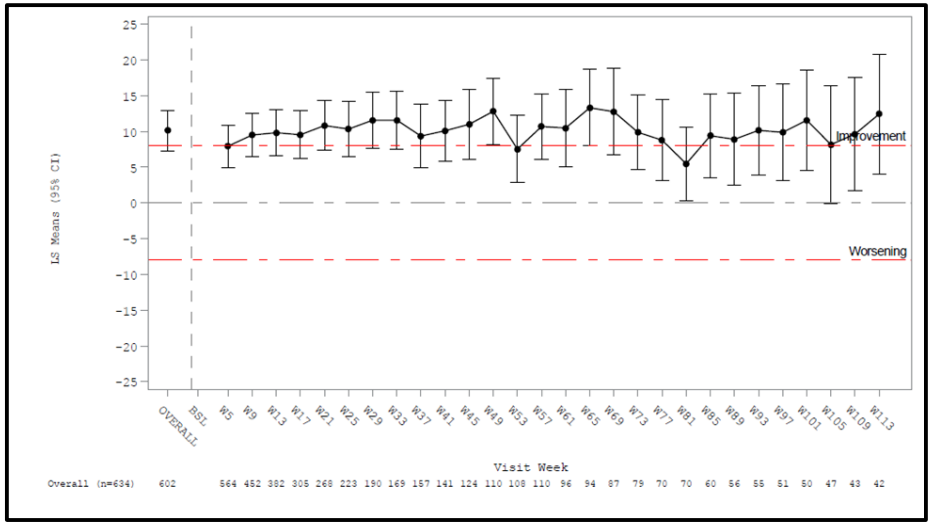


KM curves from BMS's briefing document

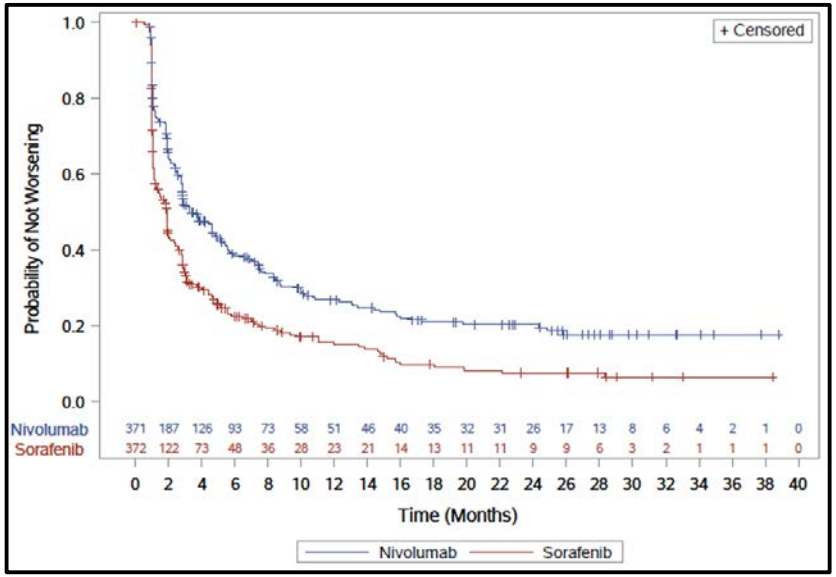
- Solid Line: Nivolumab
- Dotted Line: Sorafenib

Patient Reported Outcome Analyses

FACT-Hep difference between arms

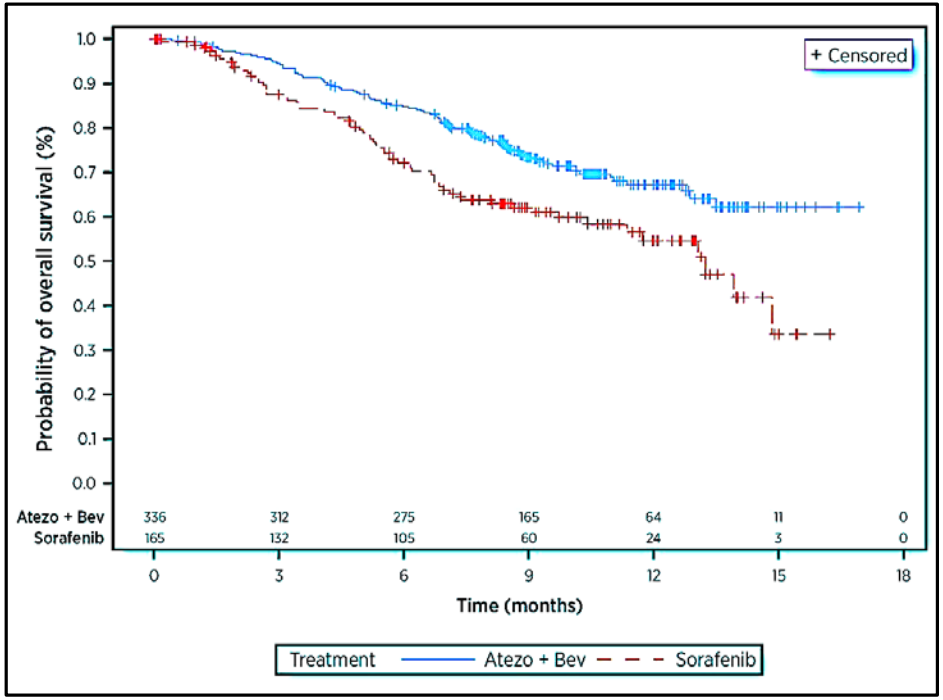


Time to deterioration FACT-Hep



KM curves from BMS's briefing document

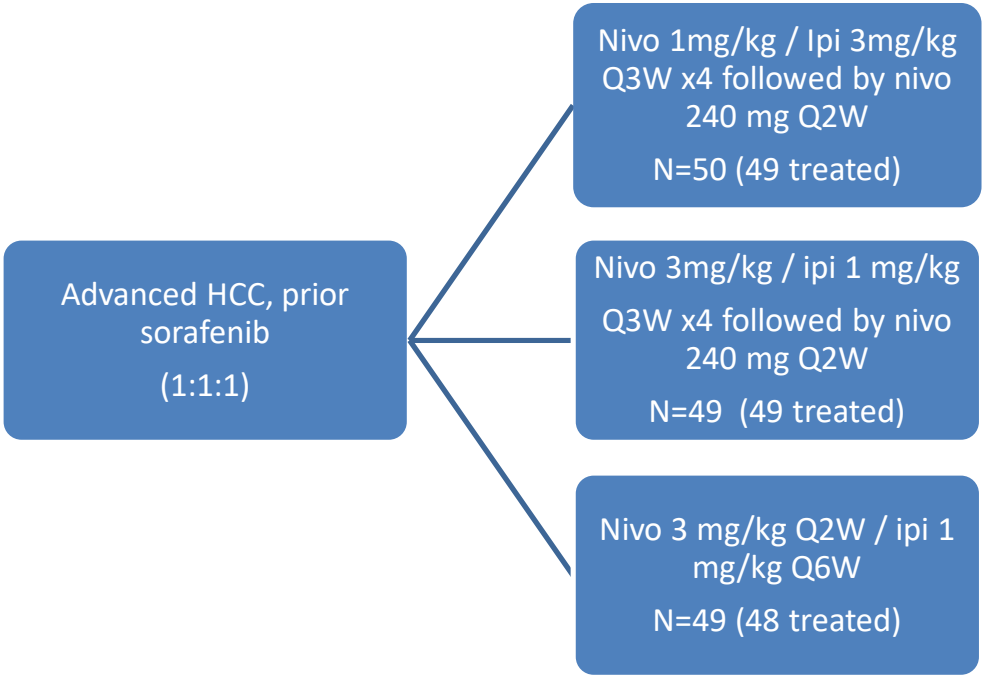
The Treatment Landscape is Changing
Atezolizumab/bevacizumab



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

CheckMate-040 Nivolumab / Ipilimumab Cohort



CheckMate-040 Nivolumab / Ipilimumab

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

Ongoing Nivolumab Trials

	CM-9DW	CM-9DX	CM-74W
N	650	530	765
Interventions	Nivo/ipi vs sorafenib or lenvatinib	Nivo vs placebo	Nivo/ipi/TACE Nivo/placebo/TACE Placebo/placebo/TACE
HCC-line of treatment	1st-line advanced HCC	Post curative resection or ablation	Intermediate stage exceeding BMU7, no prior TACE
Enrollment	Recruiting	Complete	Recruiting
Completion	2023	2023	2026
Primary Endpoints	OS	RFS	Arm A vs C (TTTP, OS)

TACE=transarterial chemoembolization; BMU7=Beyond Milan and Up-to-7; RFS=recurrence free survival; TTTP=time to TACE progression

Monotherapy Benefit/Risk Assessment

Benefits

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

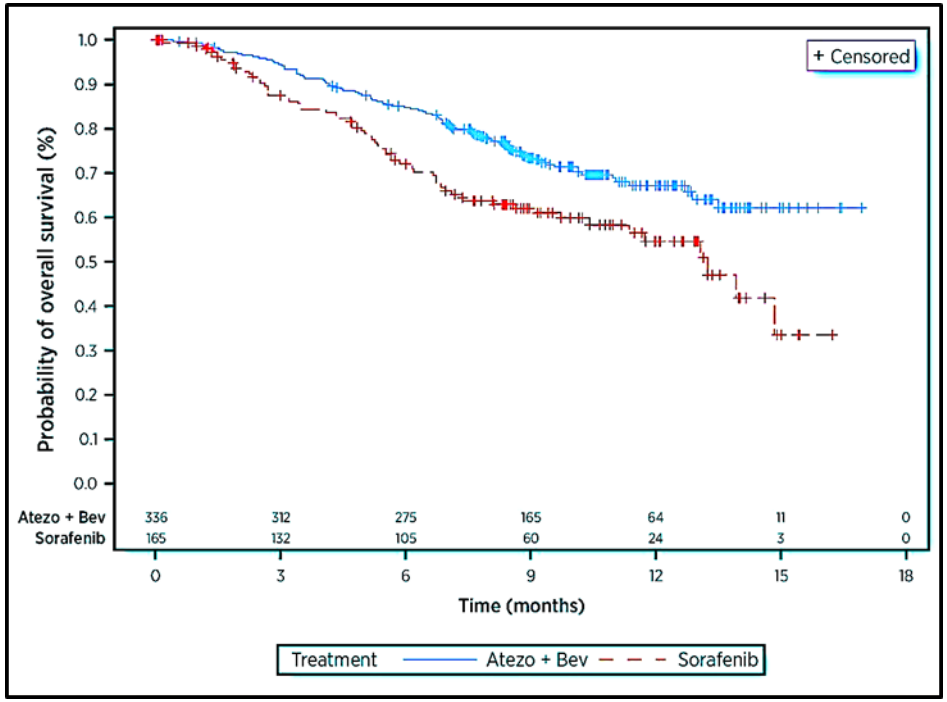
Risks

- 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?



IMbrave150

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

How to Consider Nivolumab in Combination with Ipilimumab

Parameter	Nivolumab (1 mg/kg) and Ipilimumab (3 mg/kg)
N	49
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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. Negative monotherapy trial versus sorafenib in the first-line setting.
4. The combination indication for nivolumab and ipilimumab will be maintained. The response rate of combination therapy is higher than monotherapy.

Should the indication for the monotherapy use of nivolumab in patients previously treated with sorafenib be maintained pending conduct or completion of additional trial(s)?

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