JOHANNES GUTENBERG UNIVERSITÄT MAINZ

Novel Approaches Under Investigation for Advanced HCC

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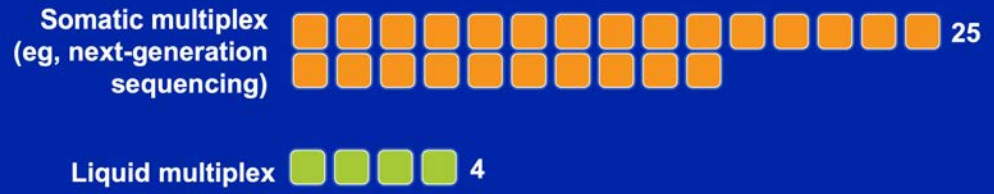
A younger patient with incurable HCC, a good PS and no relevant family history who has exhausted all approved therapies wishes to consider creative options. Which of the following genomic testing platforms would you generally order? (Select all that apply)



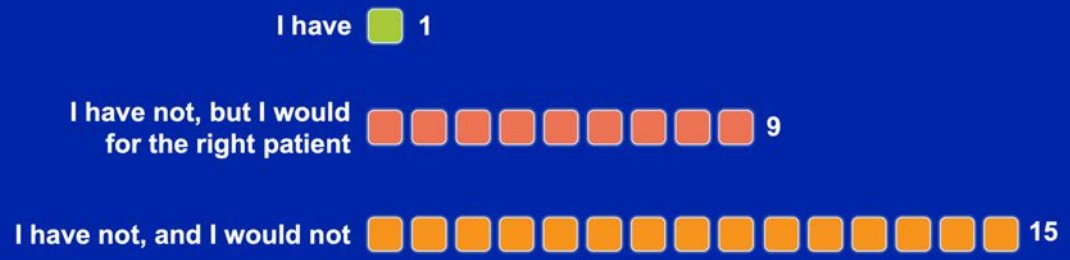
Approximately how many patients in your practice with HCC have experienced an objective response to targeted treatment because of a finding on a multiplex tissue or liquid assay?

Total patients: 25

What targeted treatments have you administered to these patients?

- FGFR4 inhibitor
- BRAF inhibitor
- Everolimus
- Ivosidenib
- PARP inhibitor

Outside of a protocol setting, have you or would you administer an anti-PD-1/PD-L1 antibody in combination with an anti-CTLA-4 antibody to a patient with HCC?



Novel Investigational Approaches for HCC

- Anti-PD-1/PD-L1 and anti-CTLA-4 combinations
- Checkpoint inhibitor and TKI combinations
- Multiplex testing and targeted therapy

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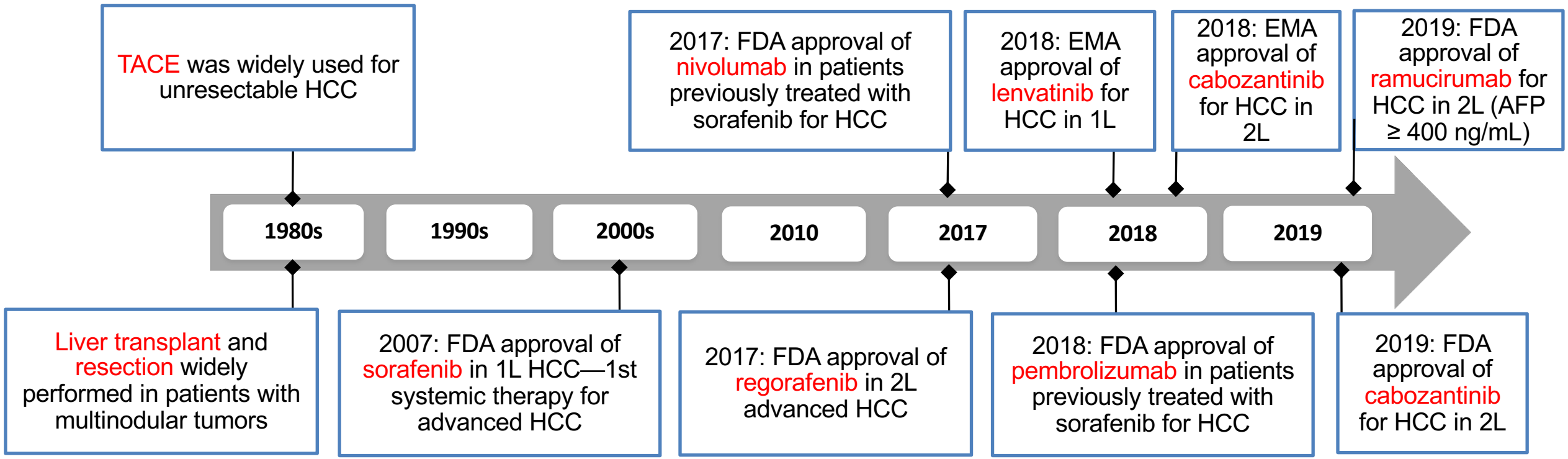
Disclosures

Advisory Committee and Consulting Agreements	Agios Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Genentech, Ipsen Biopharmaceuticals Inc, Lilly, Merck, Novartis, Roche Laboratories Inc, Sirtex Medical Ltd
Data and Safety Monitoring Board/Committee	Novartis
Speakers Bureau	Agios Pharmaceuticals Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Ipsen Biopharmaceuticals Inc, Lilly, Merck, Roche Laboratories Inc, Sirtex Medical Ltd

History of treatment landscape for HCC

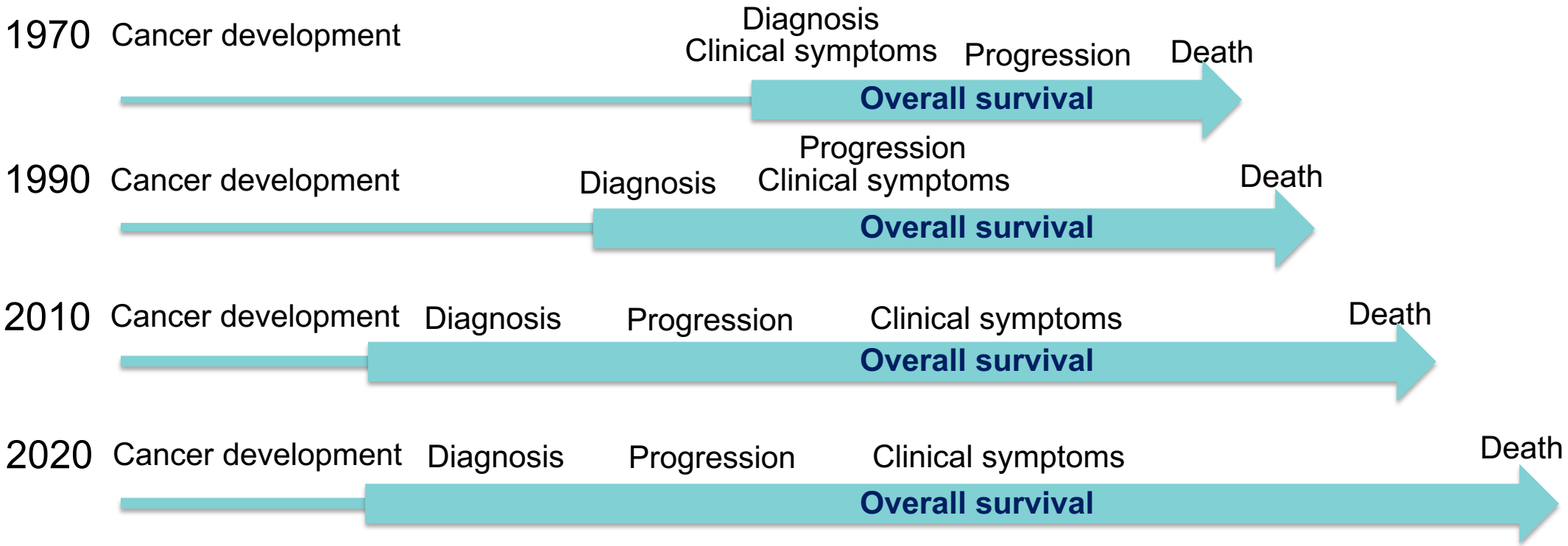
Treatment options were limited for unresectable HCC



7 (FDA) or 5 (EMA) Systemic agents have been approved for use in HCC

1L=first line; 2L=second line; FDA=US Food and Drug Administration; HCC=hepatocellular carcinoma; TACE=transarterial chemoembolization.

The Goal of Systemic Therapy in HCC is Prolonged Overall Survival (OS)



Bruix J, et al. *Gastroenterology.* 2016;150:835-853.

IO Monotherapy for HCC

Study	Treatment (target)	Patient number	Response rate (%)	Progression-free survival, months (95% CI)	Overall survival, months (95% CI)	NCT number
Monotherapy						
CheckMate 040, PI/II [1]	Nivolumab (PD-1)	214	20.0	4.0 (2.9-5.4)	NR	NCT01658878
KeyNote 224, PII [2]	Pembrolizumab (PD-1)	169	18.0	4.9 (3.4-7.2)	12.9 (9.7-15.5)	NCT02702414
PI/II [3]	Durvalumab (PD-L1)	40	10.0	2.7 (1.4-5.3)	13.2 (6.3-21.1)	NCT01693562
PIb [4]	BGB-A317 (PD-1)	27	11.1*	NR	NR	NCT02407990
PII [5]	Tremelimumab (CTLA-4)	17	17.6	6.48 (4.0-9.1)	8.2 (4.6-21.3)	NCT01008358

[1] *Lancet 2017;389:2492-2502*
[2] *Lancet Oncol 2018;19:940-952*
[3] *J Clin Oncol 2017;35 (suppl; abstr 4071)*
[4] *Ann Oncol 2017;28 (suppl_3), mdx261.139*
[5] *J Hepatol. 2013;59:81-8*
* *Confirmed + unconfirmed responses*

KEYNOTE-524: A Phase Ib trial of lenvatinib + pembrolizumab in patients with uHCC

Summary of tumour response (investigator assessment by mRECIST; efficacy analysis set)

Parameter, n (%)	Lenvatinib + pembrolizumab		
	Part 1 (n=6)	Part 2 (n=20)	Overall (N=26)
BOR, n (%)			
CR	0	1 (5.0)	1 (3.8)
PR	4 (66.7)	6 (30.0)	10 (38.5)
SD	2 (33.3)	13 (65.0)	15 (57.7)
PD	0	0	0
ORR including unconfirmed responses, n	4 (66.7)	7 (35.0)	11 (42.3)
ORR excluding unconfirmed responses, n	3 (50.0)	4 (20.0)	7 (26.9)

Ikeda M, *et al.* ASCO 2018; Abstract 4076.

KEYNOTE-524: A Phase Ib trial of lenvatinib + pembrolizumab in patients with uHCC

Summary of TEAEs (safety analysis set)

Parameter, n (%)	Lenvatinib + pembrolizumab		
	Part 1 (n=6)	Part 2 (n=24)	Overall (N=30)
TEAEs	6 (100)	24 (100)	30 (100)
Treatment-related TEAEs	6 (100)	22 (91.7)	28 (93.3)
TEAEs grade ≥3	5 (83.3)	13 (54.2)	18 (60.0)
Serious AEs	2 (33.3)	6 (25.0)	8 (26.7)
Fatal AEs	0	3 (12.5)	3 (10.0)
Dose modifications			
Lenvatinib/Pembrolizumab dose interruptions	5 (83.3)	13 (54.2)	18 (60.0)
due to TEAEs	5 (83.3)	13 (54.2)	18 (60.0)
Lenvatinib dose reductions due to TEAE			
DC of lenvatinib/pembrolizumab due to TEAEs	0	5 (20.8)	5 (16.7)

DC, discontinuation.

Ikeda M, *et al*. ASCO 2018; Abstract 4076.

News >

Pembrolizumab/Lenvatinib Combo Gets FDA Breakthrough Designation for Newly Diagnosed, Unresectable HCC

Lisa Astor
Published Online:5:01 PM, Tue July 23, 2019

LEAP 002 – Phase III, randomised, double-blind study of 1st-line pembrolizumab in combination with lenvatinib *vs* lenvatinib[1]

Key eligibility criteria (N~750)

- ≥18 years
- Confirmed radiological, histological or cytological aHCC
- ≥1 measurable lesion per RECIST v1.1 (confirmed by BICR)
- No prior systemic treatment
- Not amenable to curative therapy
- Child-Pugh A
- ECOG PS 0 or 1
- Patients with HCV infection eligible if treatment concluded ≥1 month prior to initiation
- Patients with controlled HBV

1:1*

Lenvatinib + pembrolizumab

Lenvatinib + placebo – saline

Primary endpoints:
- PFS
- OS

Secondary endpoints:
- ORR
- DOR
- DCR
- TTP
- Pharmacokinetics

Treatment until:
- PD or intolerable toxicity
- 35 cycles for pembrolizumab or placebo (lenvatinib can be continued)

Status: Enrollment underway in 102 countries;[1] recruiting (study completion July 2022)[2]

*Stratified according to geographic region, macrovascular invasion and/or extrahepatic spread, baseline alpha-fetoprotein, and ECOG PS.

1. Llovet J, *et al. J Clin Oncol* 2019;15_suppl: TPS4152; 2. NCT03713593. Available at: https://clinicaltrials.gov/ct2/show/NCT03713593. Last accessed June 2019.

COSMIC 312 – Phase III, randomised, open-label study of cabozantinib + atezolizumab *vs* sorafenib in 1st line[1]

Key eligibility criteria (N~740)

- Histological or cytological diagnosis of aHCC
- Measurable disease per mRECIST
- Not amenable to curative treatment
- Child-Pugh A
- BCLC B or C
- HBV DNA <500IU/mL with ongoing antiviral treatment

6:3:1*

- **Cabozantinib + atezolizumab**
- **Sorafenib**
- **Cabozantinib**

Study endpoints

Primary:
- PFS (RECIST v1.1)
- OS (for cabozantinib + atezolizumab *vs* sorafenib)

Secondary:
- PFS (RECIST v1.1 for cabozantinib *vs* sorafenib)

Additional:
- ORR
- TTP
- DOR
- Safety
- Quality of life

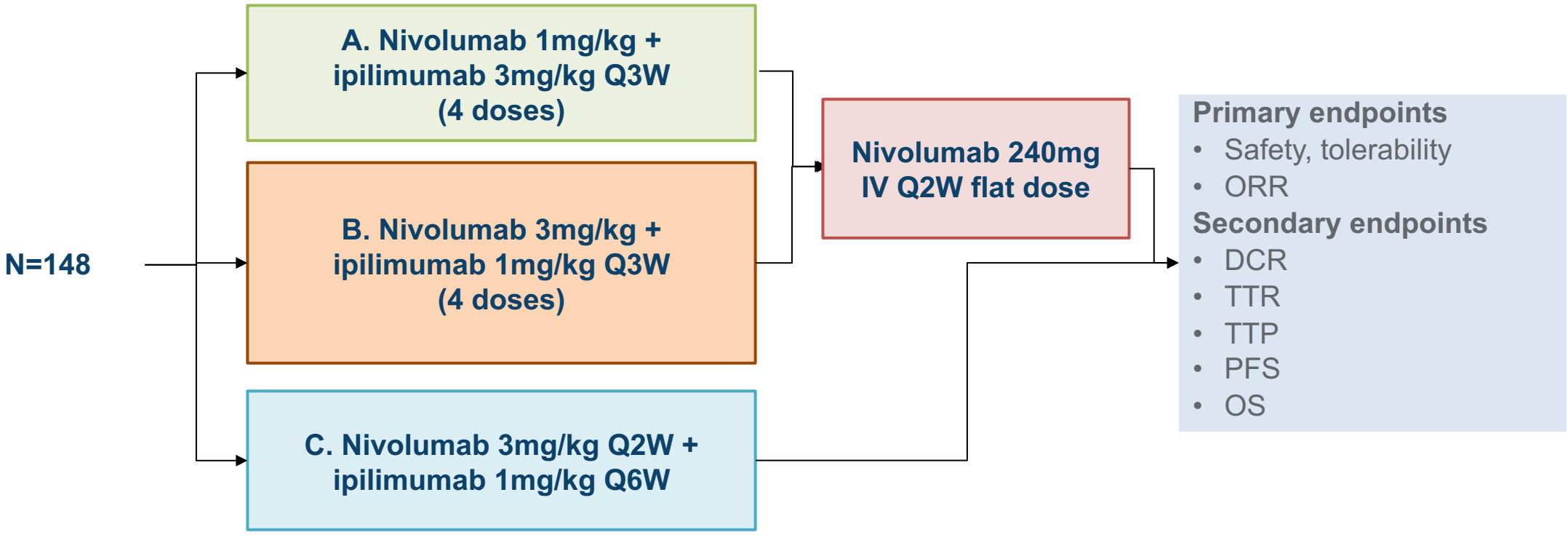
Status: Enrollment underway in 250 global sites; recruiting (study completion December 2021)[2]

Treatment until:
- PD or intolerable toxicity

*Stratified according to geographic region (Asia, other), macrovascular invasion and/or extrahepatic spread (yes/no), disease aetiology (HBV [with or without HCV], HCV [with or without HBV], other).

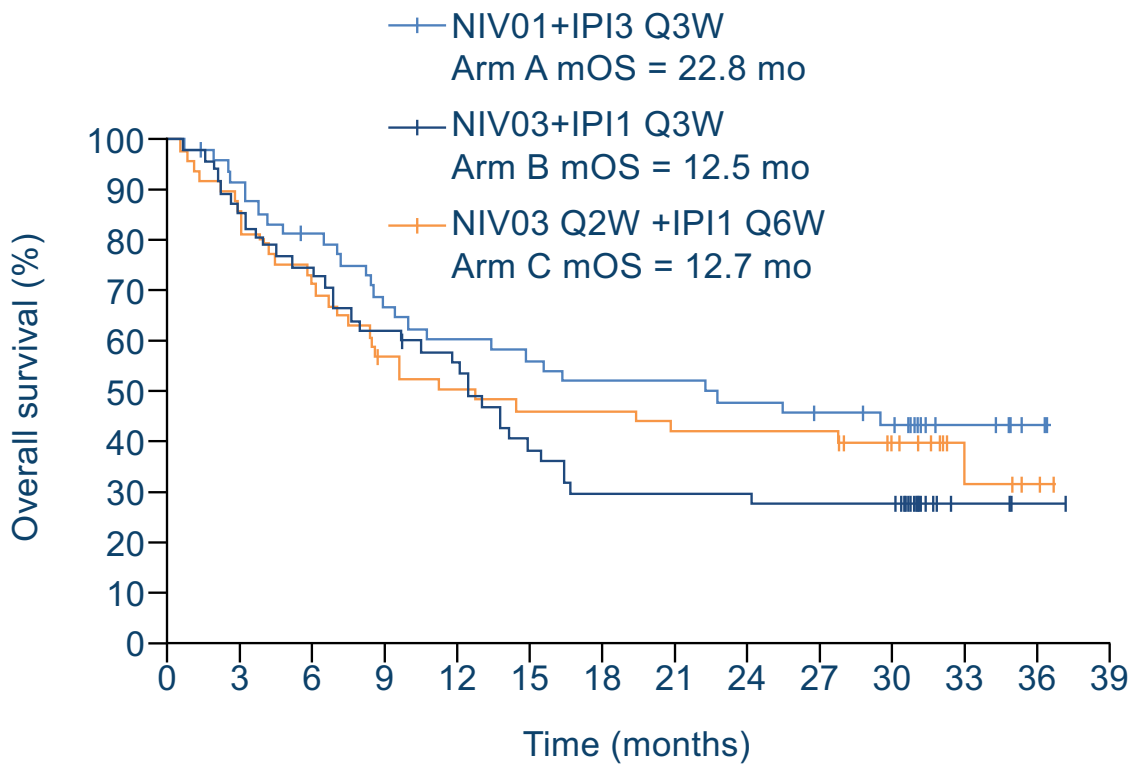
1. Kelley K, *et al.* ASCO 2019; Abstract TPS4157; 2. NCT03755791. Available at: https://clinicaltrials.gov/ct2/show/NCT03755791. Last accessed June 2019.

CheckMate 040 – efficacy of nivolumab + ipilimumab in 148 patients who had previously received sorafenib



1. Yau T, *et al. J Clin Oncol* 2019;15_suppl: 4012.

CheckMate 040 – efficacy of nivolumab + ipilimumab in 148 patients who had previously received sorafenib

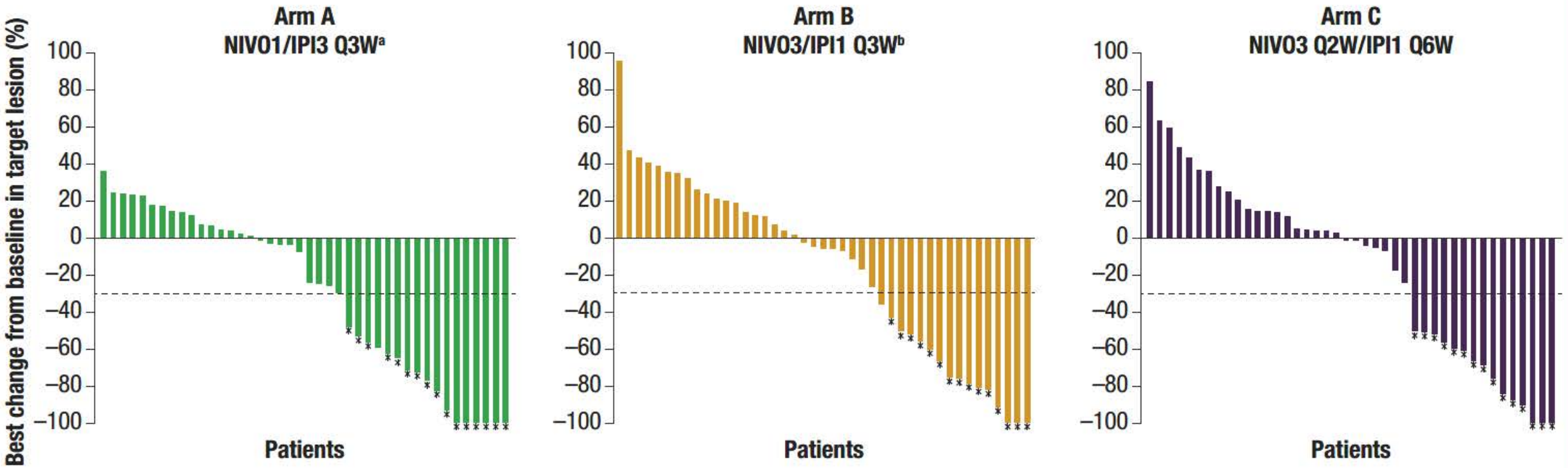


	Arm A (n=50)	Arm B (n=49)	Arm C (n=49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
Complete response	4 (8)	3 (6)	0
Partial response	12 (24)	12 (24)	15 (31)
Stable disease	9 (18)	5 (10)	9 (18)
Progressive disease	20 (40)	24 (49)	21 (43)
Unable to determine	3 (6)	4 (8)	4 (8)
DCR, n (%)	27 (54)	21 (43)	24 (49)

1. Yau T, *et al. J Clin Oncol* 2019;15_suppl: 4012.

CheckMate 040

Best change in target lesion by treatment arm



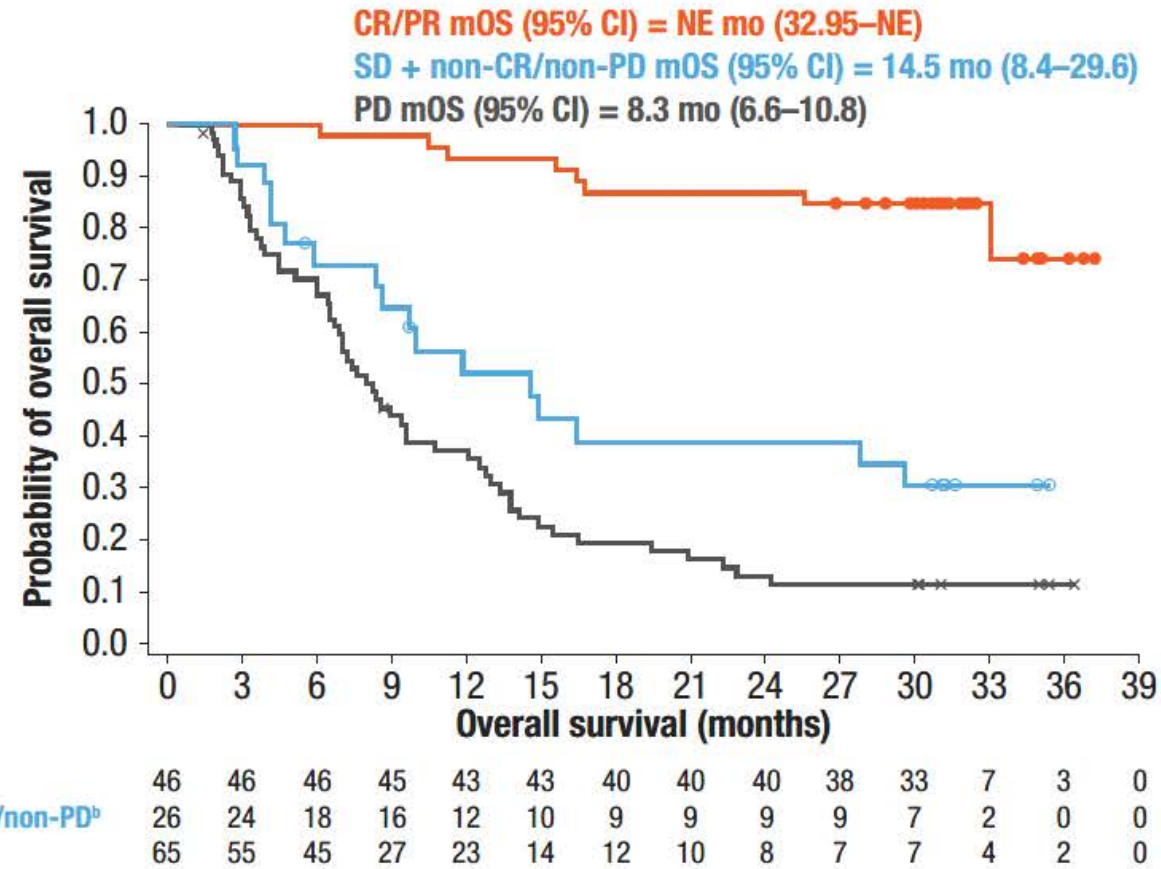
*Responders.

[a]NIVO1/IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose; [b]NIVO3/IPI1 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose.

Best change is based on evaluable target lesion measurements up to progression or start of subsequent therapy. Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1.

CheckMate 040

Overall survival by BOR in overall patient population



No. at risk[a]														
CR/PR	46	46	46	45	43	43	40	40	40	38	33	7	3	0
SD + non-CR/non-PD[b]	26	24	18	16	12	10	9	9	9	9	7	2	0	0
PD	65	55	45	27	23	14	12	10	8	7	7	4	2	0

	All patients N = 148
ORR by BICR using RECIST v1.1,[c] n (%)	46 (31)
CR	7 (5)
PR	39 (26)
SD,[d] n (%)	23 (16)
PD, n (%)	65 (44)
Unable to determine, n (%)	11 (7)
DCR,[e] n (%)	72 (49)

[c]Defined as CR + PR; [d]SD was reported as non-CR/non-PD in 2 patients in Arm A and 1 patient in Arm B who only had non-target lesions at baseline and so did not meet the definition of SD by BICR; [e]Defined as CR + PR + SD + non-CR/non-PD.

[a]11 patients did not have a scan, and therefore BOR could not be determined; [b]Non-CR/non-PD are patients who only have non-target lesions at baseline and so do not meet the definition of SD by BICR.

CheckMate 040 – safety of nivolumab + ipilimumab in 148 patients who had previously received sorafenib[1]

TRAEs ≥10% of patients, n (%)	Arm A (n=49)		Arm B (n=49)		Arm C (n=48)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any	46 (94)	26 (53)	35 (71)	14 (29)	38 (79)	15 (31)
Pruritus	22 (45)	2 (4)	16 (33)	0	14 (29)	0
Rash	14 (29)	2 (4)	11 (22)	2 (4)	8 (17)	0
Diarrhoea	12 (24)	2 (4)	6 (12)	1 (2)	8 (17)	1 (2)
AST increase	10 (20)	8 (16)	10 (20)	4 (8)	6 (13)	2 (4)
Lipase increase	7 (14)	6 (12)	6 (12)	3 (6)	8 (17)	4 (8)
Fatigue	9 (18)	1 (2)	6 (12)	0	5 (10)	0
ALT increase	8 (16)	4 (8)	7 (14)	3 (6)	4 (8)	0
Hypothyroidism	10 (20)	0	4 (8)	0	4 (8)	0
Rash maculopapular	7 (14)	2 (4)	4 (8)	0	3 (6)	0
Decreased appetite	6 (12)	0	4 (8)	0	3 (6)	0
Malaise	6 (12)	1 (2)	3 (6)	0	3 (6)	0
Adrenal insufficiency	7 (14)	1 (2)	3 (6)	0	2 (4)	0
Nausea	5 (10)	0	4 (8)	0	1 (2)	0
Pyrexia	2 (4)	0	4 (8)	0	5 (10)	0

Immune-mediated TRAEs ≥10% of patients, n (%)	Arm A (n=49)		Arm B (n=49)		Arm C (n=48)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Rash	17 (35)	3 (6)	14 (29)	2 (4)	8 (17)	0
Hepatitis	10 (20)	10 (20)	6 (12)	5 (10)	3 (6)	3 (6)
Adrenal insufficiency	9 (18)	2 (4)	3 (6)	0	3 (6)	0
Diarrhoea/colitis	5 (10)	3 (6)	1 (2)	1 (2)	1 (2)	1 (2)
Pneumonitis	5 (10)	3 (6)	0	0	0	0

1. Yau T, *et al. J Clin Oncol* 2019;15_suppl: 4012.

U.S. Food and Drug Administration Accepts for Priority Review Application for Nivolumab Plus Ipilimumab Combination for Patients with Previously Treated Advanced Hepatocellular Carcinoma

The FDA also granted nivolumab plus ipilimumab Breakthrough Therapy Designation for this potential indication

November 11, 2019 6:59 AM Eastern Standard Time

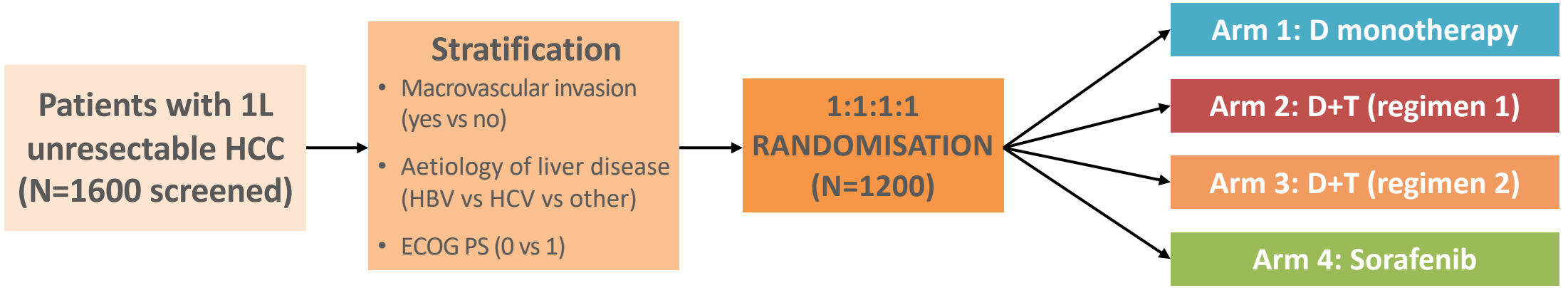
The FDA granted the application Priority Review with a Prescription Drug User Fee Act (PDUFA) goal date of March 10, 2020.

CheckMate 9DW

- ***A Randomized, Multi-center, Phase 3 Study of Nivolumab in Combination With Ipilimumab Compared to Sorafenib or Lenvatinib as First-Line Treatment in Participants With Advanced Hepatocellular Carcinoma***
  - Primary Outcome Measure:
    - Overall Survival (OS)
  - Secondary Outcome Measures:
    - Objective Response Rate (ORR)
    - Duration of Response (DOR)
    - Time to Symptom Deterioration (TTSD)
- Start 9/19
- Primary Completion 9/23

HIMALAYA Study Design

- HIMALAYA (NCT03298451) is the first randomised, open-label, multicentre, Phase 3 study to assess the efficacy and safety of durvalumab + tremelimumab combination therapy and durvalumab monotherapy versus sorafenib in the first-line treatment of patients with unresectable, histologically confirmed HCC.



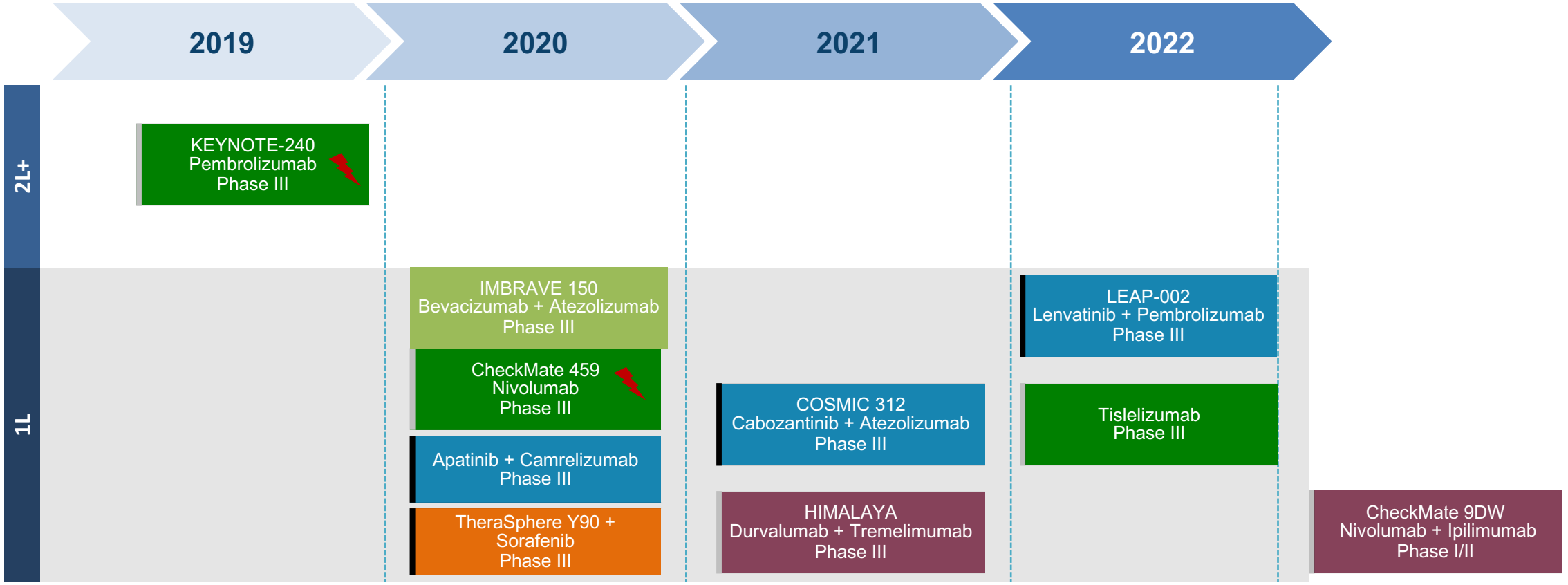
Primary Completion: 9/23

Treat until confirmed progression, unacceptable toxicity or any discontinuation criteria are met.

1L, first-line; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, chronic hepatitis B virus; HCC, hepatocellular carcinoma; HCV, chronic hepatitis C virus; T, tremelimumab.

Clinical research update: Trials to watch

Estimated study completion times based on information on clinicaltrials.gov



Legend

- TKI
- TKI + CPI
- Locoregional Therapy
- Anti-VEGF + CPI
- CPI Single
- CPI Combo

Trial did not meet statistical significance across endpoints