CI-1

Nivolumab (Opdivo®) for Patients With Hepatocellular Carcinoma Who Have Been Previously Treated With Sorafenib

April 29, 2021

Bristol Myers Squibb
Oncologic Drugs Advisory Committee

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Nivolumab (Opdivo®) Introduction

Mathias Hukkelhoven, PhD
Senior Vice President, Global Regulatory & Safety Sciences
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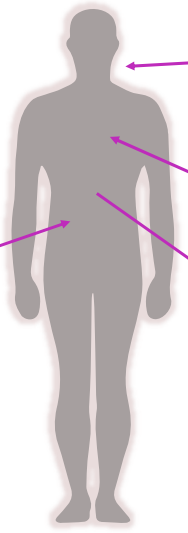
Nivolumab (OPDIVO®): FDA-Approved Cancer Types



- ✓ Squamous cell carcinoma of the head & neck
- ✓ Esophageal cancer
- ✓ Non-small cell lung cancer
- ✓ Malignant pleural mesothelioma
- ✓ Melanoma
- ✓ Urothelial carcinoma
- ✓ Hepatocellular carcinoma
- ✓ Renal cell carcinoma
- ✓ Colorectal cancer
- ✓ Gastric cancer/GEJC

Other:
- ✓ Classical Hodgkin lymphoma

GEJC – gastroesophageal junction cancer

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BMS Is Committed to the Treatment of Patients With HCC With a Broad Clinical Development Program

Early Disease	Intermediate	1st-Line Metastatic	2nd-Line+ Metastatic
CheckMate-9DX Nivolumab	**CheckMate-74W** Nivolumab + TACE ± Ipilimumab	**CheckMate-459** Nivolumab	**CheckMate-040** Nivolumab ± Ipilimumab/TKI
		CheckMate-9DW Nivolumab + Ipilimumab	

Study Ongoing

Study Completed

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Nivolumab Accelerated Approval Indication in Post-Sorafenib HCC and PMR

- Approval granted on September 22, 2017, for the *treatment of patients with **hepatocellular carcinoma (HCC) who have been previously treated with sorafenib***
- Postmarketing Requirement (PMR)*:
  - Conduct and submit the results of a multicenter, randomized trial or trials to verify and describe the clinical benefit of nivolumab over standard therapy based on an improvement in overall survival in patients with advanced hepatocellular carcinoma
- Confirmatory trials for accelerated approvals have historically been conducted in different lines of the same disease

*Original Schedule for Final Report Submission: 09/2020; Revised Schedule for Final Report Submission: 12/2020.

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Nivolumab Accelerated Approval Granted Based on Meaningful Clinical Benefit in CheckMate-040

- Approval based on Phase 1/2 CM-040, which included 154 post-sorafenib HCC patients who received nivolumab across escalation and expansion cohorts
  - Durable responses observed
  - Safety profile consistent with other cancers
- Phase 3 CM-459, evaluating nivolumab vs sorafenib in 1st-line HCC, was intended to serve as the confirmatory trial
  - Encouraging separation seen in the survival curves favoring nivolumab vs sorafenib
  - Primary endpoint of OS not statistically significant (HR 0.85 [95% CI, 0.72-1.02]; p value = 0.0752 [pre-specified statistical boundary of 0.0419])
  - Favorable safety profile with nivolumab

CM-040, CheckMate-040; CM-459, CheckMate-459.

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What You Will Hear Today

Unmet Need Thomas A. Abrams, MD Dana-Farber Cancer Institute Harvard Medical School	• Nivolumab represents an important treatment option for patients with advanced HCC post-sorafenib
Efficacy and Safety Ashwin Sama, MD BMS	• Nivolumab demonstrated clinically meaningful benefit in CM-040 in HCC patients previously treated with sorafenib, with an acceptable safety profile • Delayed separation in the survival curves favoring nivolumab vs sorafenib contributed to the outcome of CM-459
Clinical Development Program in HCC Ian Waxman, MD BMS	• CM-9DX, an ongoing, Phase 3, randomized study of nivolumab vs placebo in HCC patients following resection or local ablation, is well suited to serve as an alternative PMR
Clinical Perspective Anthony B. El-Khoueiry, MD USC Norris Comprehensive Cancer Center	• Nivolumab should remain approved as a treatment option for patients with HCC post-sorafenib while further clinical evaluation allows for confirmation of clinical benefit

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Consultants

Janet Wittes, PhD
President and Founder
WCG - Statistics Collaborative, Inc.

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Unmet Need in HCC

Thomas A. Abrams, MD
Senior Physician
Dana-Farber Cancer Institute
Assistant Professor of Medicine
Harvard Medical School

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Liver Cancer

- Globally, HCC is the 6th most commonly diagnosed malignancy and the 4th leading cause of cancer death[1,2]
  - HCC is the predominant liver cancer, accounting for ~75% of cases[3]
  - Cirrhosis is present in ~80%–90% of HCC patients[4]
- In the United States, liver cancer is a major cause of morbidity and mortality
  - 5-year survival in the United States (2010–2016) = 19.6%[5]
  - 43,000 new cases and 30,000 deaths (2020)[5]

1. Llovet JM, et al. *Nat Rev Dis Primers*. 2021;7(1):6; 2. International Agency for Research on Cancer. GLOBOCAN 2018. IARC (2020); 3. McGlynn KA, et al. *Hepatology*. 2021;73(suppl 1):4-13; 4. Davis GL, et al. *Proc (Bayl Univ Med Cent)*. 2008;21(3):266-280; 5. Surveillance, Epidemiology, and End Result Program (SEER). Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. https://seer.cancer.gov/statfacts/html/livibd.html.

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HCC Presents a Heavy Disease Burden

- Survival rates are extremely low[1]
  - —Common causes of death are tumor progression and cirrhosis complications[2,3]
- Following resection:
  - —~50% of HCC patients have recurrence[4]
  - —Median time to recurrence is <3 years[4]

1. Paradis V. *Recent Results Cancer Res.* 2013;190:21-32; 2. Ismail BES, Cabrera R. *Chin Clin Oncol.* 2013;2(4):34; 3. Dip Borunda AK, et al. ASCO 2011. Abstract e14594; 4. Shah SA, et al. *Surgery.* 2007;141(3):330-339.

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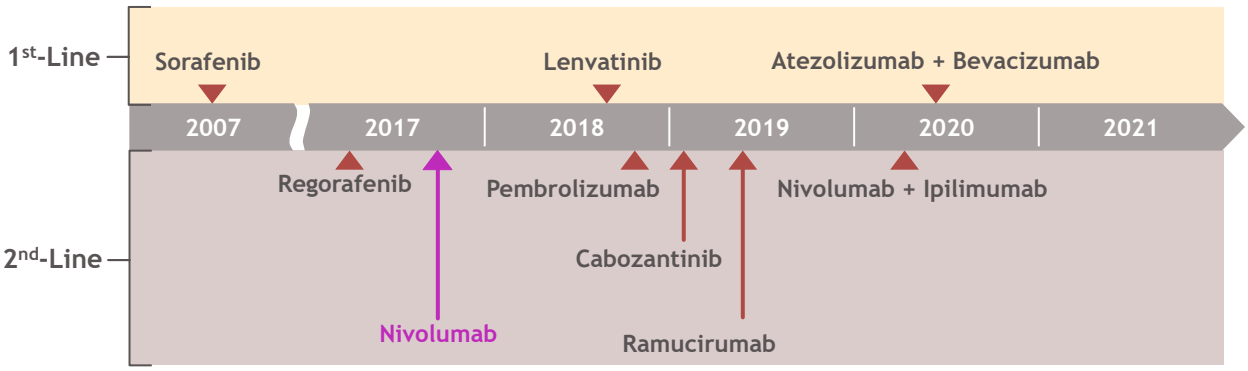
Timeline of FDA Approvals in HCC



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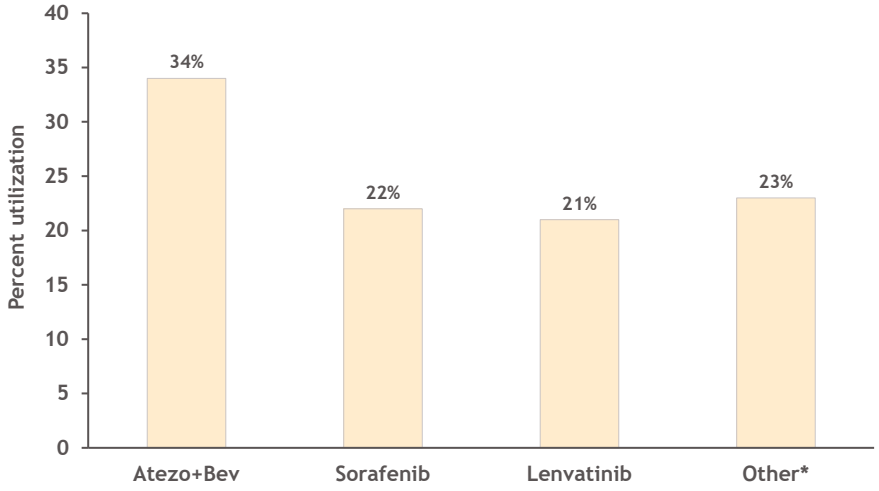
Estimated 1st-Line HCC Real-World Treatment Utilization
January 2020 Through November 2020



Sources: Based on external US claims and electronic health record data (data cut-off: 01/2020 to 11/2020); Flatiron Health (N=375).
*Includes Gemcitabine, Oxaliplatin, Capecitabine, Gem/Oxa combo, Nivolumab, Nivo+Others, Pembro, Pembro+Others, and Other I-O.

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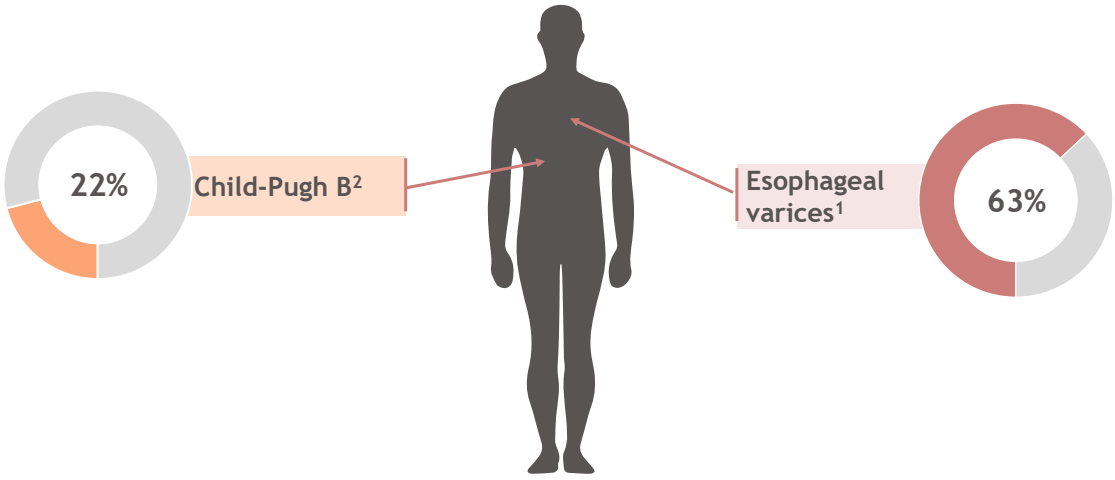
Comorbidities Limit the Use of Atezo/Bev



1. Giannini EG, et al. *Clin Gastroenterol Hepatol*. 2006;4(11):1378-1384; 2. Hsu Cy, et al. *Hepatology*. 2013;57(1):112-119.

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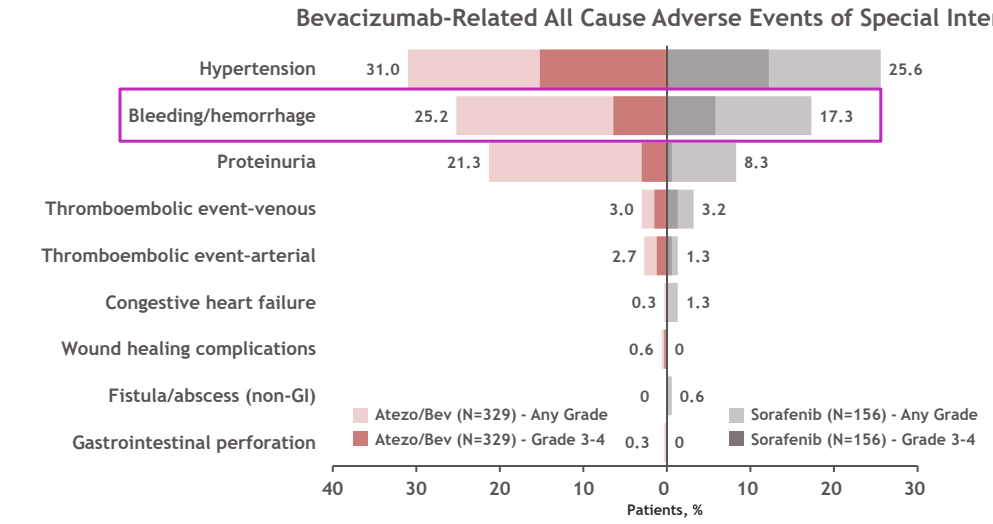
Atezo/Bev-Related Risks May Limit Its Use



Data from Finn RS, et al. N Engl J Med. 2020;382(20):1894-1905.

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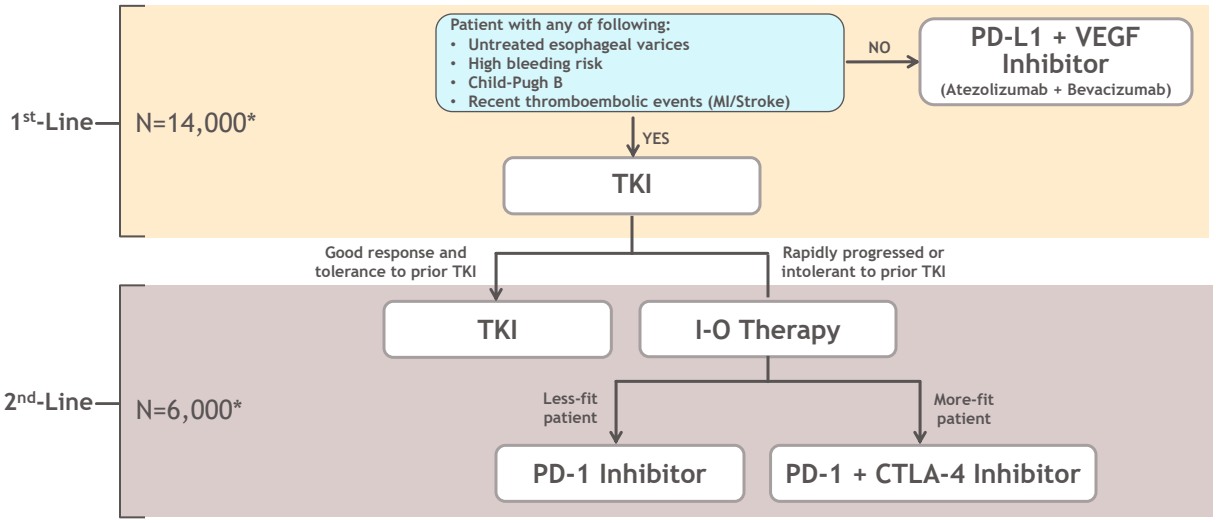
Treatment Flow in Advanced HCC



* NAACCR, 2017 (North American Association of Central Cancer Registries); NCI SEER, 2018 (National Cancer Institute); Hansmann J, et al. *Semin Intervent Radiol*. 2017;34(2):213-219; Weinmann A, et al. *Liver Int*. 2015;35(2):591-600; Ho EY, et al. *Hpb*. 2014;16(8):758-767.

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Efficacy & Safety CheckMate-040 and -459

Ashwin Sama, MD
Clinical Development Lead-HCC
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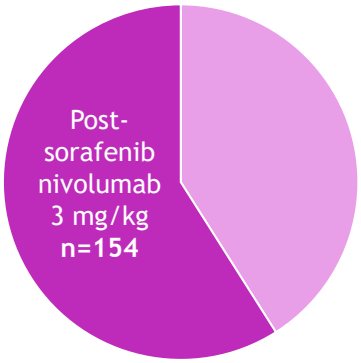
CheckMate-040: Cohort 1/2 Supported Accelerated Approval

Key eligibility criteria

- Advanced HCC not amenable to curative resection
- Child-Pugh scores ≤7 (escalation) or ≤6 (expansion)
- Sorafenib-naïve, intolerant, or progressors
- AST and ALT ≤5 × ULN
- Bilirubin ≤3 mg/dL
- Platelets ≥60,000



All Treated Population (N=262)

Key Endpoints

- Safety and tolerability
- ORR (BICR)
- DoR (BICR)

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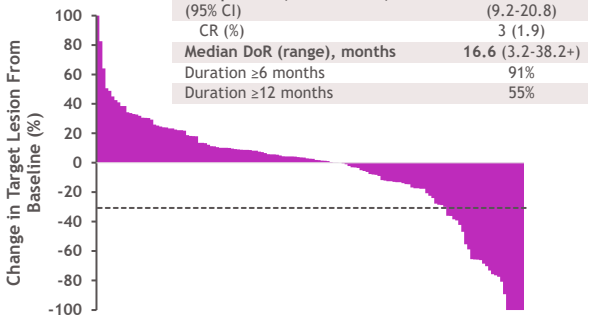
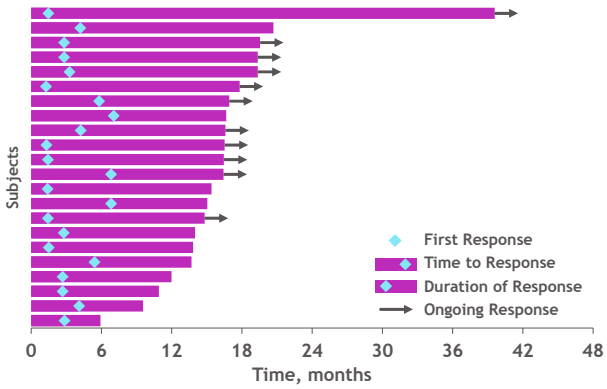
Deep and Durable Responses With Nivolumab

CheckMate-040 - Cohort 1/2

	Nivolumab (n=154)
ORR per BICR; RECIST v1.1, % (95% CI)	14.3 (9.2-20.8)
CR (%)	3 (1.9)
Median DoR (range), months	16.6 (3.2-38.2+)
Duration ≥6 months	91%
Duration ≥12 months	55%





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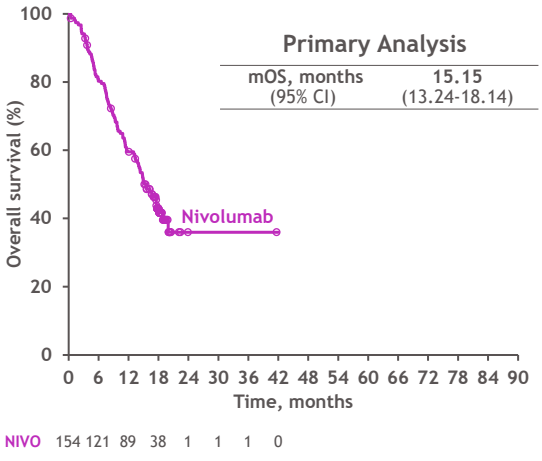
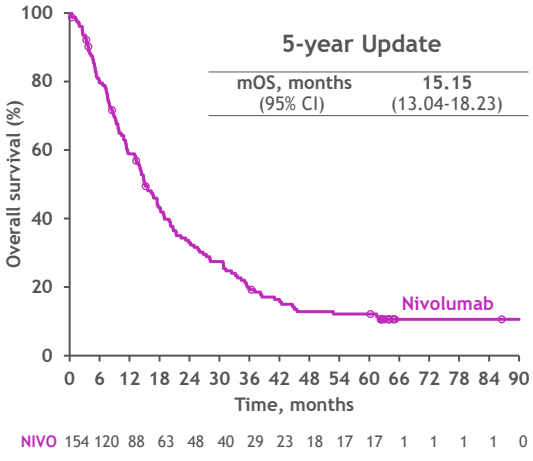
Overall Survival with Post-Sorafenib Nivolumab 3 mg/kg

CheckMate-040 - Cohort 1/2





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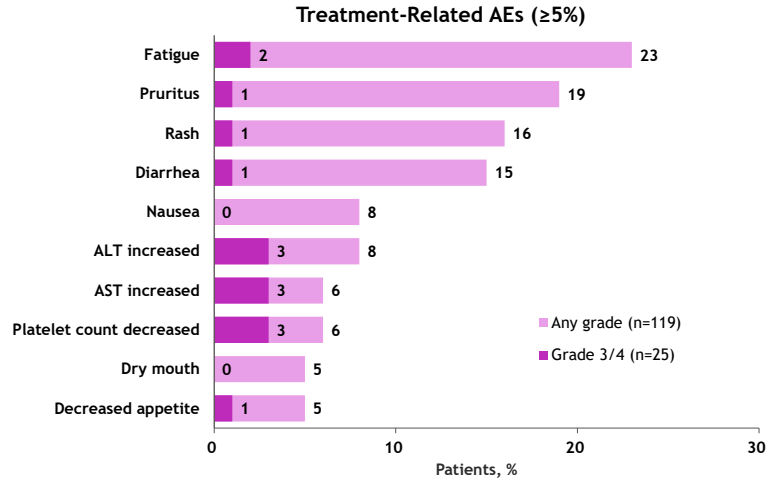
Nivolumab Safety in HCC Is Consistent With Established Safety Profile

CheckMate-040 - Cohort 1/2



- 5 treatment-related AEs leading to discontinuation
  - 2 ALT increases
  - 1 polyarthritis
  - 1 pneumonitis
  - 1 stomatitis
- 1 study drug toxicity (pneumonitis) leading to death

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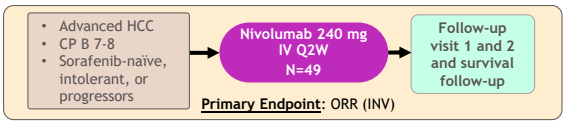
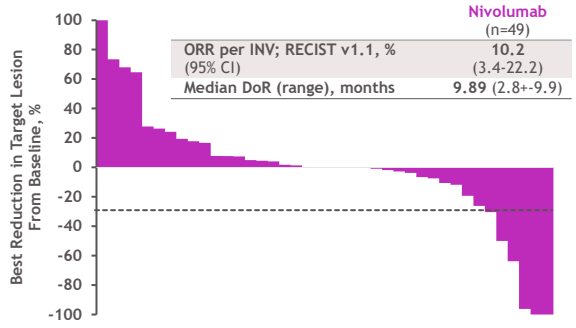
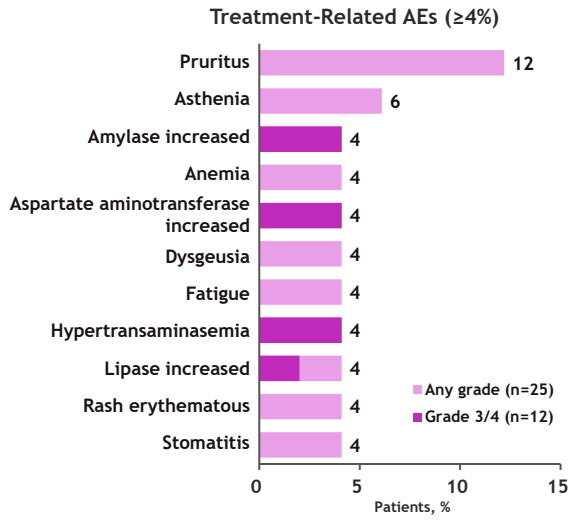
Consistent Results Observed in Child-Pugh B

CheckMate-040 - Cohort 5







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Phase 3 – 1st-Line Nivolumab vs Sorafenib
Checkmate-459

Key eligibility criteria
- aHCC not eligible for surgical and/or LRT;
- Systemic therapy naive
- Child-Pugh class A
- ECOG PS 0 or 1

Stratification factors
- Etiology (HCV vs non-HCV)
- Vascular invasion and/or extrahepatic spread (present vs absent)
- Geography (Asia vs non-Asia)

R 1:1

N=743

Nivolumab 240 mg IV Q2W n=371

Sorafenib 400 mg PO BID n=372

Unacceptable toxicity or disease progression

Endpoints:
- Primary: OS
- Key Secondary: ORR (BICR), PFS (BICR)

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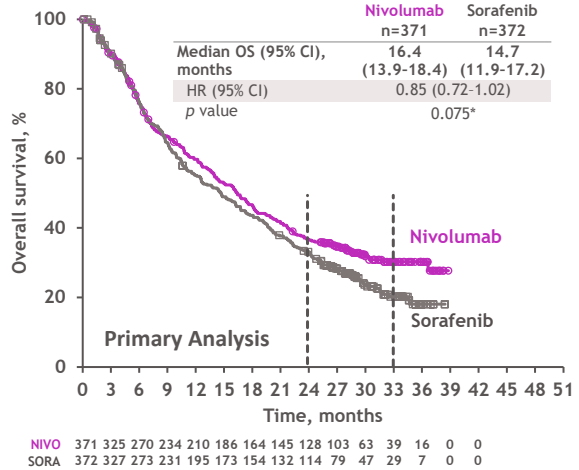
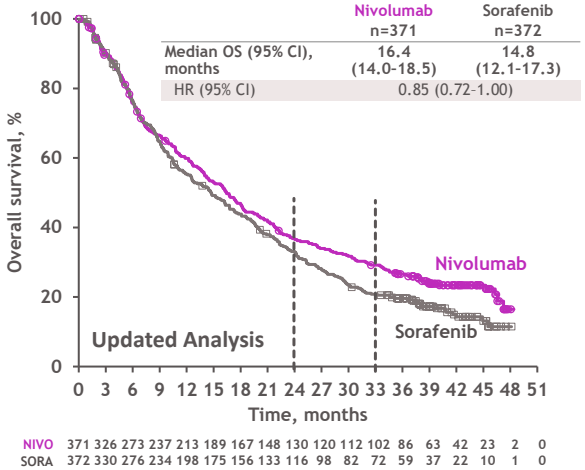
Survival Curves Separate Beyond 8 Months
Separation Maintained With Longer Follow-up
CheckMate-459





*Pre-specified statistical boundary: 0.042

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Potential Reasons OS Was Not Statistically Significant
CheckMate-459

- The observed longer delayed separation (8 months vs 5 months) in the OS curves
  - Reduced the statistical power from 90% to 50%
  - Piecewise hazard ratios:
    - First 8 months: 1.06 (95% CI, 0.81-1.37)
    - After 8 months: 0.72 (95% CI, 0.57-0.91)
- With observed longer delayed separation, sufficient follow-up is needed to appropriately capture nivolumab effect
- Observed longer delay potentially impacted by subsequent systemic therapy use (46% sorafenib arm, 38% in nivolumab arm), including high use of IO post-sorafenib (20%)

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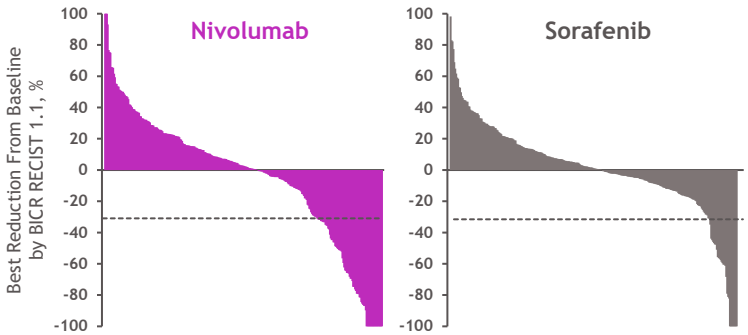
CE-10

Nivolumab Associated With a Higher Response Rate and Deeper Tumor Reduction Relative to Sorafenib
Checkmate-459



	Nivolumab n=371	Sorafenib n=372
ORR, n (%)	57 (15)	26 (7)
CR	14 (4)	5 (1)
PR	43 (12)	21 (6)
SD	130 (35)	180 (48)
Odds Ratio (95% CI)	2.41 (1.48-3.92)	
Median Duration (range), months	23.3 (3.1-34.5+)	23.4 (1.9+-28.7+)

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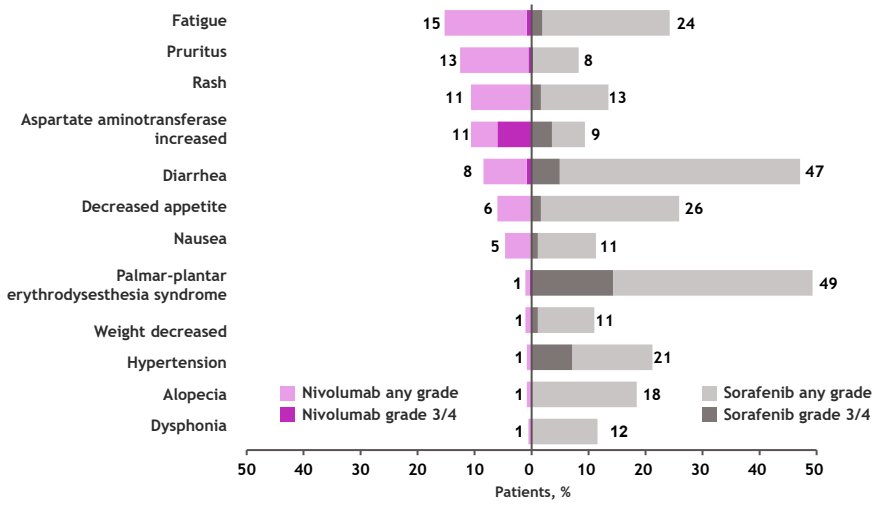
Summary of Treatment-Related Adverse Events (≥10%)
CheckMate-459



- TRAE leading to discontinuation: 7.4% with nivolumab vs 11.6% with sorafenib
- 4 deaths with nivolumab vs 1 death with sorafenib due to study drug toxicity

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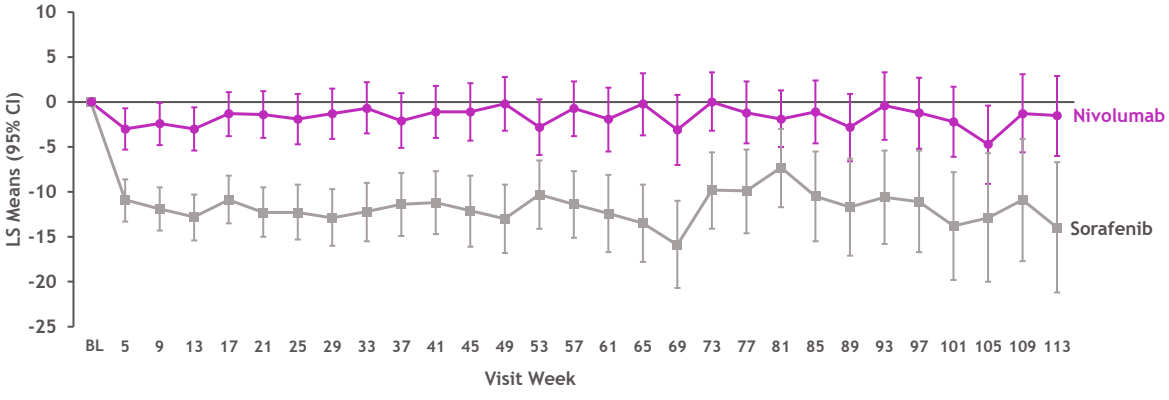
CE-12

Better HRQoL With Nivolumab vs Sorafenib (FACT-Hep)
CheckMate-459



Nivolumab (n=327)	312	291	236	212	166	145	124	112	103	97	90	80	73	70	69	60	61	56	54	48	49	43	40	38	36	37	36	32	32
Sorafenib (n=307)	290	273	216	170	139	123	99	78	66	60	51	44	37	38	41	36	33	31	25	22	21	17	16	17	15	13	11	11	10

The 95% nominal CIs are presented for descriptive purposes. Completion rates ≥79% through Week 113. Clinically important difference in QoL observed with an overall MID of 8. A longitudinal mixed-effects model was used to analyze PRO data from all on-treatment visits through Week 113 when both treatment arms still had ≥10 patients on treatment.

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CheckMate-040 and -459 Overall Summary

- Nivolumab led to deep and durable responses in CM-040
  - —Responses also observed in Child-Pugh B patients
- CM-459 failed to demonstrate statistical significance despite maintained separation of the Kaplan-Meier curves
  - —Response rate consistent with CM-040
- Safety of nivolumab was similar to that seen in other cancers
  - —Favorable and differentiated safety profile compared to sorafenib in CM-459
- HRQoL exploratory analysis favored nivolumab, with reduced side-effect burden vs sorafenib in CM-459

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Nivolumab HCC Clinical Development Program

Ian Waxman, MD
GI Development Team Lead
Bristol Myers Squibb

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CT-2

Nivolumab HCC Clinical Development Program

Completed Studies

Study Phase	Study ID	Treatment Stage	Treatment(s) Evaluated
Phase 1/2	CheckMate-040	1st-Line/2nd-Line+ Advanced/Metastatic	Nivolumab ± Ipilimumab/TKI
Phase 3	CheckMate-459	1st-Line Advanced/Metastatic	Nivolumab vs Sorafenib

Ongoing Phase 3 Studies

Study ID	Study Start/ Enrollment Status	Treatment Stage	Treatment(s) Evaluated	Final Analysis
CheckMate-9DX	Dec 2017/Complete	Early (Adjuvant)	Nivolumab vs Placebo	2023
CheckMate-9DW	Sep 2019/Recruiting	Advanced/Metastatic	Nivolumab + Ipilimumab vs Sorafenib/Lenvatinib	2023
CheckMate-74W	Sep 2020/Recruiting	Intermediate (TACE)	Nivolumab + TACE ± Ipilimumab vs TACE	2026

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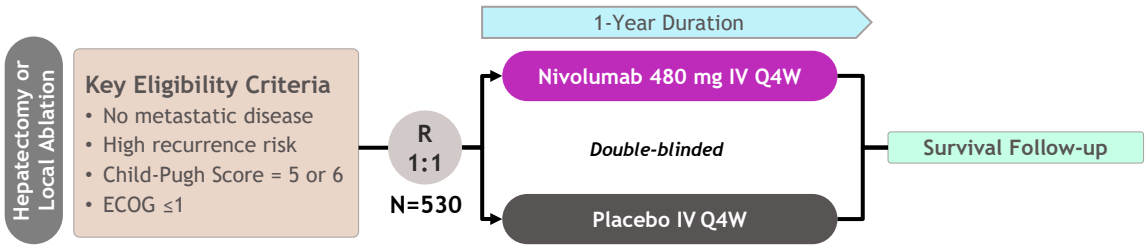
CheckMate-9DX: Fully Enrolled Phase 3 Study Evaluating Nivolumab Monotherapy in the Adjuvant Setting



Stratification factors
- Etiology (HBV vs HCV vs Uninfected)
- Curative Therapy (Resection vs Ablation)
- Microvascular Invasion (Yes vs No)

Endpoints
- Primary: Recurrence-Free Survival (BICR)
- Key Secondary: Overall Survival

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CheckMate-9DX Study Design Supports Its Use as PMR

- Recurrence-free survival (RFS)/disease-free survival (DFS) can be considered a direct measure of clinical benefit
  - Important endpoint when survival may be prolonged
  - Have been used for traditional approval for breast cancer, colorectal cancer, gastrointestinal stromal tumors, melanoma, and renal cell carcinoma
  - FDA feedback on CM-9DX indicated that a clinically meaningful improvement in RFS, that is statistically persuasive with an acceptable benefit-risk profile, may support approval
- Adjuvant nivolumab is anticipated to show improved RFS in early HCC
  - Benefit observed in 3 phase 3 adjuvant studies of nivolumab (melanoma, esophageal cancer, bladder cancer)
  - Preliminary activity of nivolumab demonstrated in early HCC[1]
- Comparison of nivolumab to placebo in CM-9DX allows for clear characterization of treatment effect with the same regimen in the same disease
  - Targets similar treatment effect (HR) as other adjuvant studies with delayed separation and cure rates assumed
  - OS will be tested hierarchically if RFS is significant

1. Kaseb A, et al. Final results of a randomized, open label, perioperative phase II study evaluating nivolumab alone or nivolumab plus ipilimumab in patients with resectable HCC. *J Clin Oncol.* 2020 38:15_suppl, 4599-4599.

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Overall Summary and Conclusions

- Nivolumab received accelerated approval for the treatment of HCC post-sorafenib in 2017 based on durable responses observed in CM-040
- Significant unmet need remains in 2nd-line HCC, given the expected continued use of 1st-line sorafenib, despite approval of Atezo/Bev
  - Nivolumab remains an important treatment option for these patients
- CM-9DX is proposed as the PMR because it can verify the benefit provided by nivolumab monotherapy in HCC

CP-1

Nivolumab HCC Clinical Perspective

Anthony B. El-Khoueiry, MD
Associate Professor of Clinical Medicine
Phase I Program Director
Director of Clinical Investigations Support Office
USC Norris Comprehensive Cancer Center

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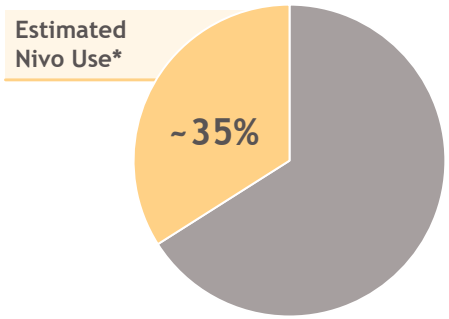
CP-2

Clinical Rationale for Nivolumab Will Remain Despite Recent Treatment Landscape Changes



Treatment Use in 2nd-Line+ HCC

- Efficacy observed across subgroups in CM-040, including Child-Pugh B patients
- All IO-naive patients going into 2nd-line should have option to use nivolumab
  - —Patients who tolerated, but progressed on TKI therapy, could experience benefit from nivolumab

*Based on external US claims and electronic health record data (data cut-off: 01/2020 to 11/2020); 34% based on IQVIA Claims (N=593); 35% based on Flatiron Health (N=159).

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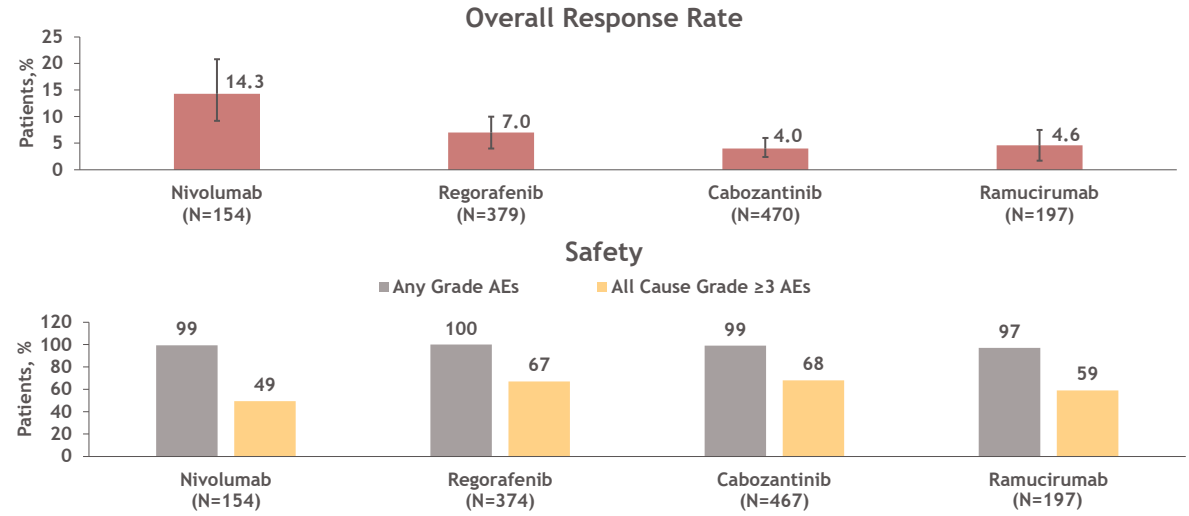
Nivolumab Offers a More Favorable Benefit Risk Than 2nd-Line VEGF Targeted Options



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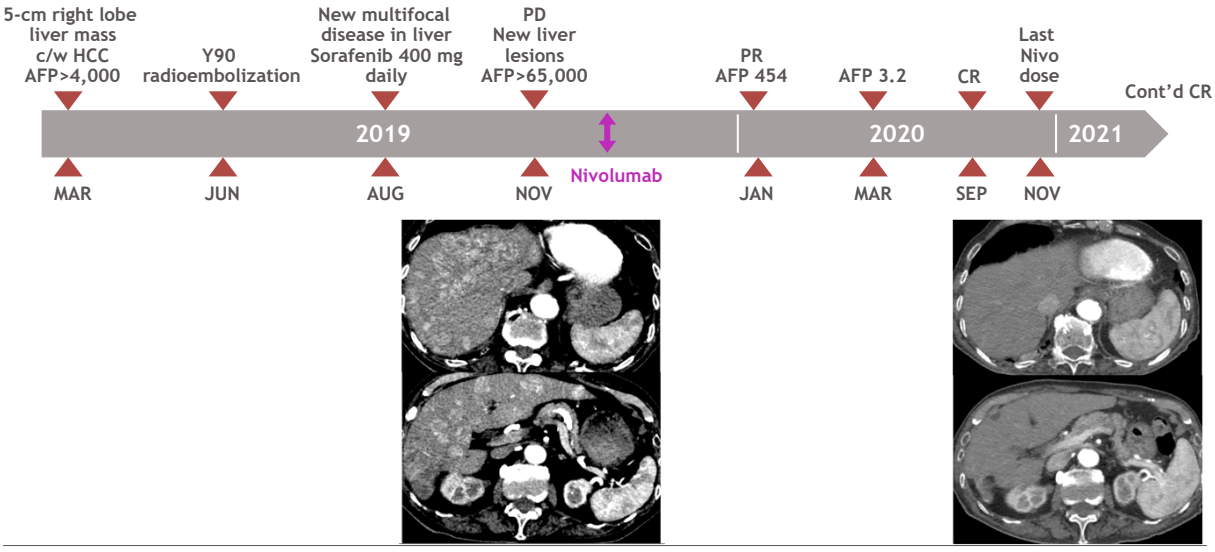
CP-4

Case Study: 88 Year-Old Asian Male



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