PRODVANCE 22

CHEMOTHERPY IN HEPATIC TUMORS- ADVANCES IN TARGETED THERAPY

Background

- **Liver cancer**
  - Fifth most common cancer
  - Second most frequent cause of cancer-related death globally
    - 854,000 new cases and 810,000 deaths per year
    - 7% of all cancers

  - **HCC** - 85- 90% of primary liver cancers

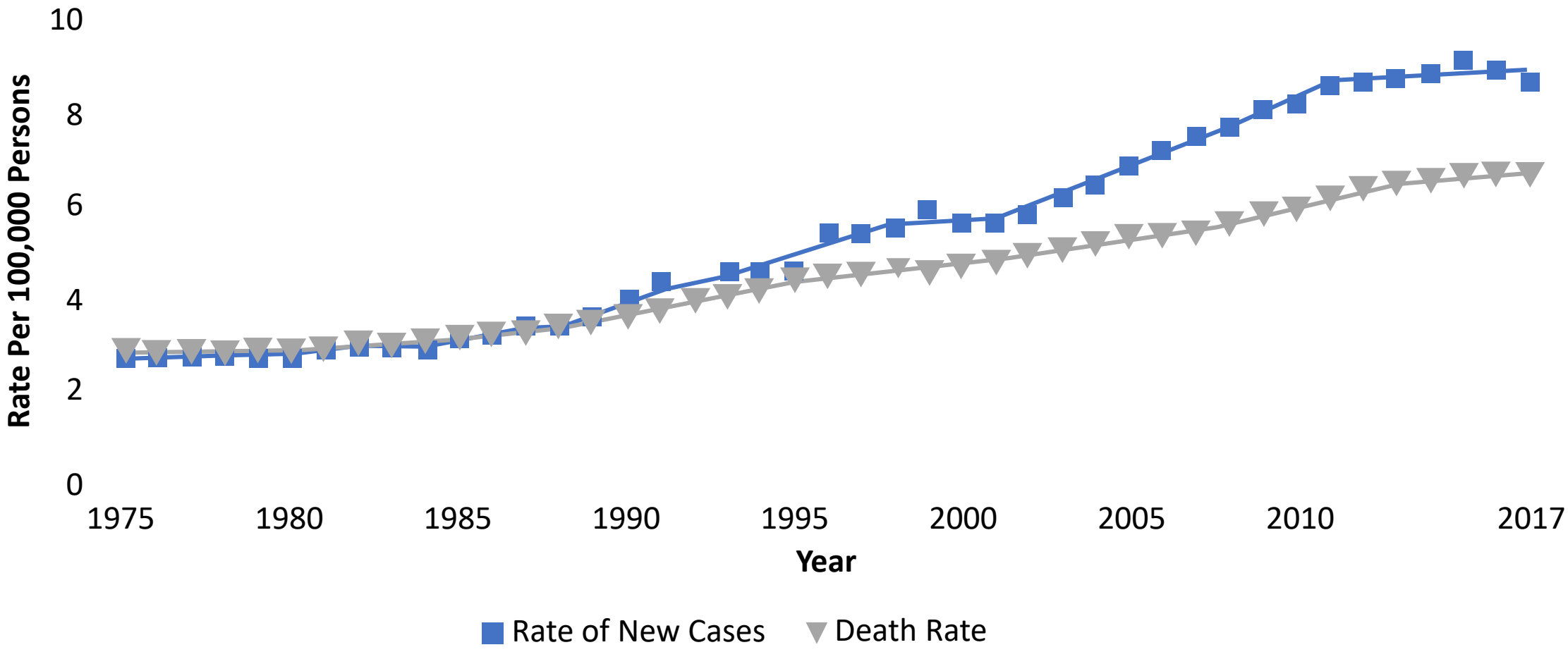
  - **Cholangiocarcinoma** 10%
  - **Fibrolamellar carcinoma** 0.5 - 1%

  - Mesenchymal Cancers of the Liver
  - **Angiosarcoma of the liver**
  - **Epithelioid haemangioendothelioma**

  - **Secondary liver cancer** - Tumors metastatic to the liver - more common than primary tumors

- Akinyemiju T, et al. JAMA Oncol 2017;3:1683–91;
- EASL CPG HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019

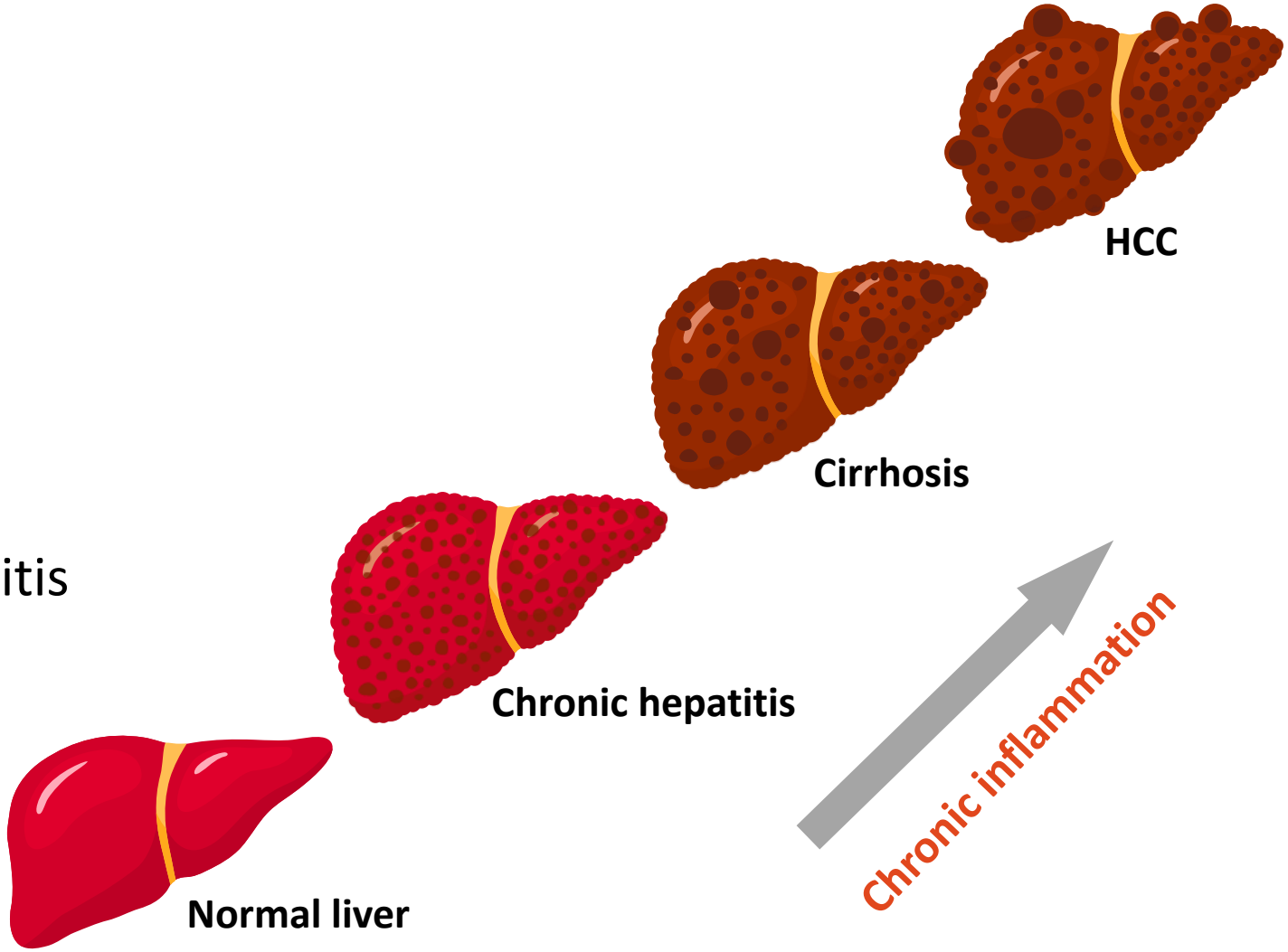
Liver Cancer Incidence and Mortality are Increasing



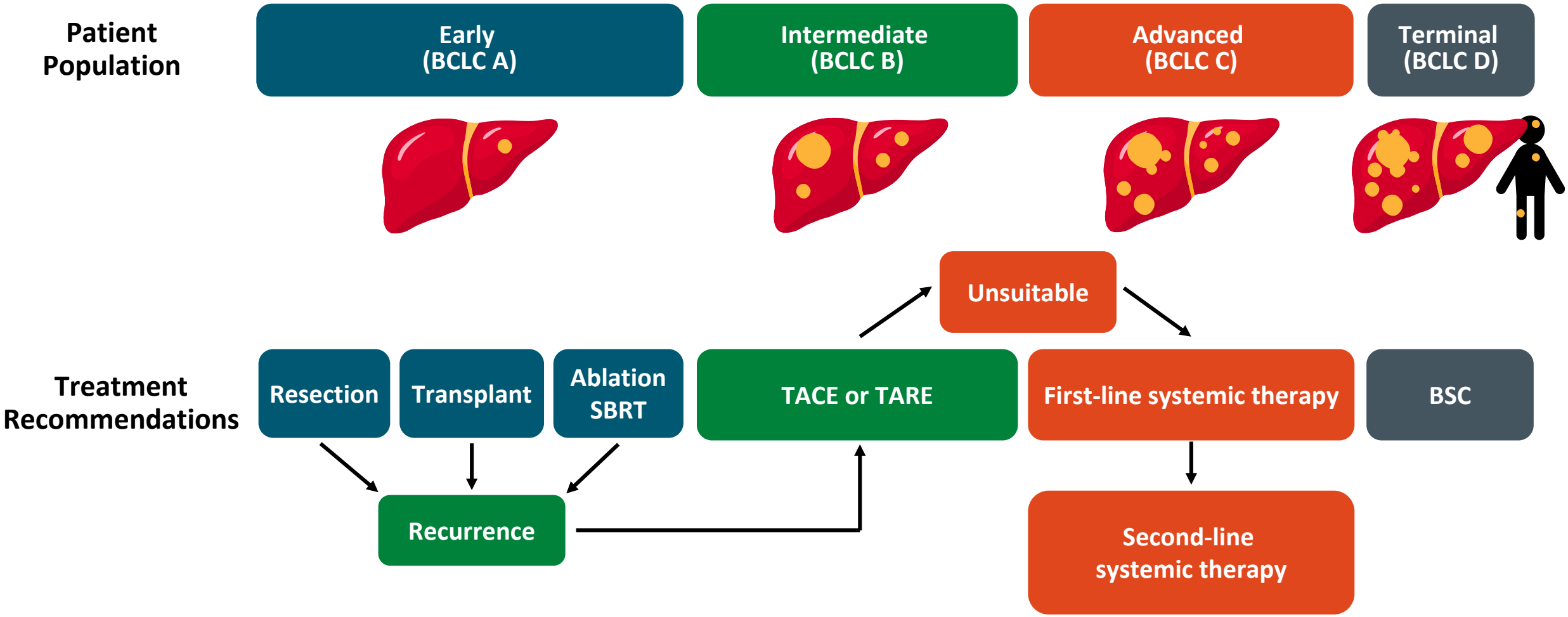
SEER Database.

Most HCC - Setting of Cirrhosis

Hep B infection
Hep C infection
Alcoholic liver disease
Nonalcoholic steatohepatitis



BCLC Staging System + Treatment Recommendations



Bruix. Gastroenterology. 2016;150:835. Llovet. Liver Transpl. 2004;10(2 suppl 1):S115.

Therapeutic options :- In advanced disease

- Immune checkpoint inhibitors (ICI)
- Adoptive transfer of immune cells
- Bispecific antibodies
- Vaccines
- Oncolytic viruses

- **HCC**- Programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- **Advanced CCA** - PD-1 ICIs antitumor responses in a minority of select patients. Adoptive transfer- promise in trials of met disease

Hepatocellular Carcinoma - The Challenge of the Tumor Microenvironment

- **Low tumor mutational burden** - Fewer somatic mutations within the tumor, reduced number of tumor-specific neoantigens lesser adaptive immune response (Nat. Genet. 2016, 48, 500–509.)
- **Immunosuppressive microenvironment** that facilitates tumor development. “immune-tolerant” environment due to its need to be accepting of new antigens encountered from food and microbial antigens delivered from the gastrointestinal tract (Crispe, I.N. The liver as a lymphoid organ. Annu. Rev. Immunol. 2009, 27, 147–163.)
- **Anti-inflammatory mediators** can be increased in patients with cirrhosis (Cancer Res. 2005, 65, 2457–2464.)

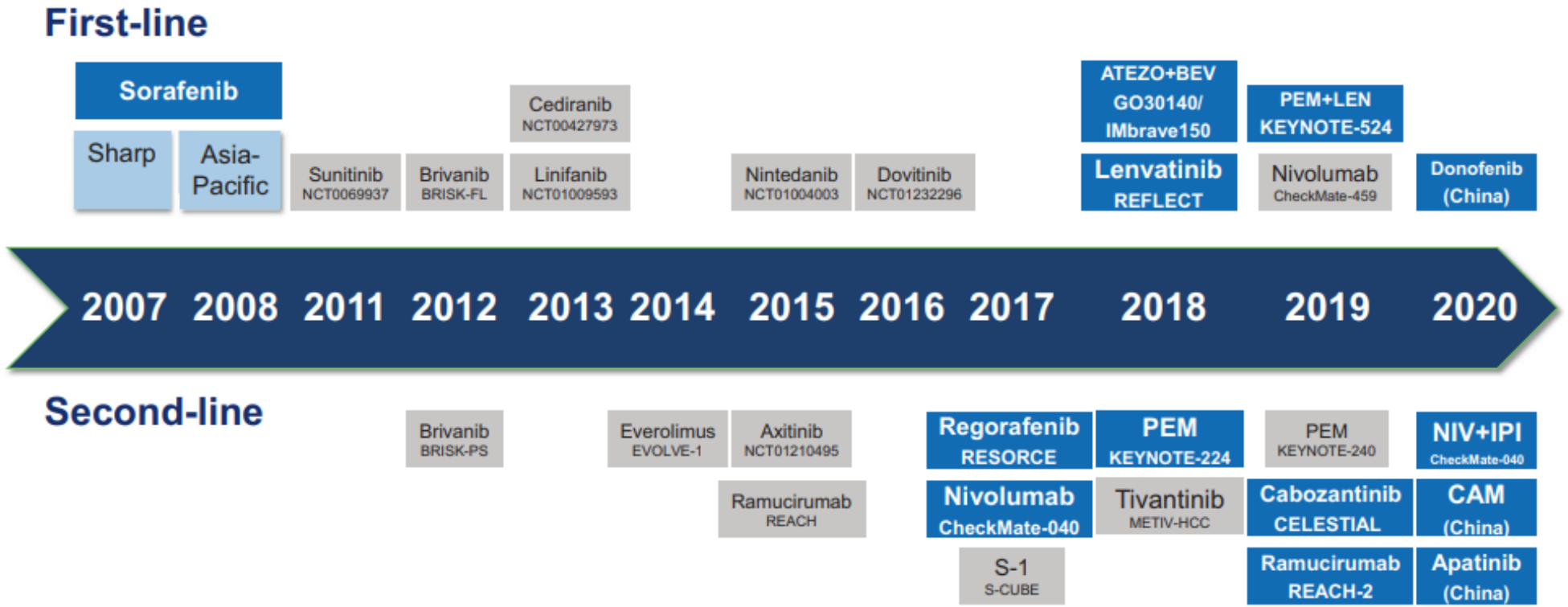
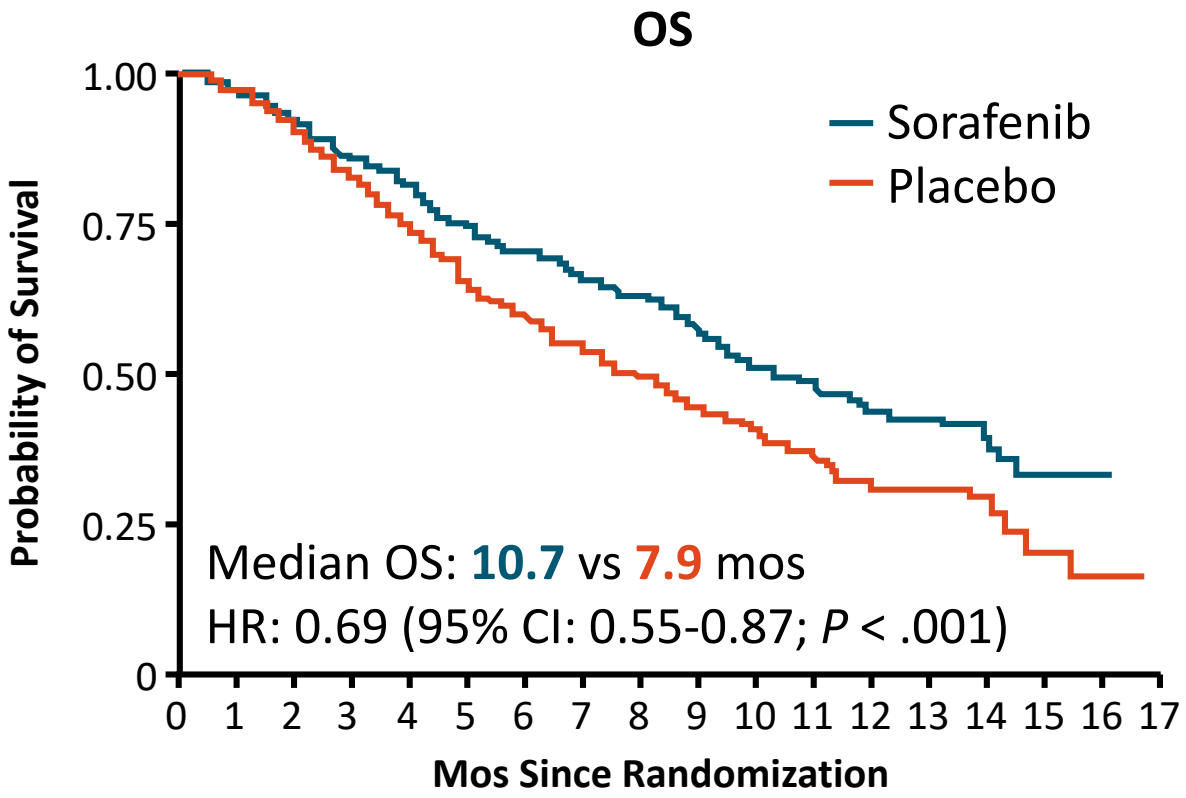
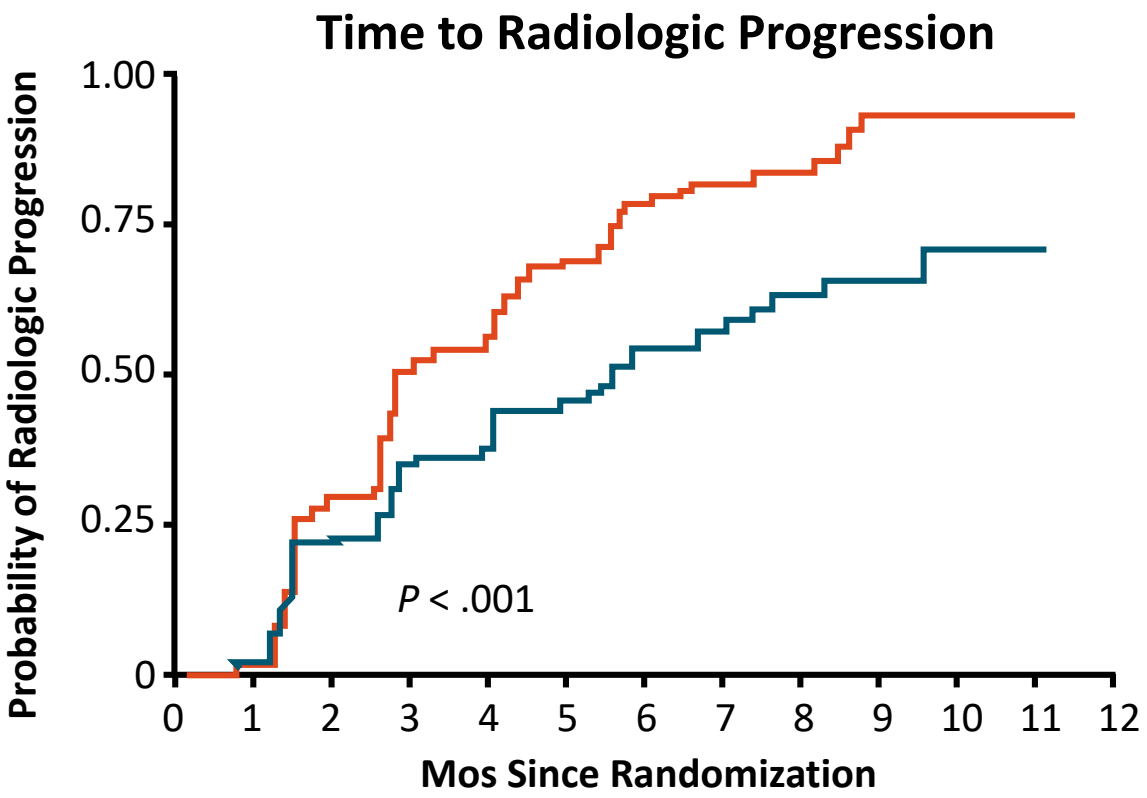


Fig. 1 Overview of the targeted agents approved for HCC. ATEZO atezolizumab, BEV bevacizumab, CAM camrelizumab, LEN lenvatinib, PEM pembrolizumab, NIV nivolumab, IPI ipilimumab

SHARP: Frontline Sorafenib Improves Survival for Advanced HCC

- Randomized, double-blind phase III trial of **sorafenib** vs **placebo** for patients with advanced HCC, Child-Pugh A (N = 602)





Llovet. NEJM. 2008;359:378.

FDA-Approved Systemic Therapy for Advanced HCC

Sorafenib

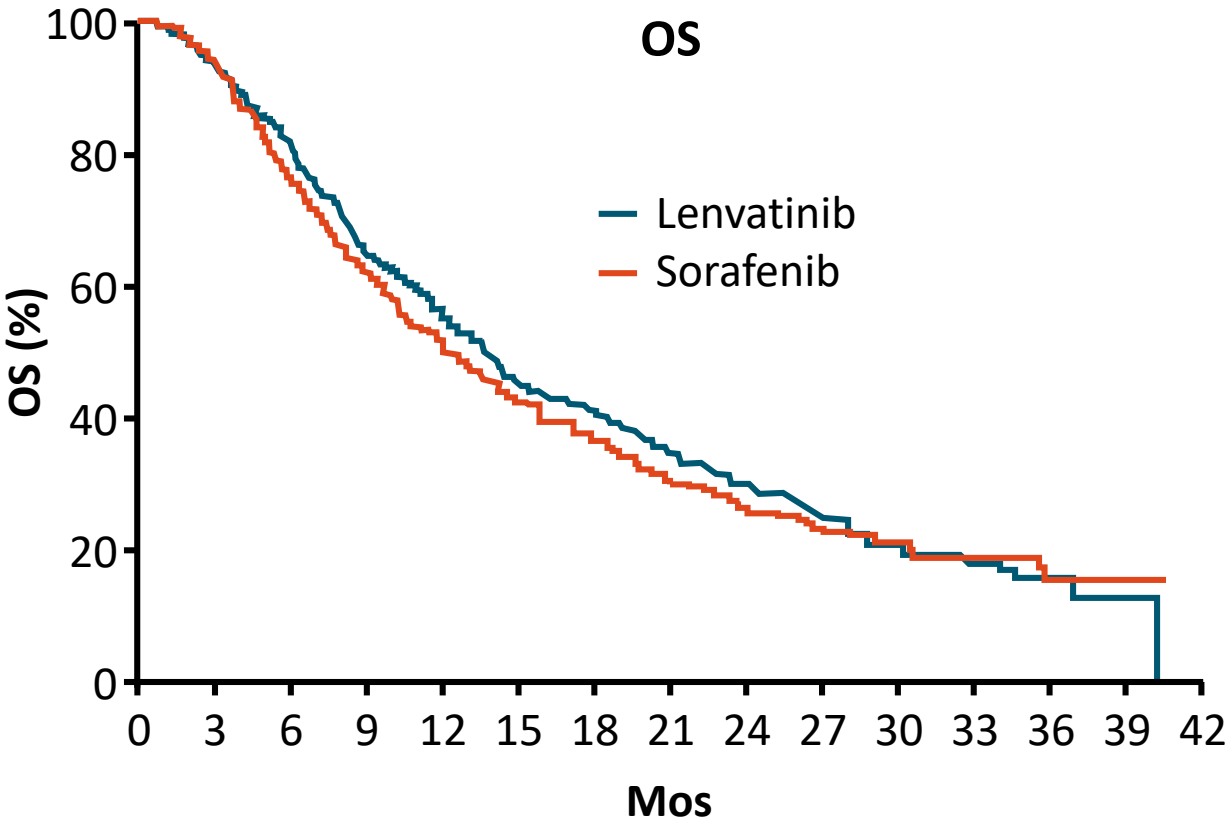
First Line
Lenvatinib
Atezolizumab + bevacizumab

Second Line and Beyond
Regorafenib
Nivolumab*
Pembrolizumab*
Cabozantinib
Ramucirumab
Nivolumab ± ipilimumab*

*Accelerated approval.

REFLECT: Frontline Lenvatinib Is Noninferior to Sorafenib for OS but Provides Better Response Rates

- Randomized, open-label, noninferiority phase III trial of **lenvatinib** vs **sorafenib** for patients with unresectable HCC, Child-Pugh A/BCLC stage B or C (N = 954)



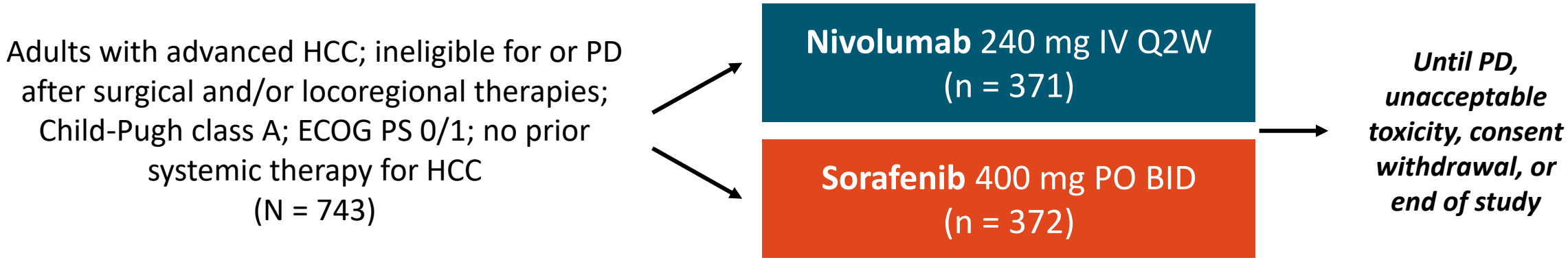
Outcome	Lenvatinib (n = 478)	Sorafenib (n = 476)	HR
mOS, mos (95% CI)	13.6 (12.1-14.9)	12.3 (10.4-13.9)	0.92 (0.79-1.06)
mPFS, mos (95% CI)	7.4* (6.9-8.8)	3.7 (3.6-4.6)	0.66 (0.57-0.77)
mTTP, mos (95% CI)	8.9* (7.4-9.2)	3.7 (3.6-5.4)	0.63 (0.53-0.73)
ORR, n (%)	115 (24.1)*	44 (9.2)	

**P* < .0001 vs sorafenib.

Kudo. Lancet. 2018;391:1163.

CheckMate 459: Nivolumab vs Sorafenib as First-line Therapy for Advanced HCC

- International, open-label, randomized phase III trial (minimum follow-up: 22.8 mos)



- Primary endpoint: OS
  - Predefined threshold for statistical significance: HR of 0.84 (*P* = .0419)
- Secondary endpoints: PFS, ORR, association between PD-L1 expression and efficacy

Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

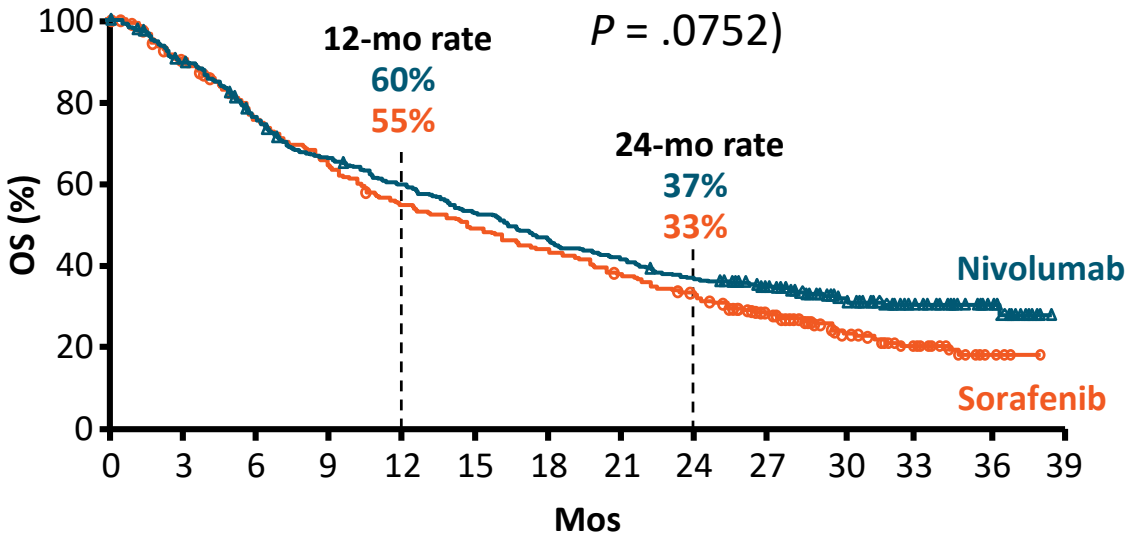
CheckMate 459: OS and PFS

Median OS, Mos (95% CI)

Nivolumab 16.4 (13.9-18.4)

Sorafenib 14.7 (11.9-17.2)

HR: 0.85 (95% CI: 0.72-1.02; *P* = .0752)

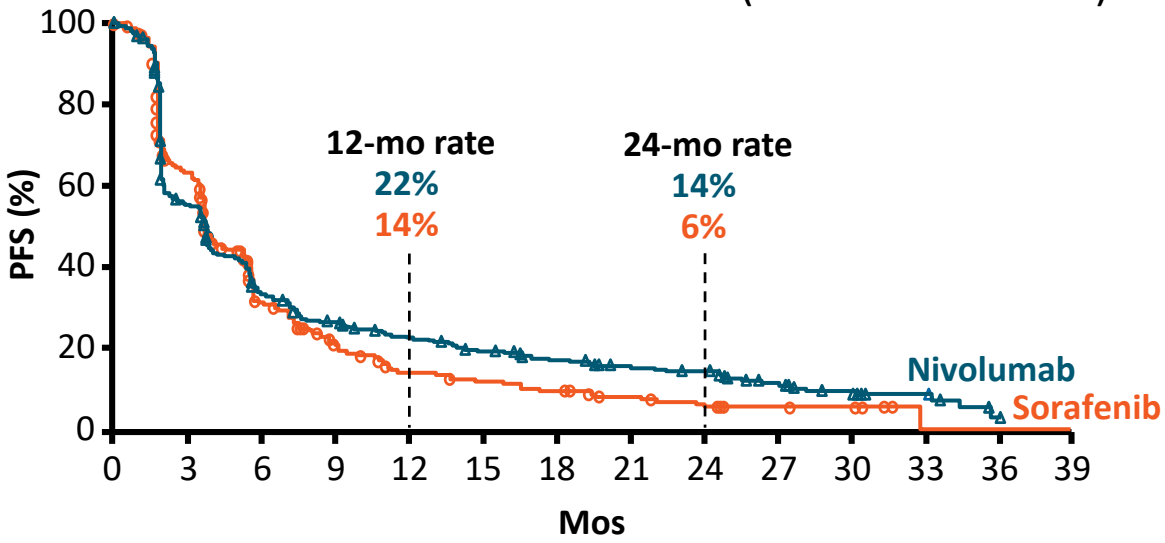


Median PFS, Mos (95% CI)

Nivolumab 3.7 (3.1-3.9)

Sorafenib 3.8 (3.7-4.5)

HR: 0.93 (95% CI: 0.79-1.10)

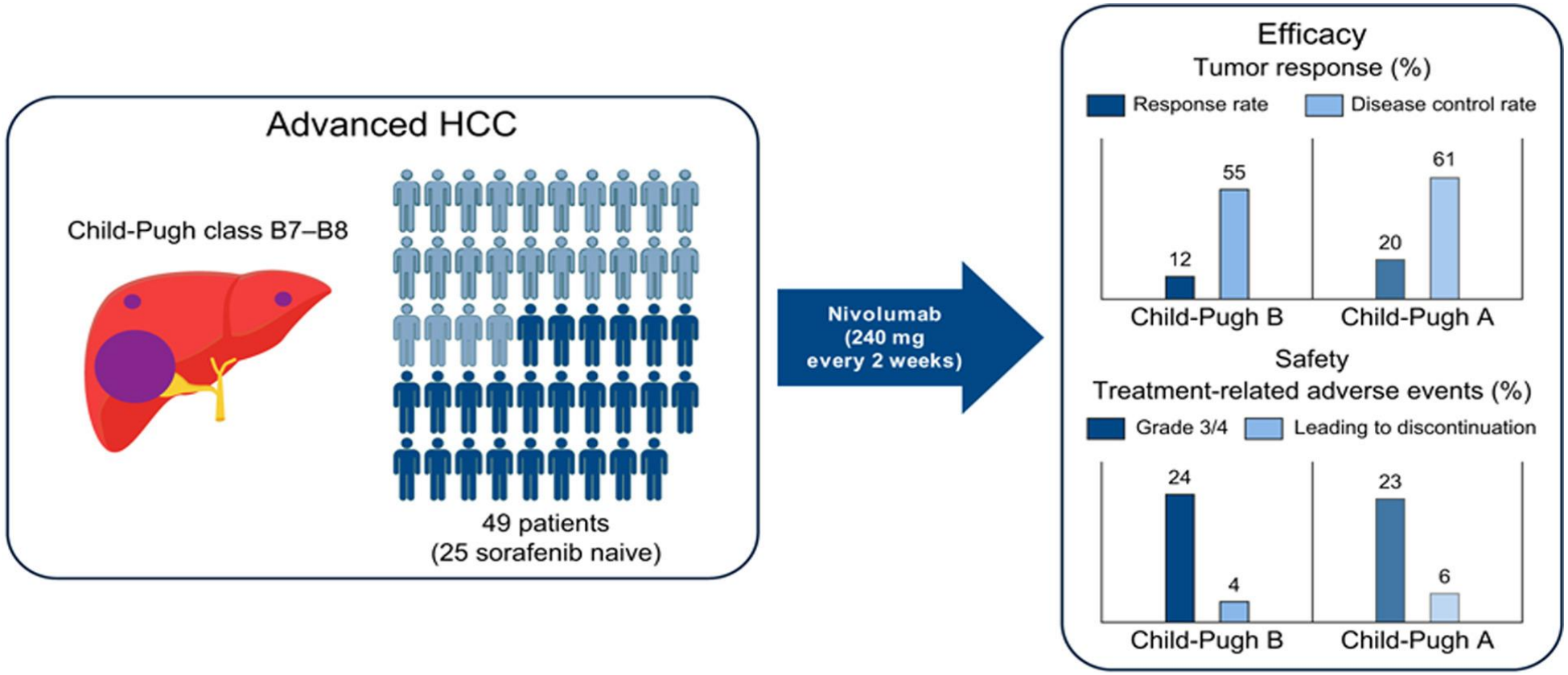


- The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit
- ORR: nivolumab, 15%; sorafenib, 7%

Yau. ESMO 2019. Abstr LBA38_PR.

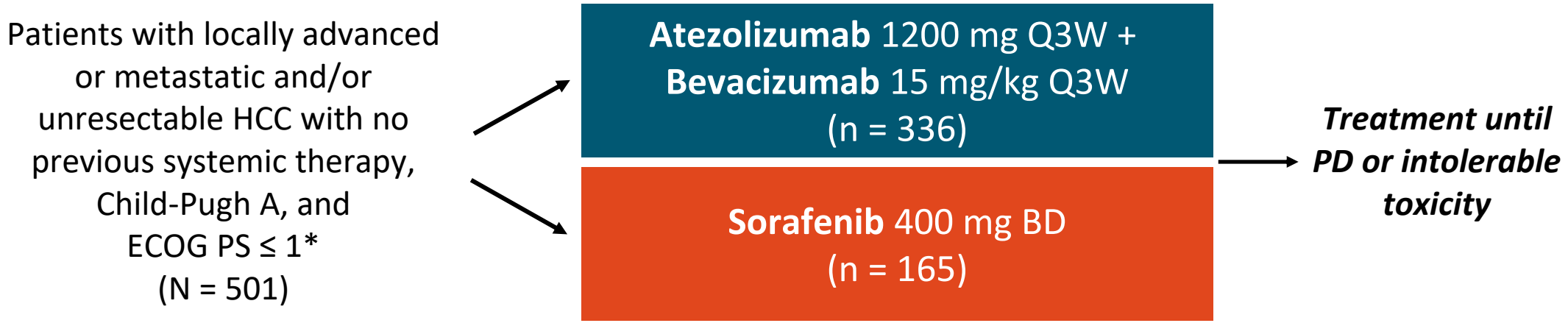
CheckMate 040: Nivolumab for Advanced HCC

Phase I/II study of Nivolumab in advanced HCC and CP B cirrhosis



IMbrave150: Atezolizumab + Bevacizumab vs Sorafenib for First-line Treatment of HCC

- Multicenter, randomized, open-label phase III trial[1]
  - GO30140: randomized phase Ib study showed potential benefit of atezolizumab + bevacizumab for patients with advanced HCC (ORR 36%)[2]

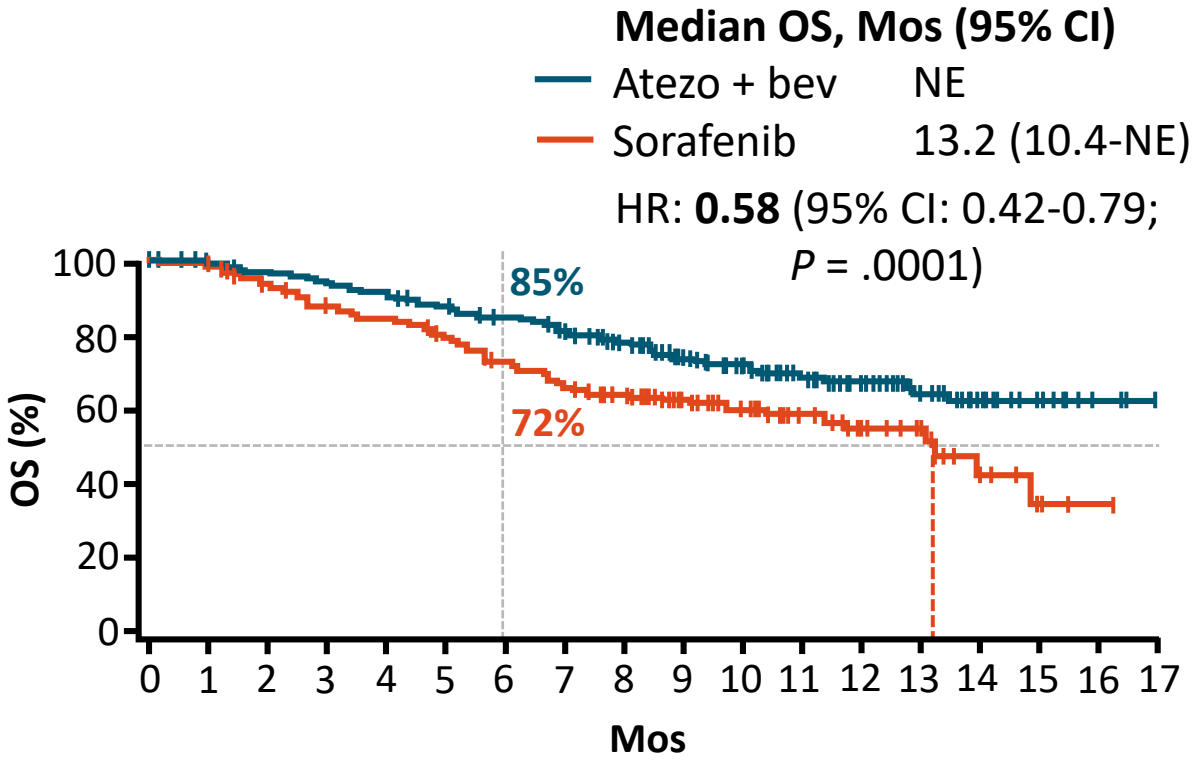


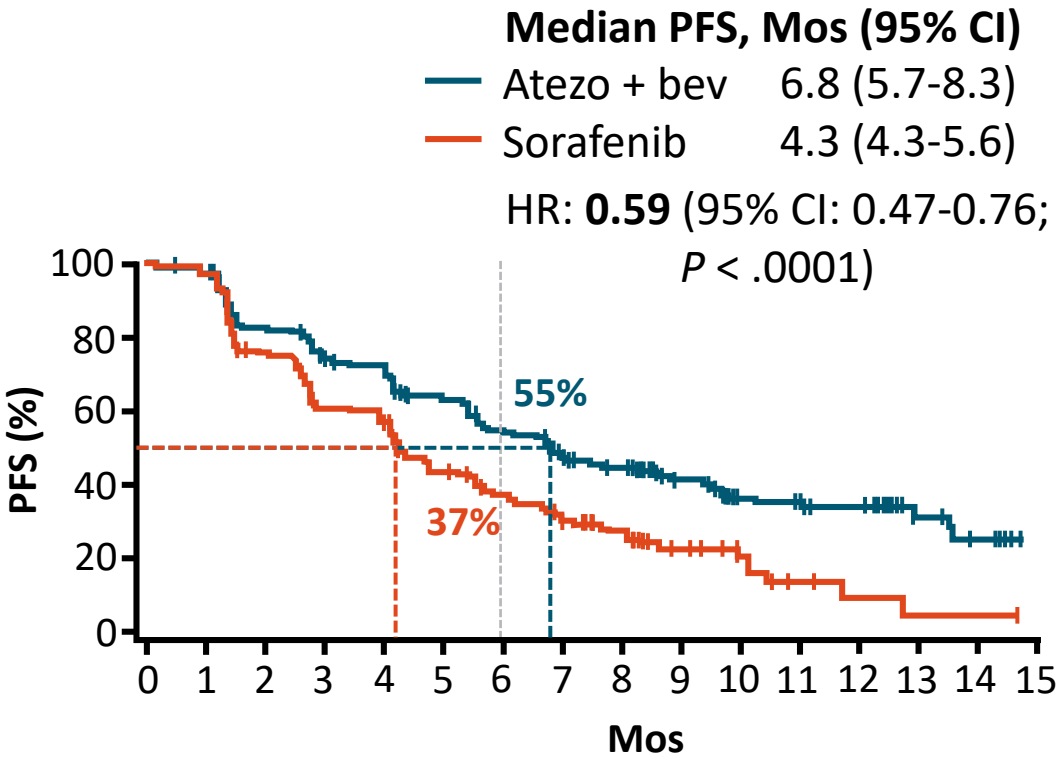
- Coprimary endpoints: OS and PFS

*Trial included subgroups of high-risk patients excluded from other contemporary phase III trials: ~ 40% had macrovascular invasion; specifically included patients with 50% hepatic involvement or main portal vein invasion or invasion of the portal vein branch contralateral to the primarily involved lobe.

1. Finn. NEJM. 2020;382:1894. 2. Lee. Lancet Oncol. 2020;21:808.

IMbrave150: OS, PFS, and Response



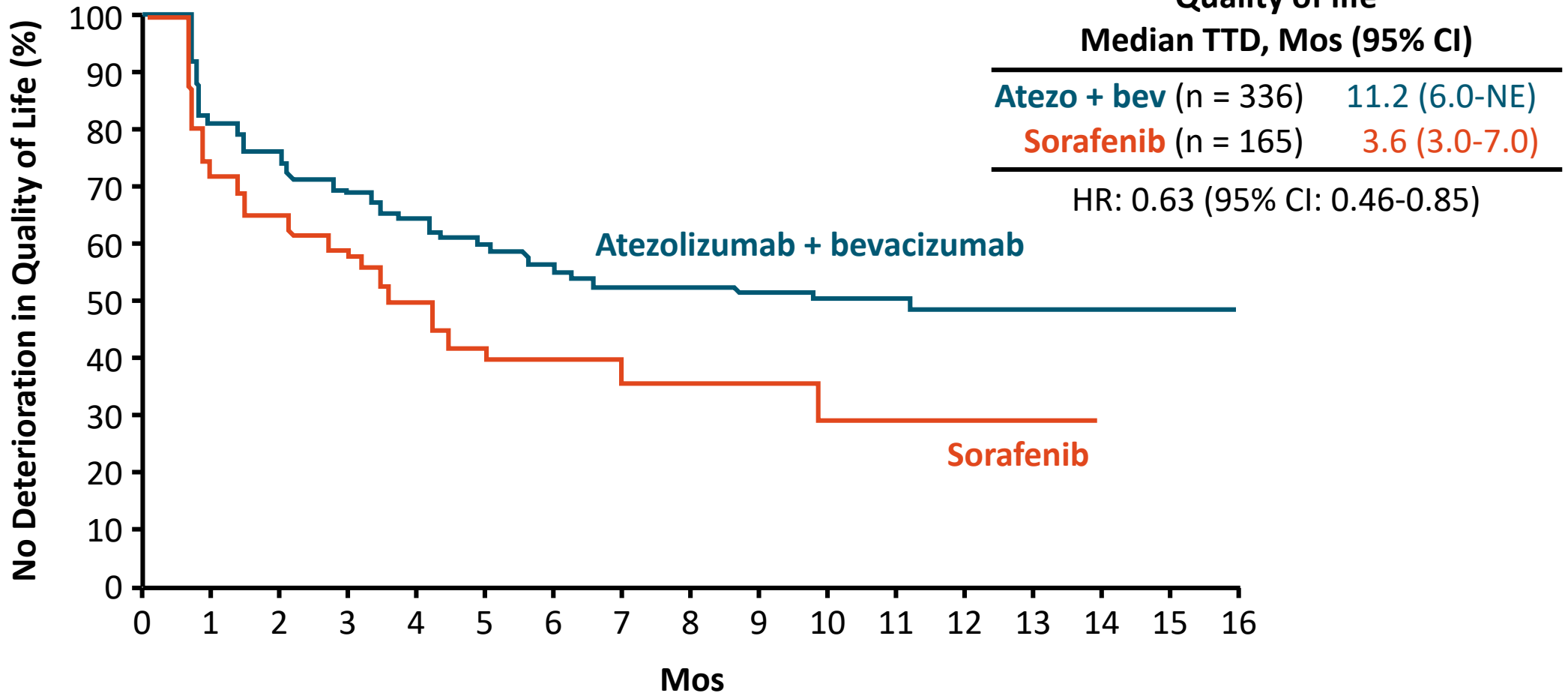


- ORR by HCC-specific modified RECIST with atezo + bev vs sorafenib: 33.2% vs 13.3%; CR rate, 10.2% vs 1.9%

Median follow-up: 8.6 mos.

Finn. NEJM. 2020;382:1894.

IMbrave150: Quality of Life (Patient Reported)

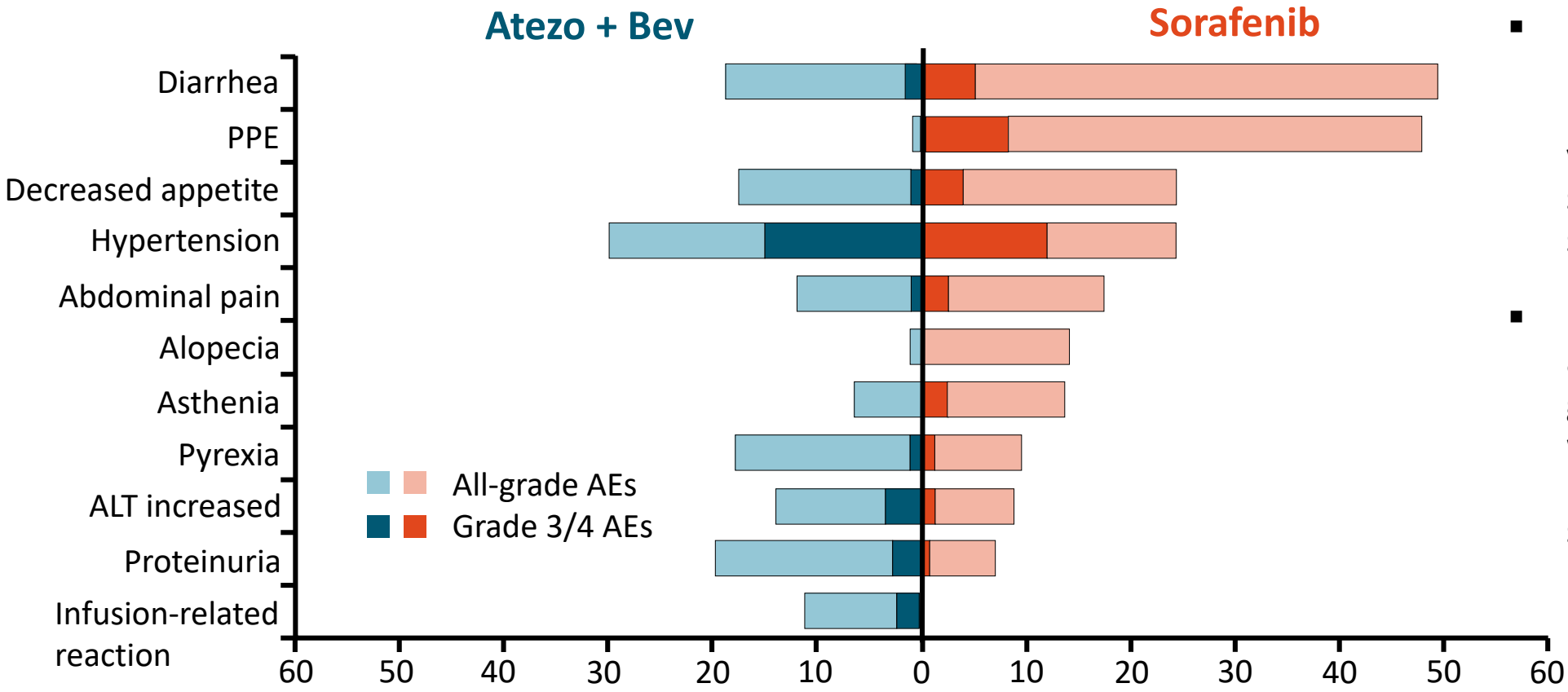


Quality of life Median TTD, Mos (95% CI)	
Atezo + bev (n = 336)	11.2 (6.0-NE)
Sorafenib (n = 165)	3.6 (3.0-7.0)

HR: 0.63 (95% CI: 0.46-0.85)

Finn. NEJM. 2020;382:1894.

IMbrave150: Safety



- EGD within 6 mos of initiating treatment required to evaluate for varices; varices of any size according to local standards of care
- Upper GI bleeding rate in atezo + bev vs sorafenib groups: 7% vs 4.5%; this was consistent with historical data in other studies of bevacizumab in HCC

≥ 10% frequency in either arm and > 5% difference between arms.

Cheng. ESMO Asia 2019. Abstr LBA3. Finn. NEJM. 2020;382:1894.

Key Warnings and Precautions for First-Line Atezolizumab/Bevacizumab

- **Atezolizumab**[1]
  - Immune-mediated pneumonitis, hepatitis, colitis, endocrinopathies
- Patients with Child-Pugh B/C cirrhosis or prior organ transplant were excluded from IMbrave150

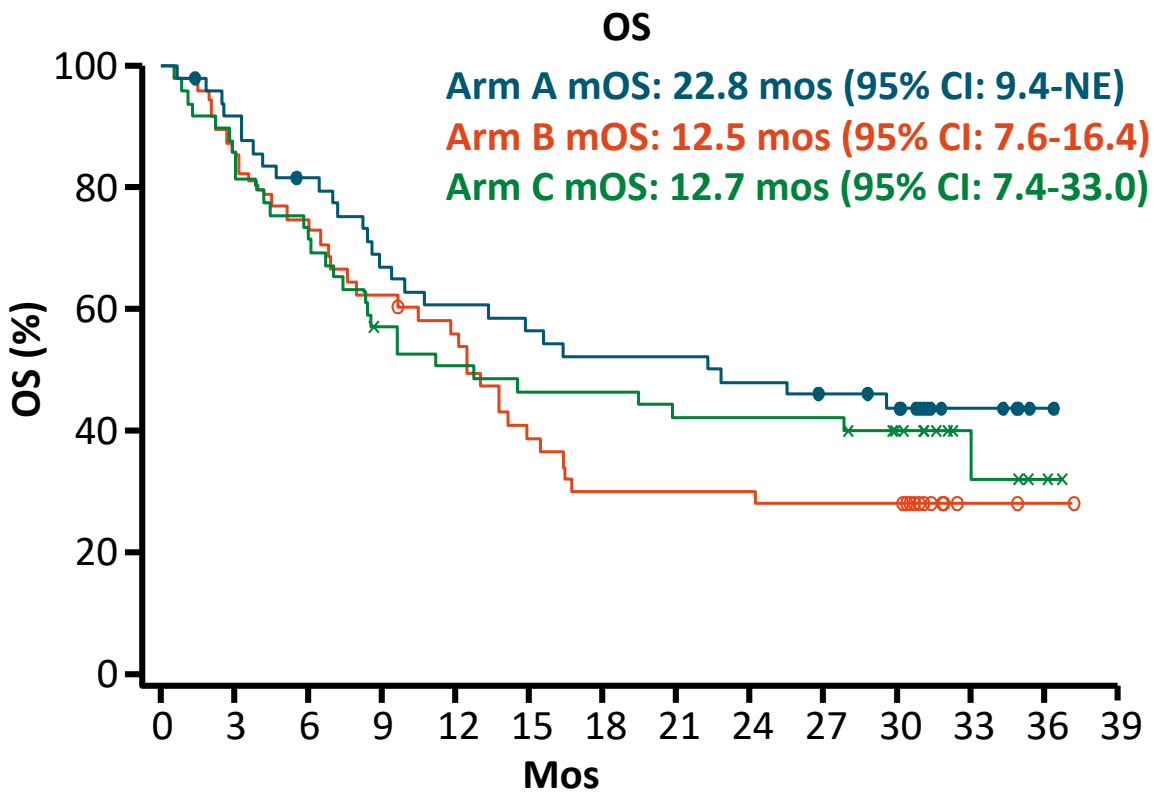
- **Bevacizumab**[2]
  - GI perforations
  - Surgery in last 28 days; incompletely healed wound
  - Recent hemoptysis or major bleed (variceal bleeding)
  - Fistula
  - Uncontrolled hypertension
  - > 2 g proteinuria
  - Congestive heart failure

1. Atezolizumab PI. 2. Bevacizumab PI.

CheckMate 040: Nivolumab + Ipilimumab for Advanced HCC

- Open-label phase I/II trial of 3 different dosing schemes of **nivolumab + ipilimumab** for patients with advanced HCC and prior sorafenib treatment; uninfected or infected with HBV or HCV; CP score A5-A6; ECOG PS 0/1

Response	Arm A NIVO1/IPI3 Q3W (n = 50)	Arm B NIVO3/IPI1 Q3W (n = 49)	Arm C NIVO3 Q2W/ IPI1 Q6W (n = 49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
BOR, n (%)			
▪ CR	4 (8)	3 (6)	0
▪ PR	12 (24)	12 (24)	15 (31)
▪ SD	9 (18)	5 (10)	9 (18)
▪ PD	20 (40)	24 (49)	21 (43)
▪ Undetermined	3 (6)	4 (8)	4 (8)
DCR, n (%)	27 (54)	21 (43)	24 (49)
Median TTR, mos (range)	2.0 (1.1-12.8)	2.6 (1.2-5.5)	2.7 (1.2-8.7)
Median DoR, mos (range)	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)

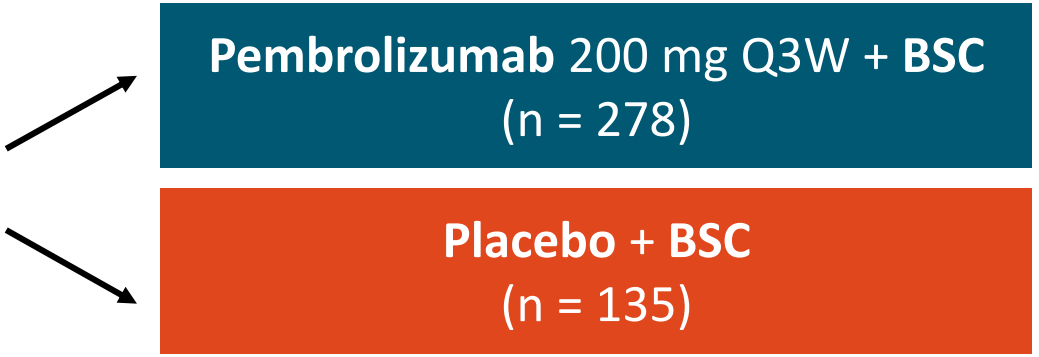


Yau. ASCO 2019. Abstr 4012.

KEYNOTE-240: Pembrolizumab for Patients With Previously Treated HCC

- KEYNOTE-224: open-label, single arm, phase II trial showed potential efficacy of pembrolizumab for patients with advanced HCC and previous sorafenib (ORR 17%)[1]
- KEYNOTE 240: randomized, double-blind phase III trial[2]

Patients with advanced HCC with intolerance to or PD on or after sorafenib; Child-Pugh A; BCLC stage B/C; ECOG PS ≤ 1; no invasion of main portal vein
(N = 413)



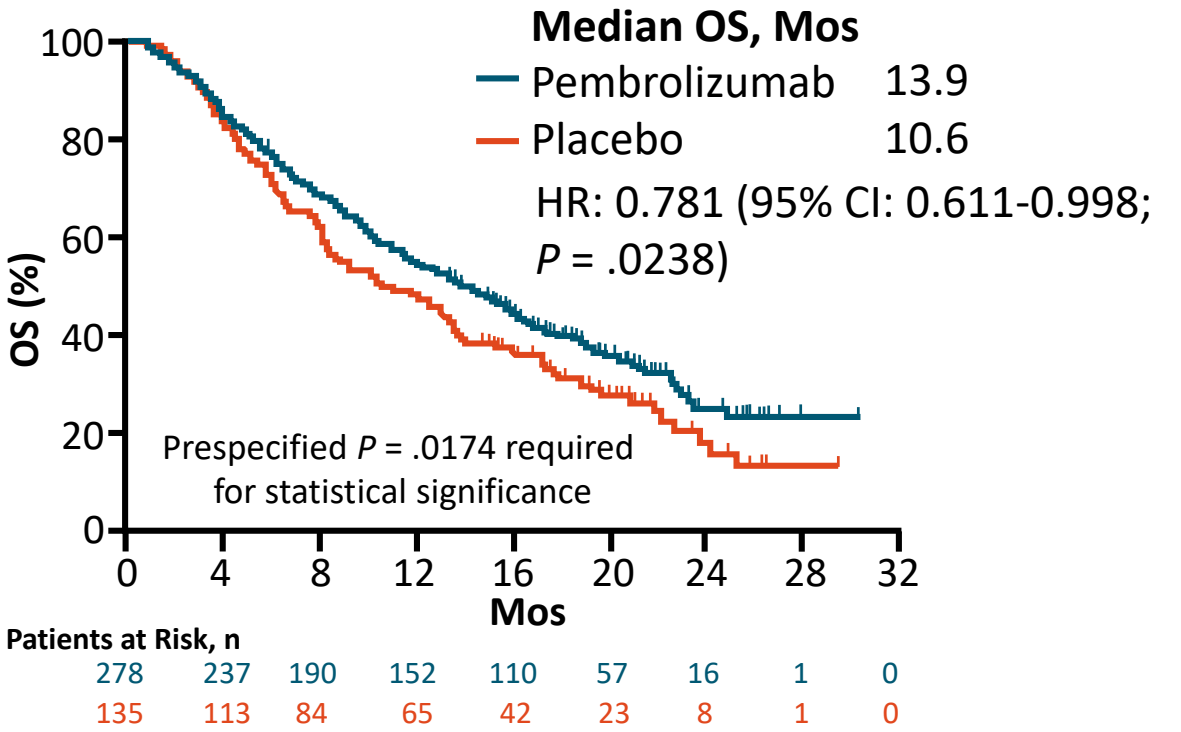
- Coprimary endpoints: PFS,* OS
  - Efficacy boundaries: PFS at first interim cutoff, *P* = .0020 (primary analysis for PFS); OS at final analysis cutoff, *P* = .0174
- Secondary endpoints: ORR,* DoR, DCR, TTP, safety

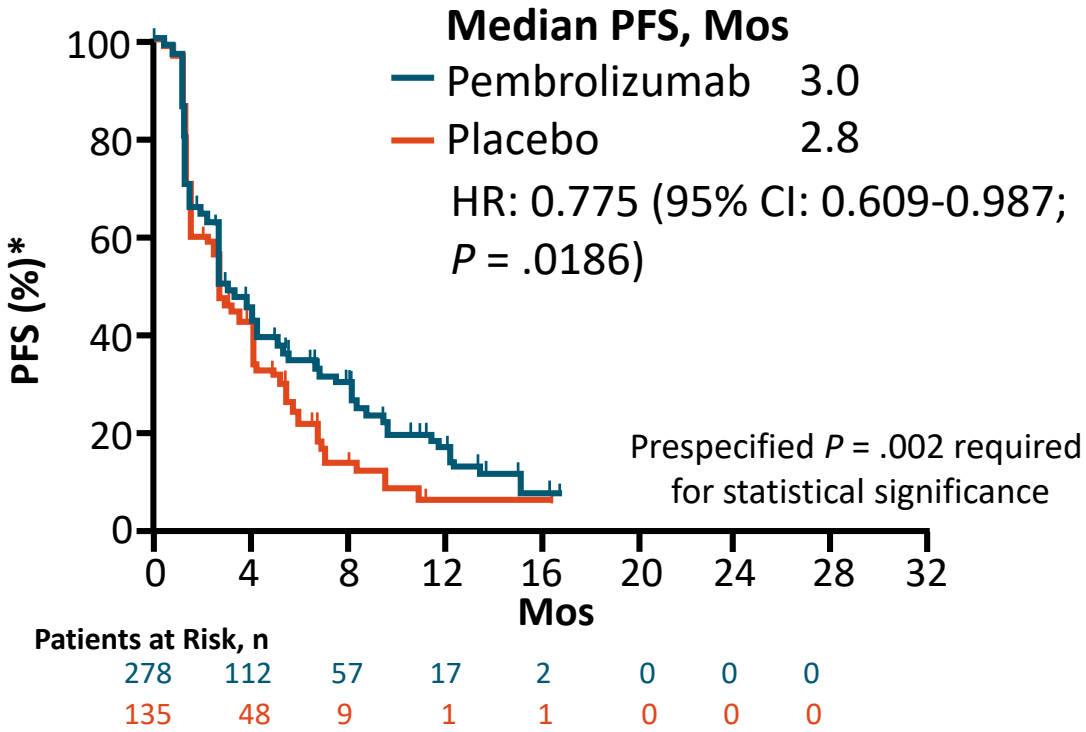
*PFS, secondary response outcomes centrally reviewed.

1. Finn. JCO. 2020;38:193. 2. Zhu. Lancet Oncol. 2018;19:940.

KEYNOTE-240: Survival and Response

- Failed to reach prespecified level of statistical significance for OS and PFS





- ORR was significantly higher with pembrolizumab vs placebo (18.3% vs 4.4%; *P* = .00007), median DoR was 13.8 mos with pembrolizumab

*Primary analysis.

Finn. JCO. 2020;38:193.

Key Phase III Trials With Immunotherapy Combinations for First-line Treatment of Advanced HCC

Trial	Treatment	Key Supporting Data
LEAP-002 (NCT03713593)	**Lenvatinib + pembrolizumab** vs lenvatinib	▪ KEYNOTE-524 (phase Ib study*): ORR 36%,† mOS 22 mos with lenvatinib + pembrolizumab (N = 104)[1]
HIMALAYA (NCT03298451)	**Durvalumab ± tremelimumab** vs sorafenib	▪ Study 22 (phase I/II study*): ORR 24%†, mOS 19 mos with a single dose of tremelimumab 300 mg followed by monthly durvalumab (N = 332)[2]
COSMIC-312 (NCT03755791)	**Cabozantinib + atezolizumab** vs sorafenib	▪ Cabozantinib active 2L and 3L therapy for HCC (phase III CELESTIAL study); early studies in solid tumors suggest efficacy of combination[3,4]
CheckMate 9DW (NCT04039607)	**Nivolumab + ipilimumab** vs sorafenib or lenvatinib	▪ CheckMate 040 (phase Ib study*): ORR up to 32%,† mOS up to 23 mos (N = 148)[5]

*Patients previously treated with systemic therapy included. †RECIST v1.1.

1. Finn. JCO. 2020;38:2960. 2. Kelley. ASCO 2020. Abstr 4508. 3. Abou-Alfa. NEJM. 2018;379:54.
4. Agarwal. ESMO 2018. Abstr 872P. 5. Yau. ASCO 2019. Abstr 4012.

HIMALAYA TRIAL – STRIDE Tremelimumab (T) and durvalumab (D) as first-line therapy

- HIMALAYA open-label, multicentre, phase 3 study, in which pts with uHCC and no prior systemic therapy.

- Randomisation:
- STRIDE (T 300 mg plus D 1500 mg [one dose] plus D 1500 mg every 4 weeks [Q4W]),STRIDE (N=393)
- D (1500 mg Q4W),), D (N=389),
- S (400 mg twice daily), S (N=389)
- or T 75 mg Q4W (4 doses) plus D 1500 mg Q4W (T75+D).

HIMALAYA TRIAL

- The primary objective - overall survival (OS) for STRIDE vs S.
- The secondary objective was OS noninferiority (NI) of D to S.
- Secondary endpoints - PFS, ORR; RECIST v.1.1, DoR, safety

- **RESULTS:**
- OS was significantly improved for STRIDE vs S (hazard ratio [HR], 0.78; 96% [CI], 0.65–0.92; p=0.0035).
- D met the objective of OS NI to S (HR, 0.86; 96% CI, 0.73–1.03).
- ORRs were higher for STRIDE (20.1%) and D (17.0%) than for S (5.1%).

HIMALAYA TRIAL

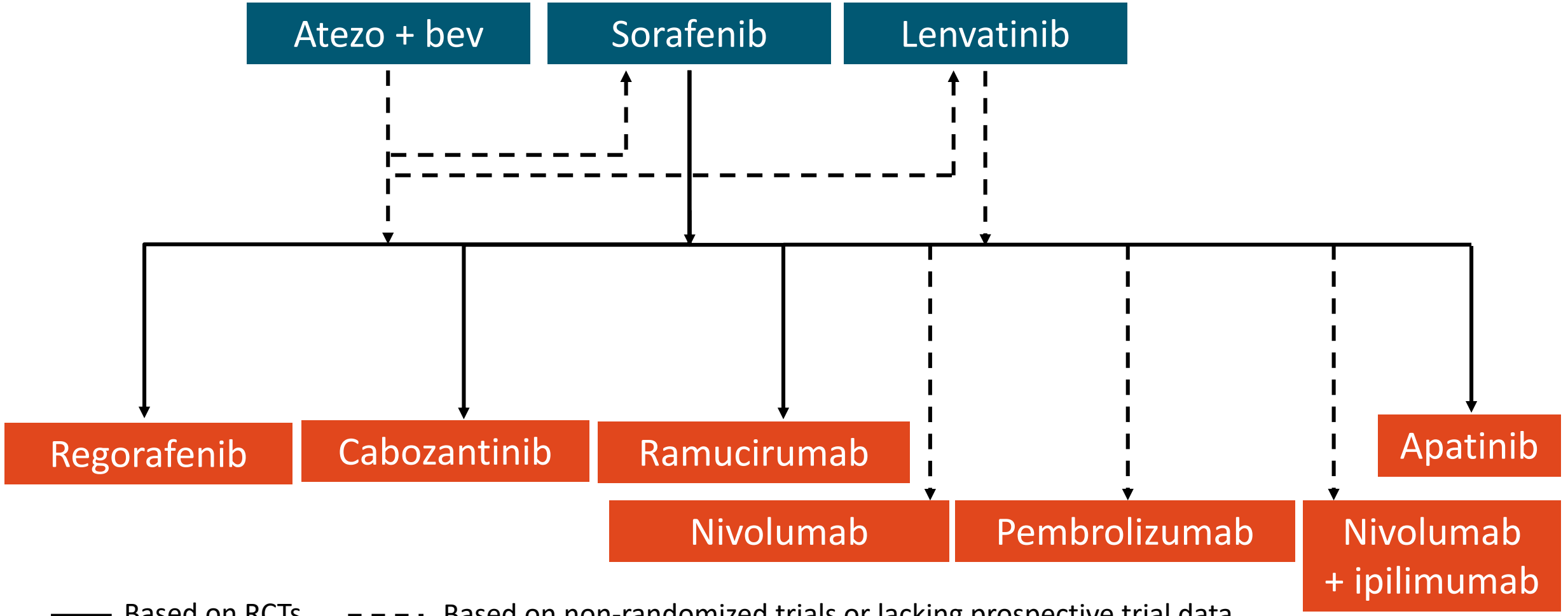
	STRIDE (n=393)	D (n=389)	S (n=389)
Median follow-up, mo	16.1	16.5	13.3
Deaths at DCO, %	66.7	72.0	75.3
Median OS (95% CI), mo	16.4 (14.2–19.6)	16.6 (14.1–19.1)	13.8 (12.3–16.1)
24/36-mo OS rate, %	40.5/30.7	39.6/24.7	32.6/20.2
Median PFS (95% CI), mo	3.8 (3.7–5.3)	3.7 (3.2–3.8)	4.1 (3.8–5.5)
ORR, %	20.1	17.0	5.1
Median DoR, mo	22.3	16.8	18.4
Grade 3/4 TRAE, %	25.8	12.9	36.9
Serious TRAE, %	17.5	8.2	9.4
Grade 5 TRAE, %	2.3	0	0.8
TRAE leading to discontinuation, %	8.2	4.1	11.0

Targeted Therapies for Patients Previously Treated With Sorafenib: Positive Phase III Trials

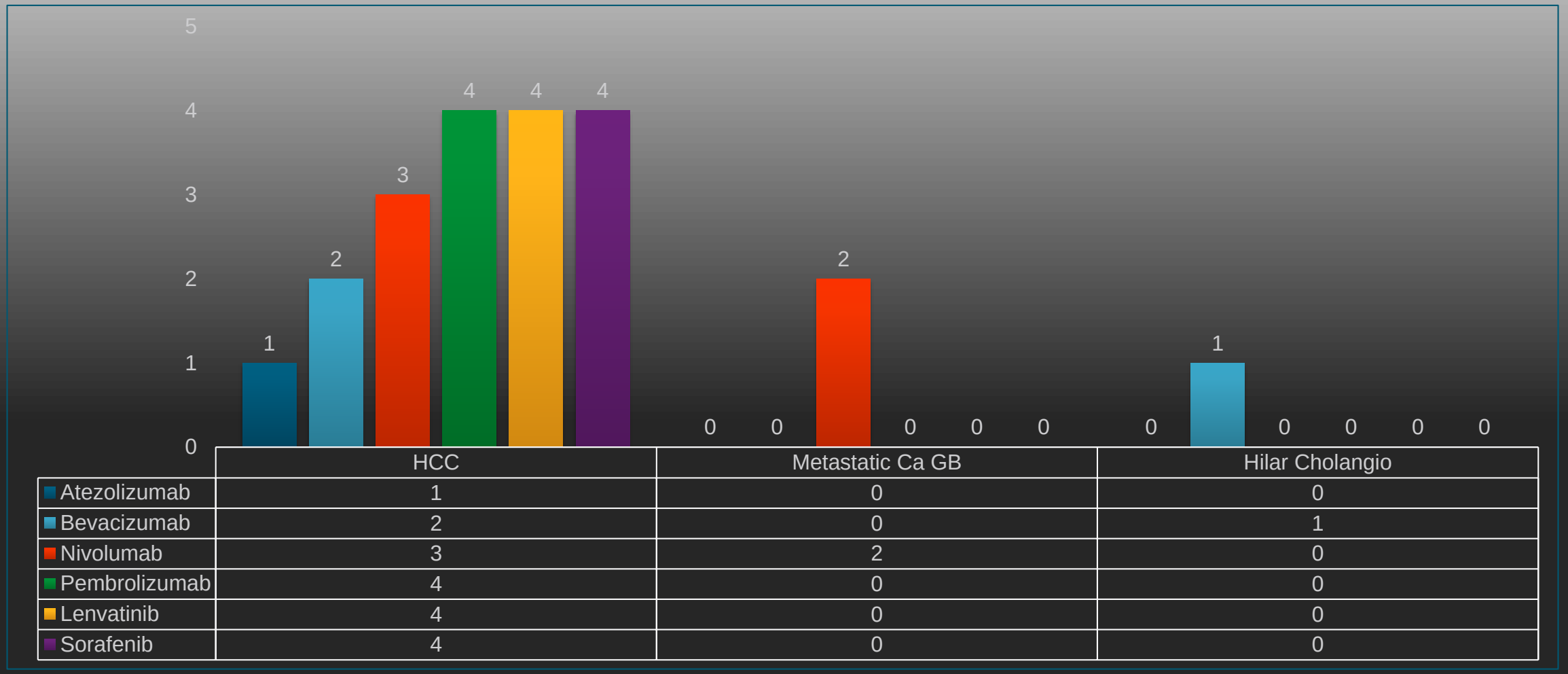
Drug; Trial Name	Mode of Action	N	Median OS, Mos (vs Placebo)	HR (95% CI)
Regorafenib (RESORCE)[1]	Multitargeted TKI	573	10.6 vs 7.8	0.63 (0.50-0.79)
Cabozantinib (CELESTIAL)[2]	Multitargeted TKI	707	10.2 vs 8.0	0.76 (0.63-0.92)
Ramucirumab (REACH-2)[3]	Anti-VEGFR2 mAb	292	8.5 vs 7.3	0.71 (0.53-0.95)
Apatinib (AHELP)[4]	VEGFR2 inhibitor	393	8.7 vs 6.8	0.785 (0.617-0.998)

1. Bruix. Lancet. 2017;389:56. 2. Abou-Alfa. NEJM. 2018;379:54. 3. Zhu. Lancet Oncol. 2019;20:282. 4. Li. ASCO 2020. Abstr 4507.

What Patients Might Be Optimal Candidates for Second-line Immunotherapy?



Army hospital data(Jan 21 – June22)



	HCC	Metastatic Ca GB	Hilar Cholangio
Atezolizumab	1	0	0
Bevacizumab	2	0	1
Nivolumab	3	2	0
Pembrolizumab	4	0	0
Lenvatinib	4	0	0
Sorafenib	4	0	0

Outcomes in Biliary Cancers

Early stages of disease - better prognosis -5-year survival in the range of 75–85% patients Advanced GBC - 5-year survival in the range of 5% (10-Institution Study from the United States Extrahepatic Biliary Malignancy Consortium. Am. Surg. 2017, 83, 679–686.The Landmark Series: Gallbladder Cancer. Ann. Surg. Oncol. 2020, 27, 2846–2858.)

Median OS distal, perihilar, intrahepatic CCA (after surgical resection) - 21.9 months, 35–40 months, and 18–39 months (Outcomes in biliary malignancy. J. Surg. Oncol. 2014, 110, 585–591. Treatment and survival of resected and unresected distal cholangiocarcinoma: A nationwide study. Acta Oncol. 2019, 58, 1048–1055)

Therapies at Hand

First-line treatment - gemcitabine with cisplatin (superior to gemcitabine monotherapy)

Triple combination therapy with folinic acid, 5-FU, and oxaliplatin more promising regimen but more toxic

Second-line therapies - combinations of chemotherapy and/or small-molecule inhibitors including VEGF inhibitors / IDH1 inhibitors / FGFR2 inhibitors

Immune Checkpoint Inhibitors

Anti-PD-1 ICIs have not yet demonstrated robust utility for CCA and GBC.

Phase II study (NCT02628067) / phase Ib study (NCT02054806) - pembrolizumab in advanced biliary tract cancer, durable antitumor activity was only noted among 6–13% of patients.

(Results from the **KEYNOTE-158** and **KEYNOTE-028** studies. Int. J. Cancer 2020, 147, 2190–2198)

Phase II trial (NCT02829918) -Nivolumab for advanced, refractory biliary tract cancer -- modest ORR of 11%, including one partial response, and a disease control rate of 50%.

(A Phase 2 Multi-institutional Study of Nivolumab for Patients with Advanced Refractory Biliary Tract Cancer. JAMA Oncol. 2020, 6, 888–894).

Table 1. Completed clinical trials assessing the use of immune checkpoint inhibitors (ICIs) for the treatment of biliary tract cancer.

Study Name	Agent	Target	Phase	Patients	Setting	Outcomes
Anti PD-1/PD-L1 monotherapy						
NCT02829918	Nivolumab	PD-1	2	54	Second line and subsequent	mPFS 3.68 months mOS 14.2 months ORR 22%
JapicCTI-153098	Nivolumab	PD-1	1	30	Second line and subsequent	mPFS 1.4 months mOS 5.2 months ORR 3%
KEYNOTE-028	Pembrolizumab	PD-1	1b	24	Pretreated (PD-L1 positive tumors)	mPFS 1.8 months mOS 5.7 months ORR 13%
KEYNOTE-158	Pembrolizumab	PD-1	2	104	Second line and subsequent	mPFS 2 months mOS 7.4 months ORR 5.8%
NCT01938612	Durvalumab	PD-L1	1	42	Second line and subsequent	mPFS 2 months mOS 8.1 months ORR 4.8%
Anti PD-1/PD-L1 combination with CTLA4 inhibitors						
CA209-538	Nivolumab Ipilimumab	PD-1 CTLA4	2	39	Second line and subsequent	mPFS 2.9 months mOS 5.7 months ORR 23%
NCT01938612	Durvalumab Tremelimumab	PD-L1 CTLA4	2	65	Second line and subsequent	mOS 10.1 months ORR 10.8%
Dual PD-L1 and TGFβ blockade						
NCT02699514	Bintrafusp alfa	PD-L1 TGFβ-RII	1	30	Second line and subsequent	mPFS 2.5 months mOS 12.5 months ORR20%
NCT03833661	Bintrafusp alfa	PD-L1 TGFβ-RII	2	159	Second line and subsequent	ORR 10.1%
ICIs plus chemotherapy						
JapicCTI-153098	Nivolumab cisplatin/gemcitabine	PD-1	2	30	First line	mPFS 4.2 months mOS 15.4 months ORR 37%

Way ahead - BTC

- Approx 45% of biliary tract tumors express high levels of immune checkpoint inhibitors such as IDO-1, LAG-3, HAVCR2, TNFRSF9, BTLA, CD274, PDCD1, and TNFRSF4.

NCT04641871	I	Active, not recruiting	Combination immune checkpoint inhibitors (PD-1 with LAG-3 or TIM-3)	N/A	200
NCT04672434	I	Recruiting	Combination immune checkpoint inhibitors (PD-1 with CD73)	N/A	100
NCT03872947	I	Recruiting	Monoclonal antibody against undisclosed tumor-associated antigen with immune checkpoint inhibitors (PD-1 or CTLA-4)	Imiquimod Cream, Irinotecan, Leucovorin, 5-FU, Gemcitabine, Cisplatin, Carboplatin, Ramucirumab, Paclitaxel	75
NCT03801083	II	Recruiting	TIL adoptive cell transfer	N/A	59
NCT03633773	I/II	Recruiting	MUC-1 CAR-T cell	N/A	9
NCT04951141	I	Recruiting	GPC3 CAR-T cells	N/A	10
NCT01868490	I/II	Recruiting	CIK adoptive cell transfer	N/A	13
NCT03942328	I	Recruiting	Autologous dendritic cells	External Beam Radiation Therapy, Pneumococcal 13-valent Conjugate Vaccine	26
NCT04853017	I/II	Recruiting	Peptide vaccine against KRAS mutations	N/A	159

Future Directions and Novel Approaches

Immunotherapy beyond ICIs

- adoptive cell transfer (ACT) of immune cells.
- cytokine-induced killer (CIK)
- CAR-T immunotherapy

In Conclusion

The aggressive tumor biology, reduced tumor mutational burden, and immunosuppressive tumor microenvironment characteristic of hepatobiliary cancers have significantly delayed the development and adoption of novel immunotherapies.

ICIs are now standard of care in patients with unresectable or metastatic HCC.

Immunotherapy - valuable treatment option in select patients with CCA and GBC

Immunotherapy represents a potential avenue for developing new treatments,

THANK YOU