New Directions in the Management of HCC

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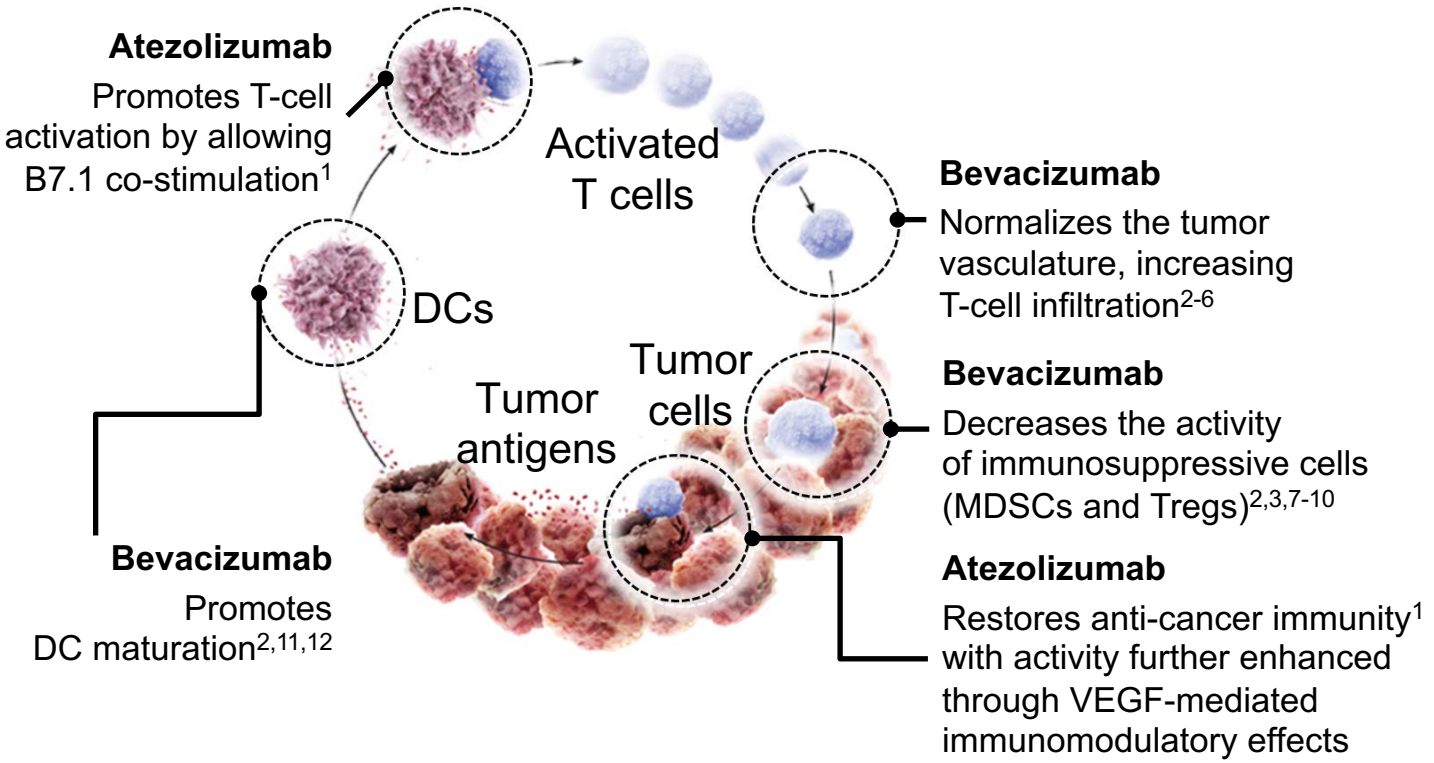
The Challenge

- Progress in systemic therapy has been slow
- Incremental improvements with sequential VEGFR TKIs
- Immune checkpoint inhibitors have demonstrated single-agent activity in advanced HCC but phase 3 studies did not meet their endpoints
- How do we improve outcomes with IO in HCC?
  - Biomarker select those patients that are most likely to benefit
  - Novel combinations that increase efficacy

Courtesy of Richard S Finn, MD

Combining VEGF Inhibition and Anti-PD-1/PD-L1 Agents



- Bevacizumab (anti-VEGF) is an antiangiogenic agent with additional immunomodulatory effects
- In combination, bevacizumab may further enhance atezolizumab's efficacy by reversing VEGF-mediated immunosuppression to promote T-cell infiltration into the tumor

1. Chen DS, Mellman I. *Immunity*. 2013;39:1-10. 2. Hegde PS et al. *Semin Cancer Biol.* 2018;52:117-124. 3. Wallin JJ et al. *Nat Commun*. 2016;7:12624. 4. Goel S et al. *Physiol Rev*. 2011;91:1071-1121. 5. Motz GT et al. *Nat Med*. 2014;20:607-615. 6. Hodi FS et al. *Cancer Immunol Res*. 2014;2:632-642. 7. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol*. 2009;9:162-174. 8. Roland CL et al. *PLoS One*. 2009;4:e7669. 9. Facciabene A et al. *Nature*. 2011;475:226-230. 10. Voron T et al. *J Exp Med*. 2015;21:139-148. 11. Gabrilovich DI. *Nat Med*. 1996;2:1096-1103. 12. Oyama T et al. *J Immunol*. 1998;160:1224-1232.

Courtesy of Richard S Finn, MD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Richard S. Finn, M.D., Shukui Qin, M.D., Masafumi Ikeda, M.D., Peter R. Galle, M.D., Michel Ducreux, M.D., Tae-You Kim, M.D., Masatoshi Kudo, M.D., Valeriy Breder, M.D., Philippe Merle, M.D., Ahmed O. Kaseb, M.D., Daneng Li, M.D., Wendy Verret, Ph.D., Derek-Zhen Xu, M.D., Sairy Hernandez, Ph.D., Juan Liu, Ph.D., Chen Huang, M.D., Sohail Mulla, Ph.D., Yulei Wang, Ph.D., Ho Yeong Lim, M.D., Andrew X. Zhu, M.D., Ph.D., and Ann-Lii Cheng, M.D., for the IMbrave150 Investigators*

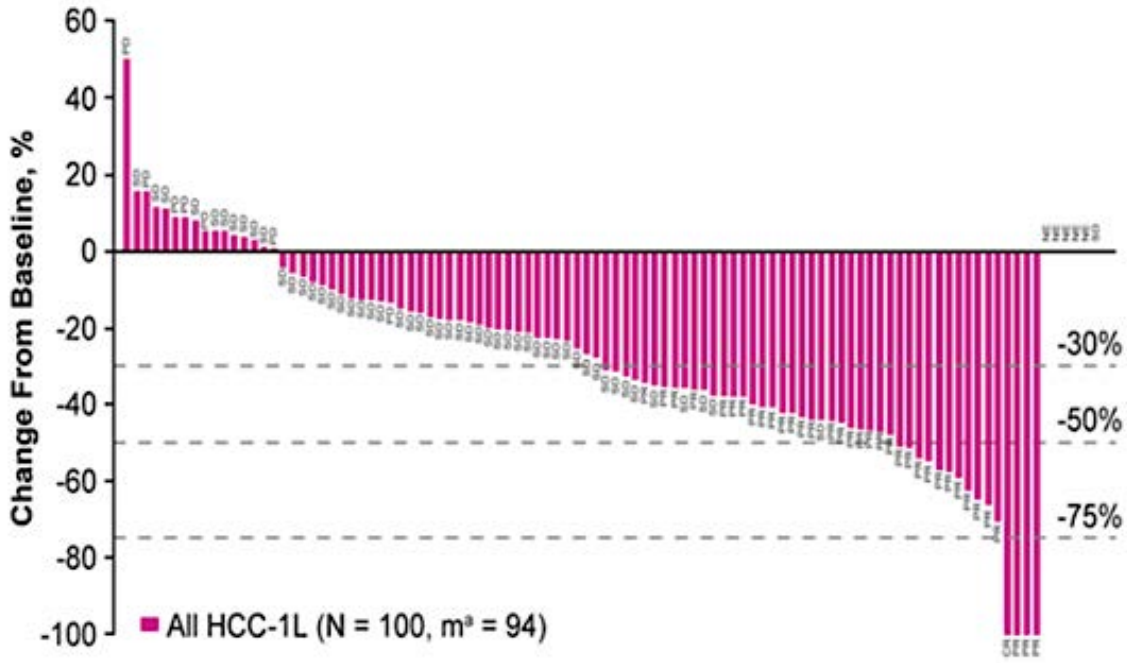
Courtesy of Richard S Finn, MD

KEYNOTE-524: Lenvatinib+Pembrolizumab Efficacy Outcomes

Parameter	Lenvatinib + Pembrolizumab (N = 100)
	RECIST v1.1 per IIR
ORR (confirmed responses), n (%) (95% CI)[a]	36 (36) (26.6–46.2)
Best overall response, n (%)	
Complete response	1 (1)
Partial response	35 (35)
Stable disease[b]	52 (52)
Progressive disease	7 (7)
Unknown/not evaluable	5 (5)
Median DOR[c] for confirmed responders, months (95% CI)[d]	12.6 (6.9–NE)
Median TTR for confirmed responders, months (range)	2.8 (1.2–7.7)
Disease control rate, n (%) (95% CI)[a]	88 (88) (80.0–93.6)

[a]The 95% CIs are calculated using an exact method of binomial distribution (Clopper–Pearson method); [b]includes unconfirmed partial response, noncomplete response/ nonprogressive disease, and durable stable disease; [c]the Kaplan–Meier method was used for estimating DOR; [d]the 95% CIs are based on a generalized Brookmeyer and Crowley method.

Percentage Change From Baseline in Sum of Diameters of Target Lesions at Postbaseline Nadir (IIR; RECIST v1.1)

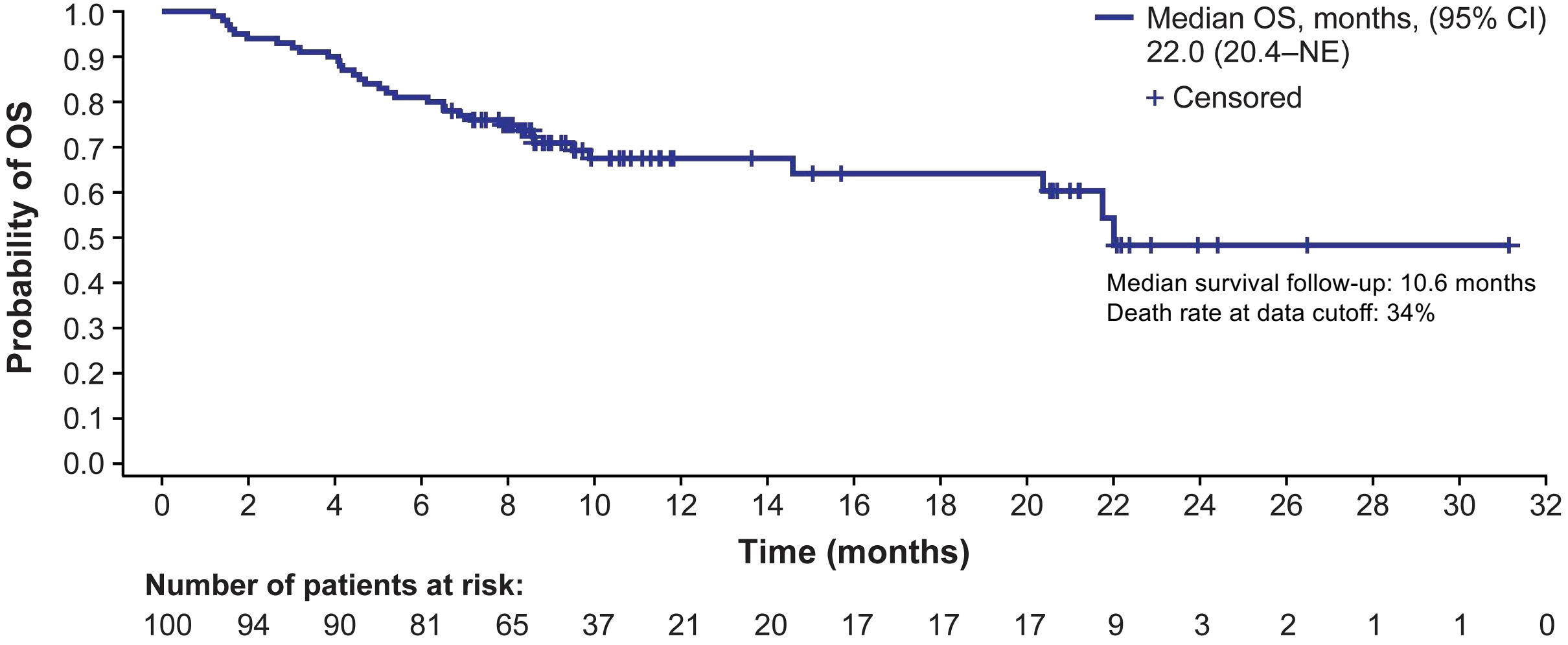


[a]m = number of patients with both baseline and postbaseline values for the sum of diameters of target lesions.

- Finn et al JCO 2020.

Courtesy of Richard S Finn, MD

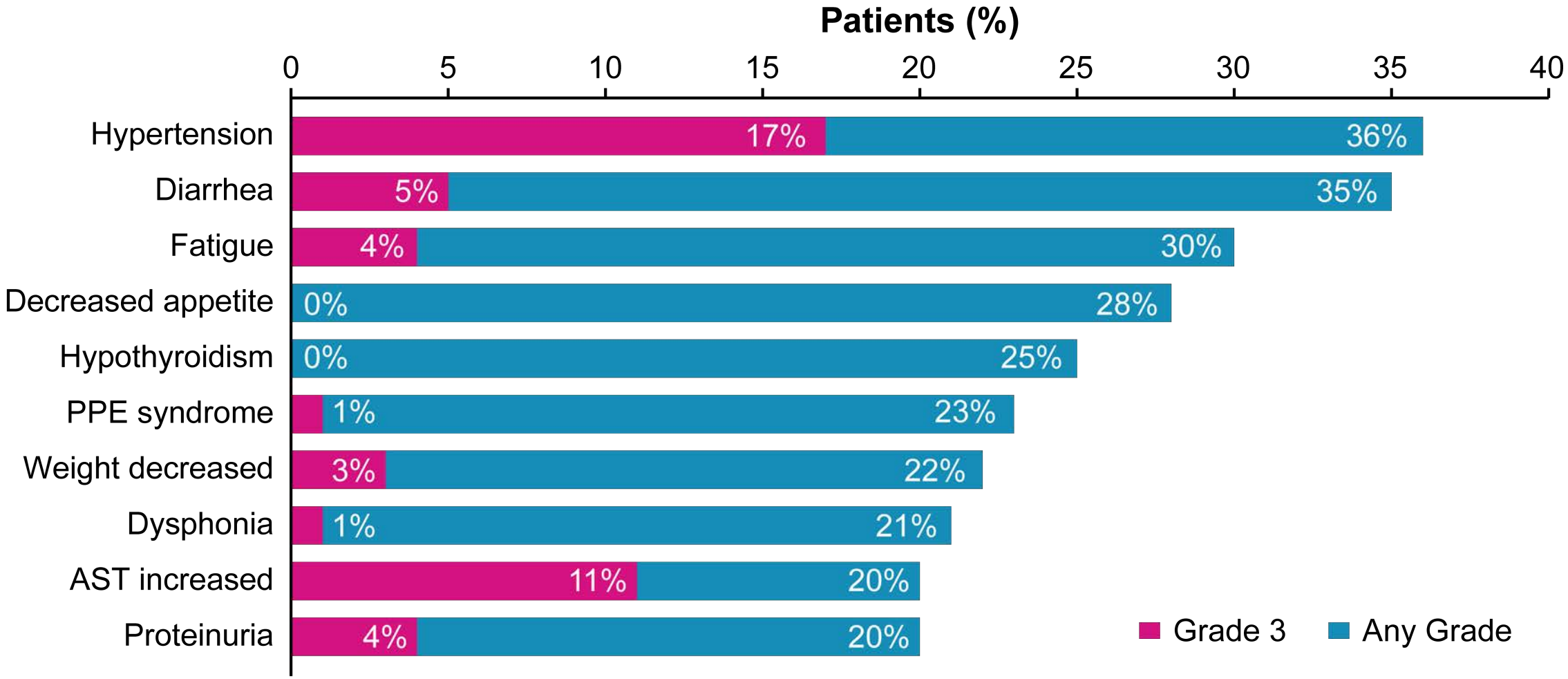
KEYNOTE-524 Kaplan-Meier Estimates of OS



- Finn et al JCO 2020.

Courtesy of Richard S Finn, MD

KEYNOTE-524 Most Common TRAEs[a] (≥ 20% of Patients)



[a]There was 1 grade 4 treatment-related AE (leukopenia/neutropenia).

- Finn et al JCO 2020.

Courtesy of Richard S Finn, MD

KEYNOTE-524 Safety

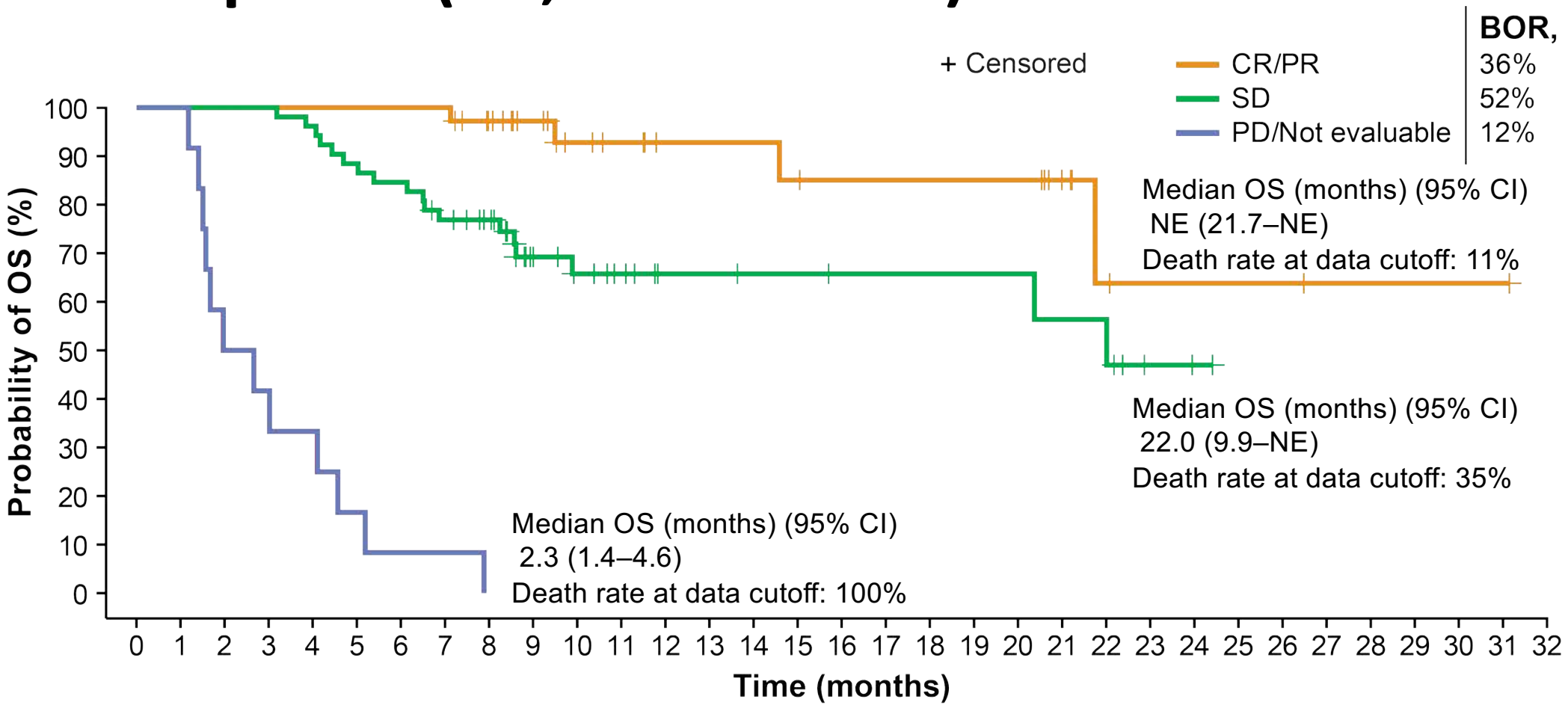
- Median duration of exposure
  - Overall treatment duration[a]: 7.9 months (minimum: 0.2; maximum: 31.1)
  - Lenvatinib: 7.6 months (minimum: 0.2; maximum: 31.1)
  - Pembrolizumab: 7.4 months (minimum: 0.03; maximum: 23.5)
- 95% Of patients had ≥ 1 TRAE
- 67% Of patients had grade ≥ 3 TRAEs
  - Grade 3: 63%
  - Grade 4: 1% (leukopenia / neutropenia, n = 1)
  - Grade 5: 3% (acute respiratory failure / acute respiratory distress syndrome, n = 1; abnormal hepatic function, n = 1; intestinal perforation, n = 1)

[a]The duration between the earliest start date of the first dose of either medication and the latest date of last dose of either medication.

- Finn et al JCO 2020.

Courtesy of Richard S Finn, MD

KEYNOTE-524 Kaplan–Meier Estimates of OS by Best Overall Response (IIR; RECIST v1.1)



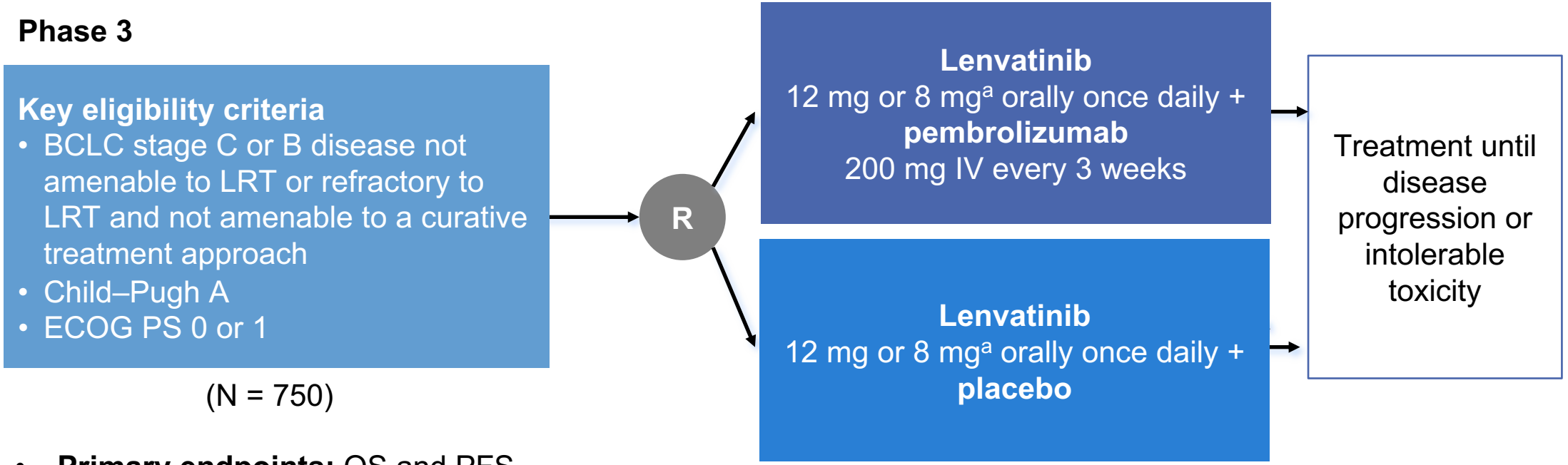
Number of patients at risk:

CR/PR	36	36	36	36	36	36	36	36	31	24	19	17	12	12	12	11	10	10	10	10	10	6	3	2	2	2	2	1	1	1	1	1	0
SD	52	52	52	52	50	46	44	39	34	22	18	13	9	9	8	8	7	7	7	7	7	6	6	2	1	0	0	0	0	0	0	0	0
PD/Not evaluable	12	12	6	5	4	2	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- Finn et al EASL 2020.

Courtesy of Richard S Finn, MD

LEAP-002: First-Line Lenvatinib Plus Pembrolizumab Versus Lenvatinib Plus Placebo in Advanced HCC[1]



- **Primary endpoints:** OS and PFS
- **Secondary endpoints:** ORR, DOR, DCR, and safety

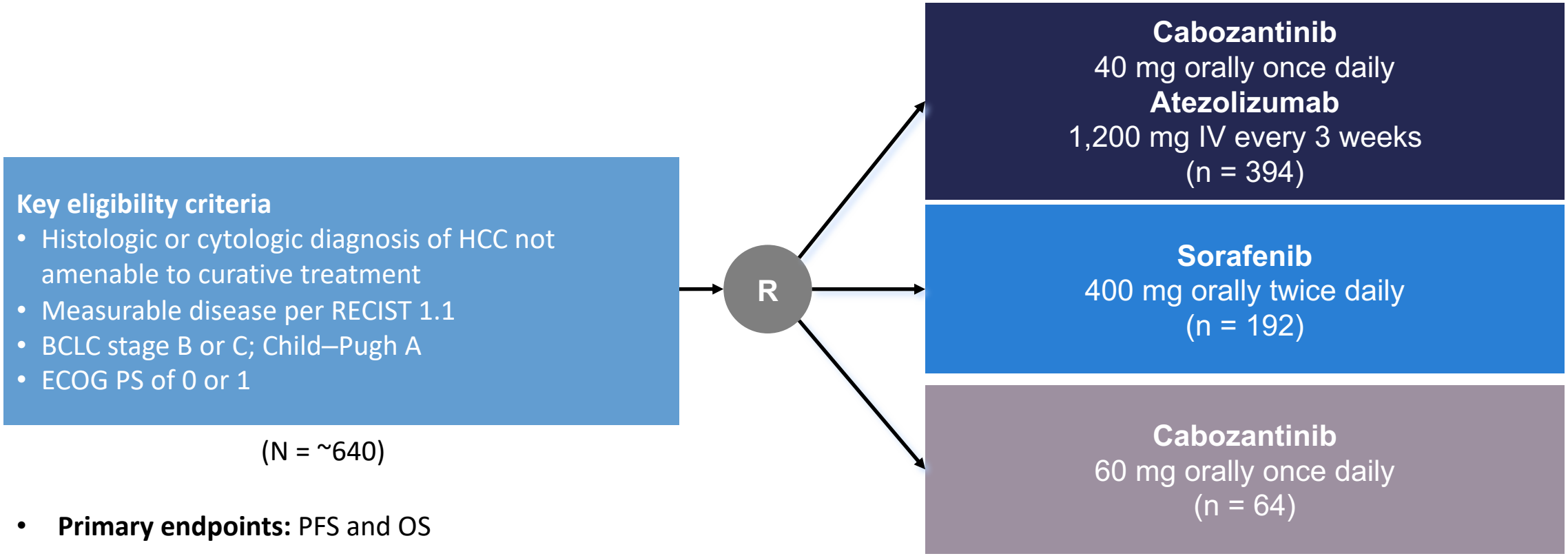
[a] 12 mg (for participants with screening body weight ≥60 kg) or 8 mg (for participants with screening body weight <60 kg).

1. https://clinicaltrials.gov/ct2/show/NCT03713593. Accessed May 13, 2019.

Courtesy of Richard S Finn, MD

Phase 3 COSMIC-312 Study: Cabozantinib ± Atezolizumab Versus Sorafenib in Advanced HCC[1]

Study in Adults With Advanced HCC Who Have Not Received Prior Systemic Anticancer Therapy in the Advanced Setting



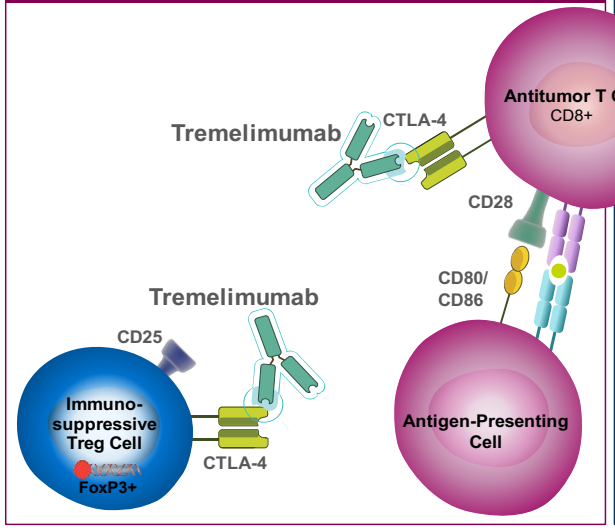
- **Primary endpoints:** PFS and OS

1. https://clinicaltrials.gov/ct2/show/NCT03755791. Accessed May 13, 2019.

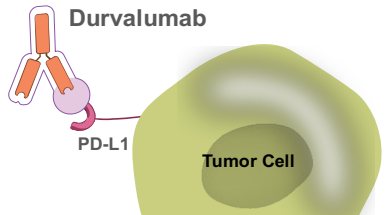
Courtesy of Richard S Finn, MD

Revisiting anti-CTLA-4 and anti-PD-(L)1 Combination Strategy

Tremelimumab Blocks Suppressive T-Cell Signaling in the Lymph Node



Durvalumab Inhibits Suppressive PD-1/ PD-L1 Interactions in the TME

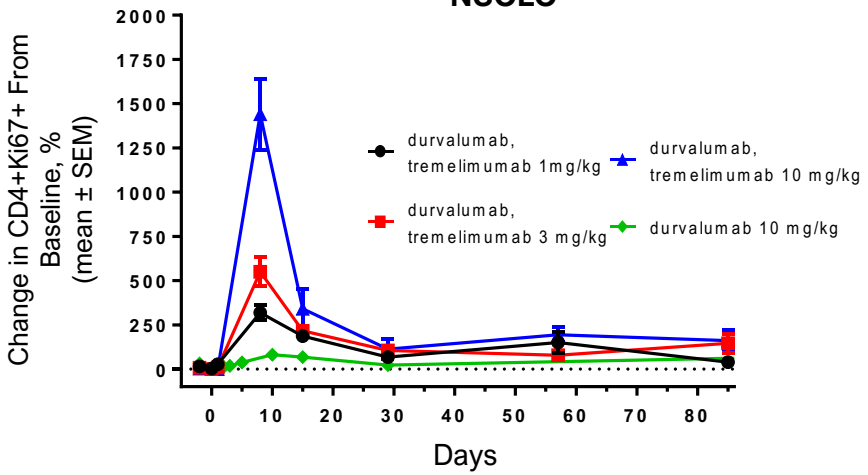


Durvalumab continues to maintain immune activity through inhibition of interactions between PD-1 induced on activated T cells and IFN-γ-driven PD-L1 expression in the TME.[1-3]

In solid tumors, ICI regimens incorporating higher doses of anti-CTLA-4 combined with anti-PD-(L)1 are often associated with improved OS compared to those with lower doses of anti-CTLA-4 but with increased toxicity.[4-9]

- High-dose T combined with D results in an initial burst of peripheral T-cells in patients with NSCLC.[10]
- Similarly in melanoma, the initial dose of ipilimumab + nivolumab causes a proliferative burst of peripheral Tcells, which is not repeated at subsequent doses.[11]

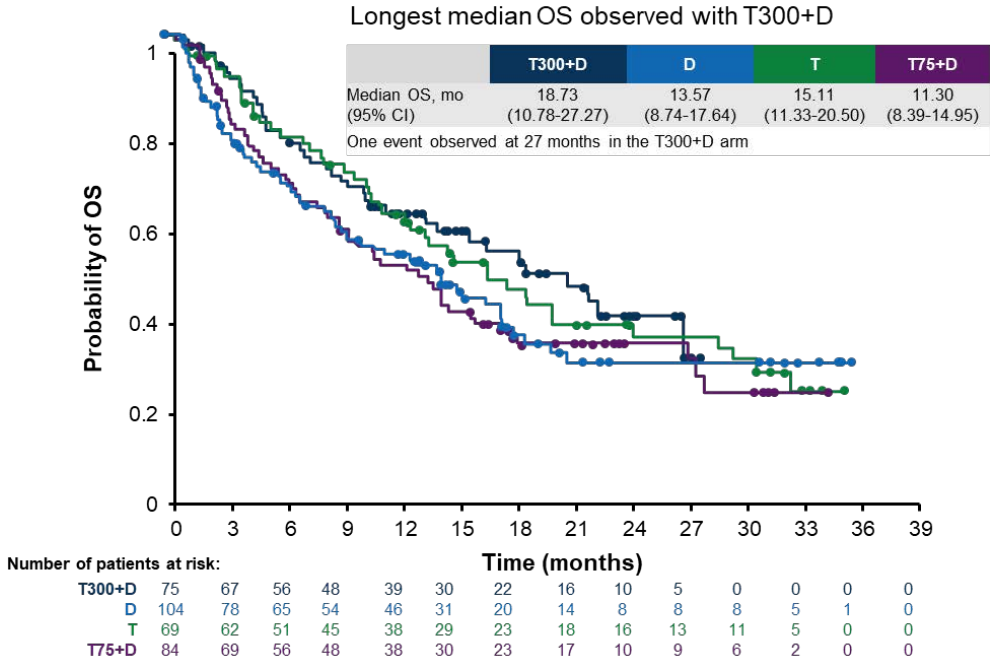
NSCLC[10]



Could a single priming dose of tremelimumab with durvalumab improve immune-mediated clinical activity in HCC patients while minimizing toxicity?

1. Huang, et al. *Nature,* 2017. 60-65; 2. Kamphorts, et al. *PNAS,* 2017. 4993-4998; 3. Butte, et al. *Immunity,* 2007. 111-122; 4.Yau, et al. *J Clin Oncol,* 2019. abstr 4012; 5. Naumann, et al. *Ann Oncol,* 2019. v851-v934; 6. Hellmann, et al. *J Cin Oncol,* 2017. abstr 8503; 7. Sharma, et al. *J Clin Oncol,* 2019. 1608-1616; 8. Janjigian, et al. *J Clin Oncol,* 2018. 2836-2844; 9. Weber, et al. *J Clin Oncol,* 2012. 2691-2697; 10. Antonia, et al. Lancet Oncol, 2016. 299-308. 11. Souza, et al. *Cancer Res*, 2018. abstr CT 104.

Phase 2 Trial: Tremelimumab and Durvalumab[1]

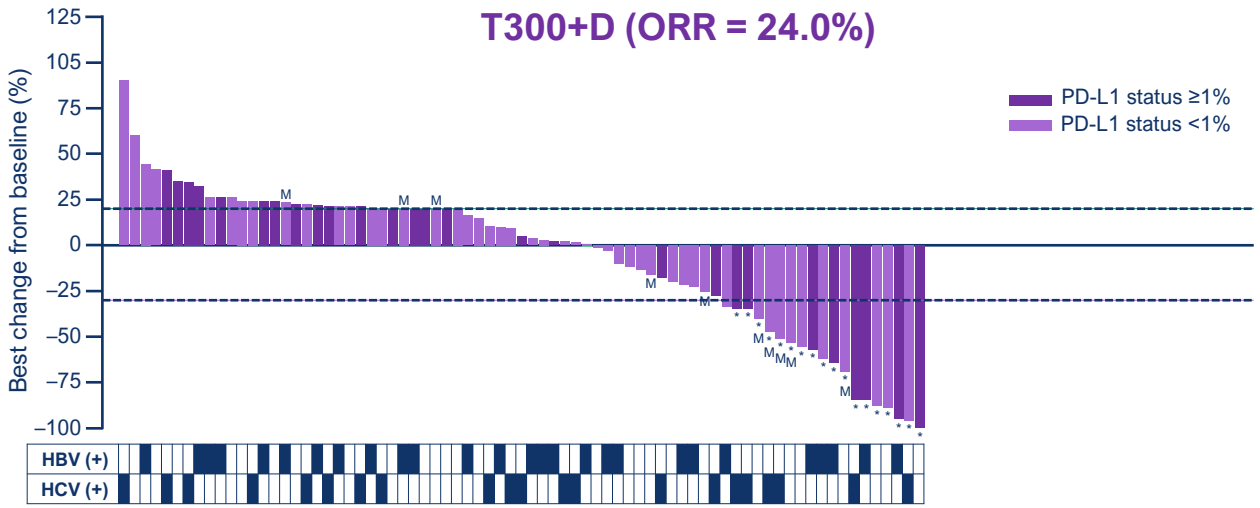


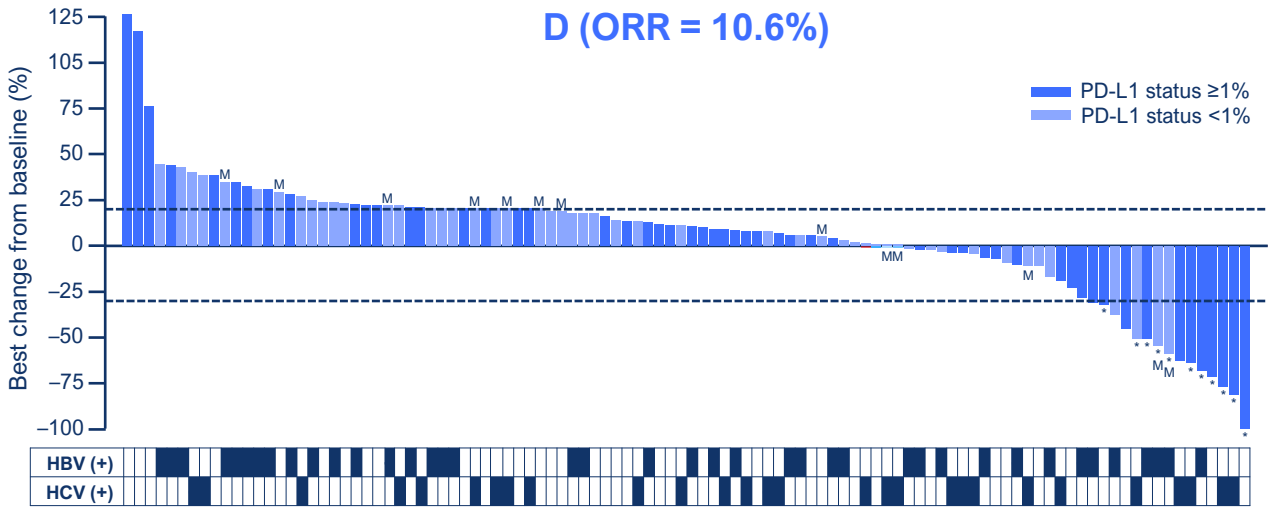
	T300+D (n = 75)	T75+D (n = 84)	D (n = 104)	T (n = 69)
Grade 3/4 TRAEs, %	35.1	24.4	17.8	42.0
Serious TRAEs, %	13.5	11.0	10.9	21.7
Grade 5 TRAEs, n	0	1[a]	3[b]	0
Discontinuation due to TRAEs, %	10.8	6.1	7.9	11.6
ORR, % (95% CI)	24.0 (14.9-35.3)	9.5 (4.2-17.9)	10.6 (5.4-18.1)	7.2 (2.4-16.1)
Median DoR, mo	NR	13.2	11.2	24.0

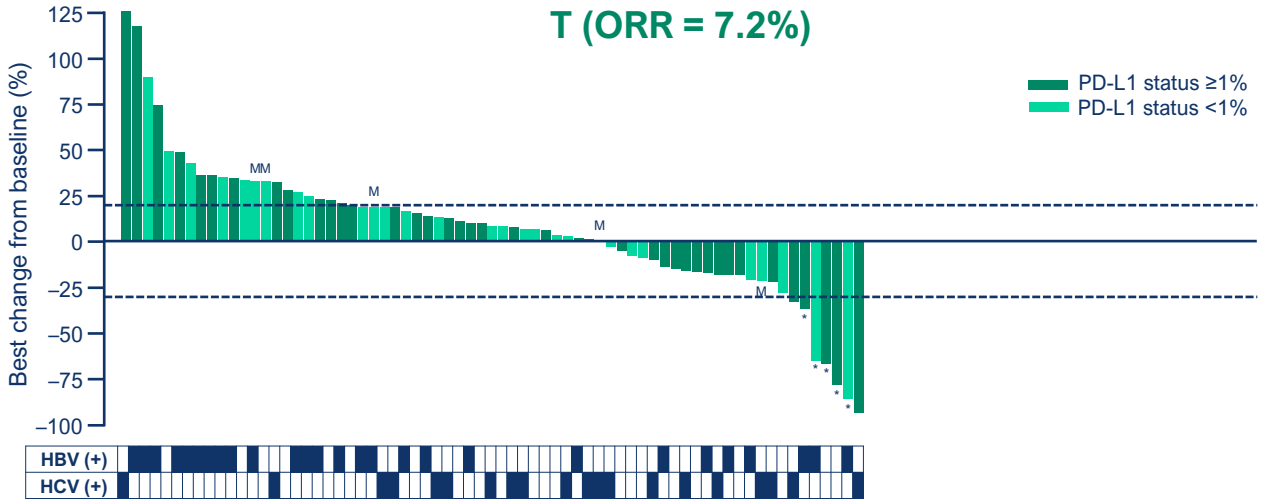
1. Kelley RK et al. ASCO 2020. Abstract 4508.

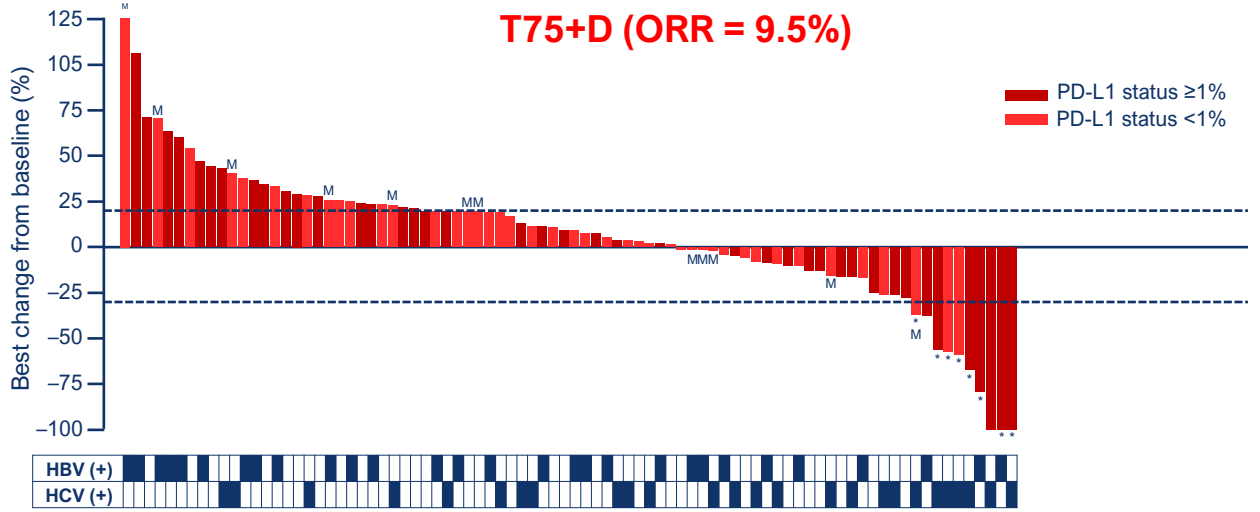
Courtesy of Richard S Finn, MD

Responses Observed Regardless of PD-L1 or Viral Status







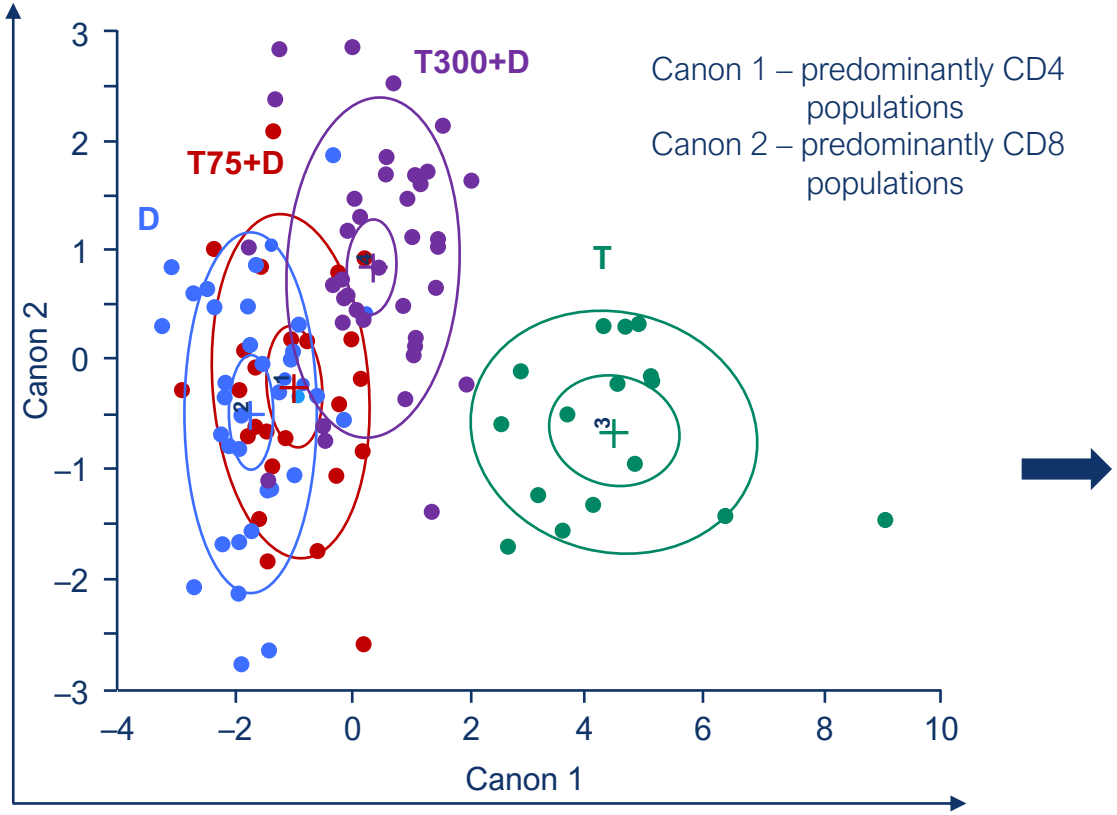


Courtesy of Richard S Finn, MD

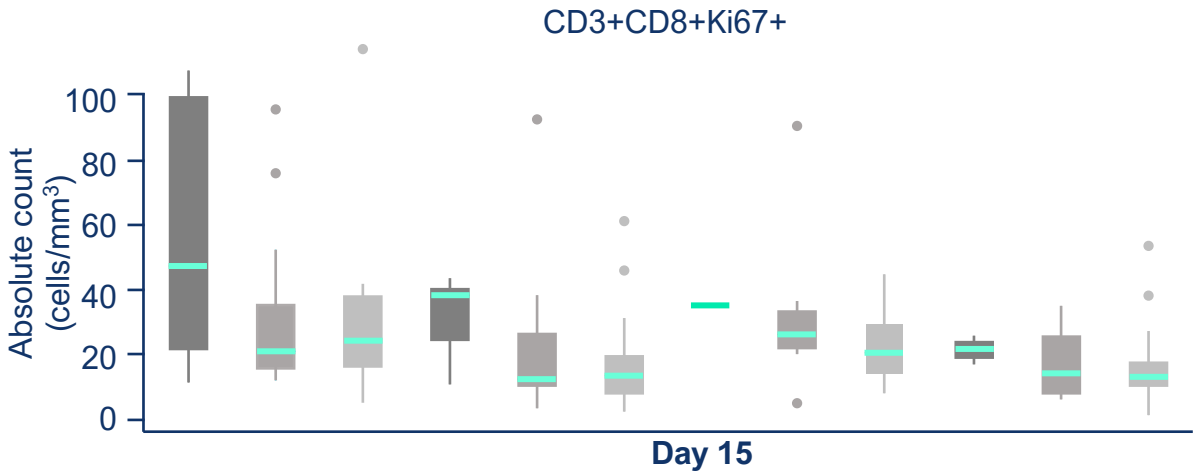
*Responders; M, PD-L1 status missing
PD-L1 status is calculated as total number of tumor cells and tumor-associated immune cells positive for PD-L1 divided by tumor area

Pharmacodynamic Biomarker Analysis

T300+D Drives an Acute Expansion of CD8+ Lymphocytes that is Associated with Response



Quadratic Discriminant Analysis of 26 lymphocyte populations on day 15 shows that T300+D patients are maximally differentiated by a lymphocyte population predominantly composed of CD3+CD8+Ki67+ T cells

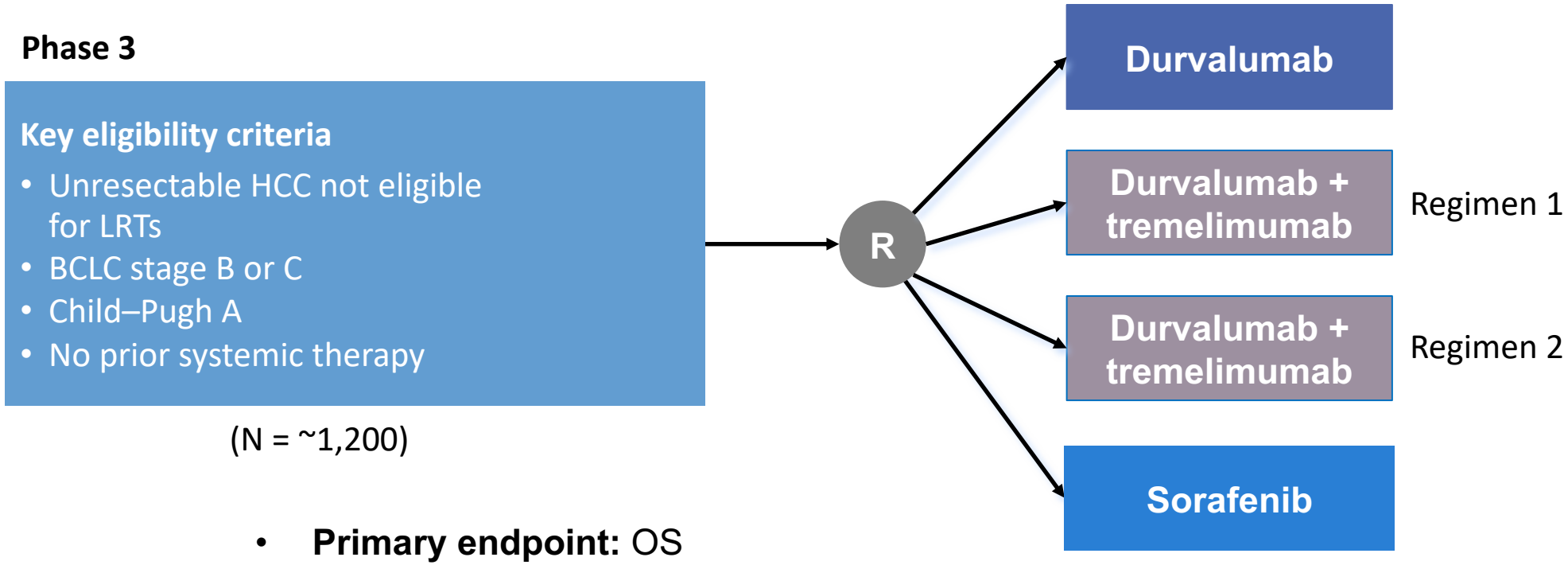


	T300+D			D			T			T75+D		
	CR/PR	SD	PD	CR/PR	SD	PD	CR/PR	SD	PD	CR/PR	SD	PD
Median	47	20.5	24	38	12	13	35	26	20	21.5	14	13
Count	9	18	19	3	9	23	1	7	8	2	8	18

Elevated CD8+Ki67+ T cells on day 15 are associated with CR/PR

Highest median CD8+Ki67+ T cells occurred in CR/PR in T300+D arm

Phase III HIMALAYA Trial: Durvalumab Plus Tremelimumab Versus Sorafenib[1]

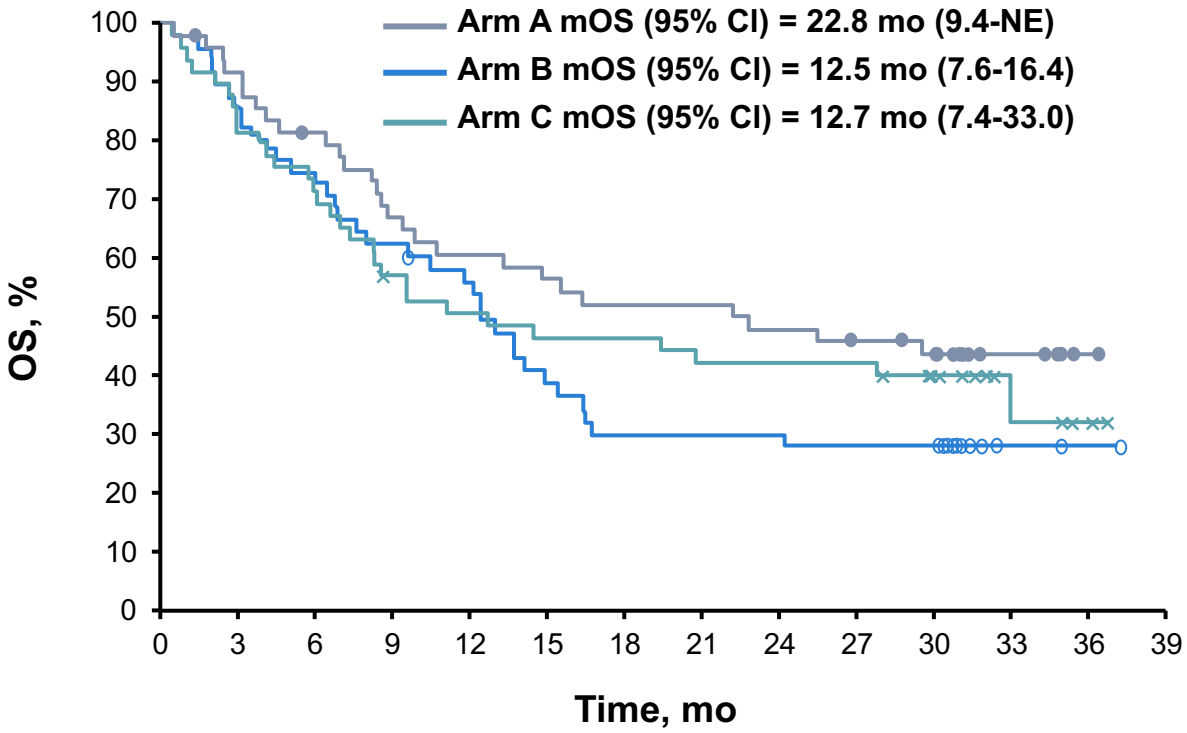


- **Primary endpoint:** OS
- **Other endpoints:** TTP, PFS, ORR, DCR, DOR, and QOL

Courtesy of Richard S Finn, MD

CheckMate-040: Nivolumab + Ipilimumab Efficacy Results[1,2]

	Arm A NIVO1/IPI3 Q3W (n = 50)	Arm B NIVO3/IPI1 Q3W (n = 49)	Arm C NIVO3 Q2W/ IPI1 Q6W (n = 49)
ORR by BICR using RECIST v1.1, 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)
Unable to determine	3 (6)	4 (8)	4 (8)
DCR, n (%)	27 (54)	21 (43)	24 (49)
Median TTR (range), months	2.0 (1.1–12.8)	2.6 (1.2–5.5)	2.7 (1.2–8.7)
Median DOR (range), months	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)



- Similar ORR, DCR, and DOR were observed across treatment arms
  - Consistently high ORR (>30%) was achieved in all treatment arms
  - In total, 7 patients had complete response (4 in arm A and 3 in arm B)
- Arm A: NIVO1/ IPI3 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose
- Arm B: NIVO3/ IPI1 Q3W × 4 followed by nivolumab 240 mg IV Q2W flat dose
- ORR is defined as CR + PR
- SD does not include 2 patients in arm A and 1 patient in arm B who were reported as non-CR/non-PD
- DCR is defined as CR + PR + SD + non-CR/non-PD

1. El-Khoueiry AB et al. ILCA 2019. Abstract O-13. 2. Yau T et al JAMA Onc 2020

Courtesy of Richard S Finn, MD

CheckMate-040: Nivolumab + Ipilimumab Treatment-related Adverse Events

Summary of TRAEs	Arm A NIVO1/IPI3 Q3W* N = 49		Arm B NIVO3/IPI1 Q3W** N = 49		Arm C NIVO3 Q2W/IPI1 Q6W N = 48	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any TRAE, n(%)	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
Diarrhea	12 (24)	2 (4)	6 (12)	1 (2)	8 (17)	1 (2)
AST increased	10 (20)	8 (16)	10 (20)	4 (8)	6 (13)	2 (4)
Upase Increased	7 (14)	6 (12)	6 (12)	3 (6)	8 (17)	4 (8)
Fatigue	9 (18)	1 (2)	6 (12)	0	5 (10)	0
ALT increased	8 (16)	4 (8)	7 (14)	3 (6)	4 (8)	0
Hypothyroidism	10 (20)	0	4 (8)	0	4 (8)	0
Rash maculo-papular	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

- Rates of any grade TRAEs:
  - 94% Arm A
  - 71% Arm B
  - 79% Arm C
- Types of TRAEs similar across all treatment arms

Yau T et al JAMA Onc 2020

Courtesy of Richard S Finn, MD

CheckMate-040: Nivolumab + Ipilimumab Immune-mediated Adverse Events

Summary of IMAEs	Arm A NIVO1/IPI3 Q3W* N = 49		Arm B NIVO3/IPI1 Q3W** N = 49		Arm C NIVO3 Q2W/IPI1 Q6W N = 48	
n(%)	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
Diarrhea/colitis	5 (10)	3 (6)	1 (2)	1 (2)	1 (2)	1 (2)
Pneumonitis†	5 (10)	3 (6)	0	0	0	0
Nephritis/renal dysfunction	0	0	1 (2)	0	1 (2)	1 (2)
Hypersensitivity	0	0	1 (2)	1 (2)	1 (2)	0
Hypophysitis	1 (2)	0	0	0	1 (2)	1 (2)
Hyperthyroidism	0	0	1 (2)	0	1 (2)	0
Hypothyroidism/ thyroiditis	0	0	0	0	1 (2)	0
Diabetes mellitus	0	0	0	0	0	0

- Most common IMAEs in all arms: rash, hepatitis, and adrenal insufficiency
- Arm A had higher rates of IMAEs compared with Arms B and C

Yau T et al JAMA Onc 2020

Courtesy of Richard S Finn, MD

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

Courtesy of Richard S Finn, MD

Conclusions

- IMbrave150 trial validated IO in a phase 3 study in combination with VEGF targeting
  - Atezolizumab+bevacizumab
  - Phase III ORIENT-32 trial (China only): sintilimab combined with a bevacizumab biosimilar in patients with advanced HCC
- Other novel combinations are showing promising results in early phase studies
- IO + VEGFR TKIs
  - Lenvatinib+pembrolizumab (LEAP-002)
  - Cabozantinib+atezolizumab (COSMIC-312)
- Anti-PD-1/PD-L1 + Anti-CTLA-4
  - Nivolumab+ipilimumab (CheckMate 9DW)
  - Durvalumab+tremelimumab (HIMALAYA)

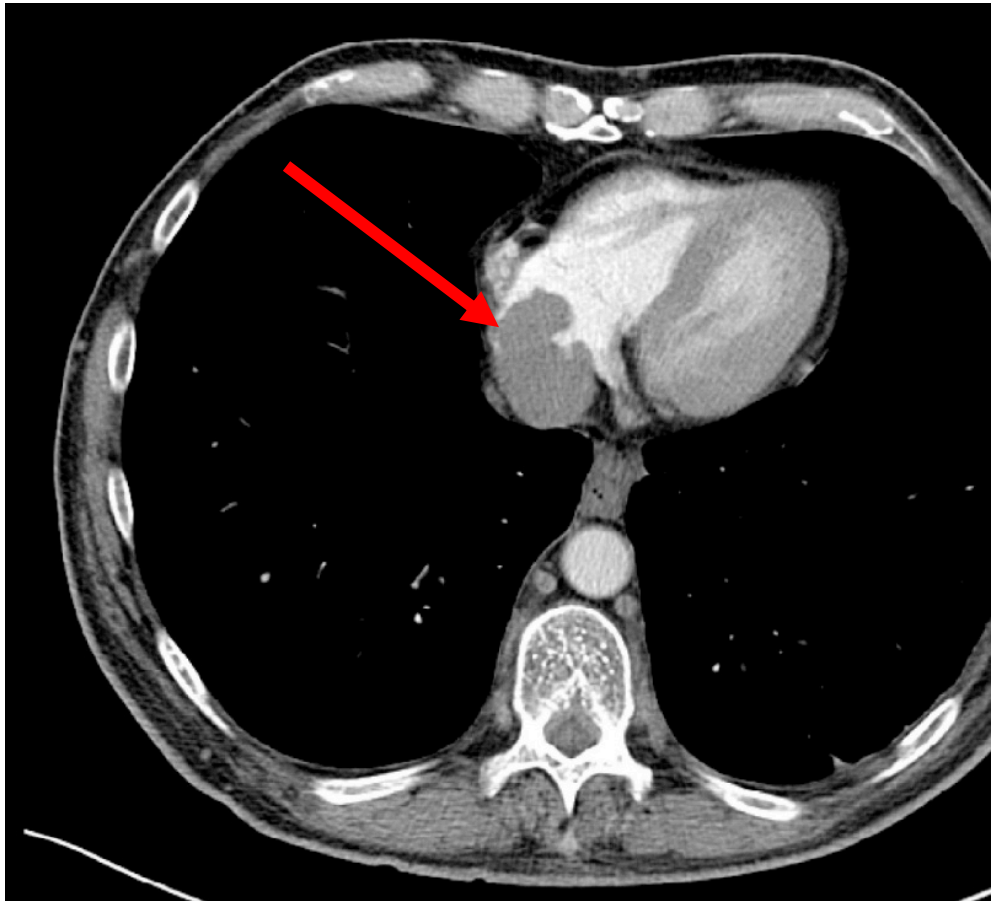
Courtesy of Richard S Finn, MD

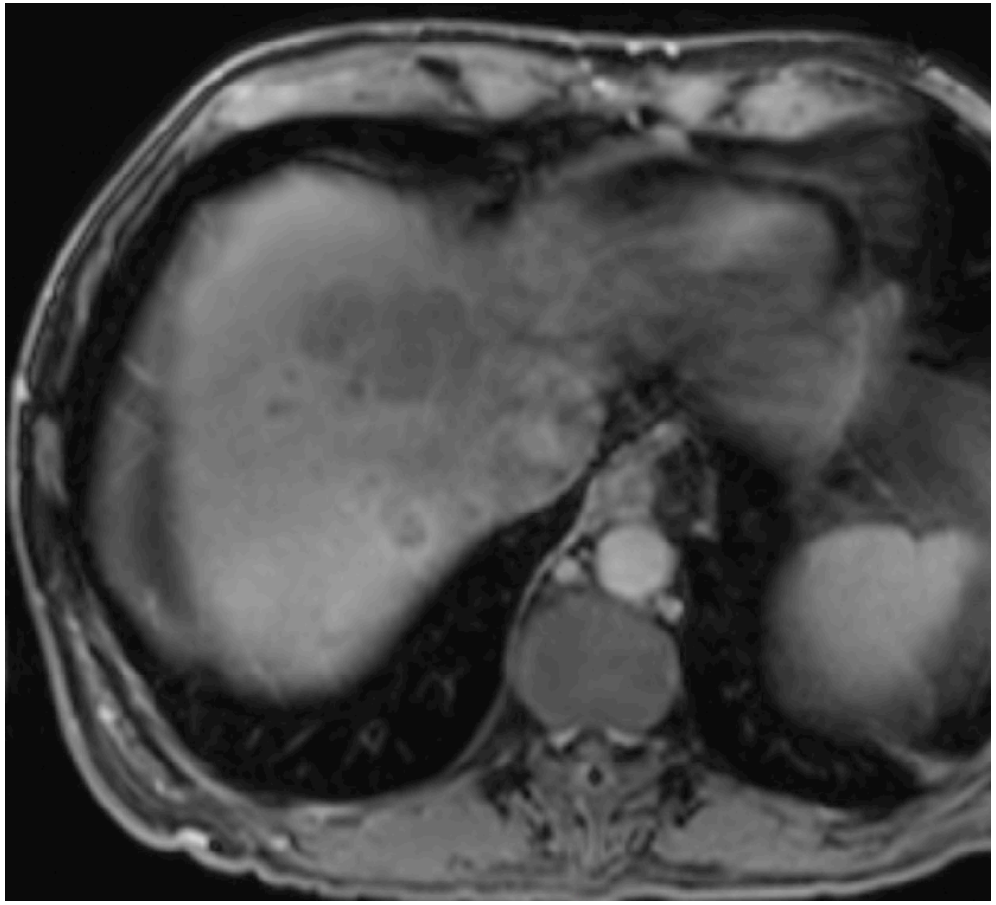
Case: Len/pembro for first-line advanced HCC

- 65 y.o. male who presented in late November of 2019, with progressive ascites, and muscle wasting. Ultimately, a CT scan was done on 12/20/19, which showed cirrhotic liver, with multiple enhancing liver lesions, largest 5.5cm compressing and invading his IVC.
- Labs done on 1/2/20 showed AFP of 1357, and positive for Hep C. Previous to this, he states he was not aware of being Hep C positive, but did use IV drugs in his teen years.
- WBC 7.0, Hgb 15.7, plts 89, Cr 0.5, T bili 1.4, Alb 3.8, AST 96, ALT 38.
- ECOG PS 2.

Courtesy of Richard S Finn, MD

Case: Len/pembro for first-line advanced HCC, continued





Courtesy of Richard S Finn, MD

Case: Len/pembro for first-line advanced HCC, continued

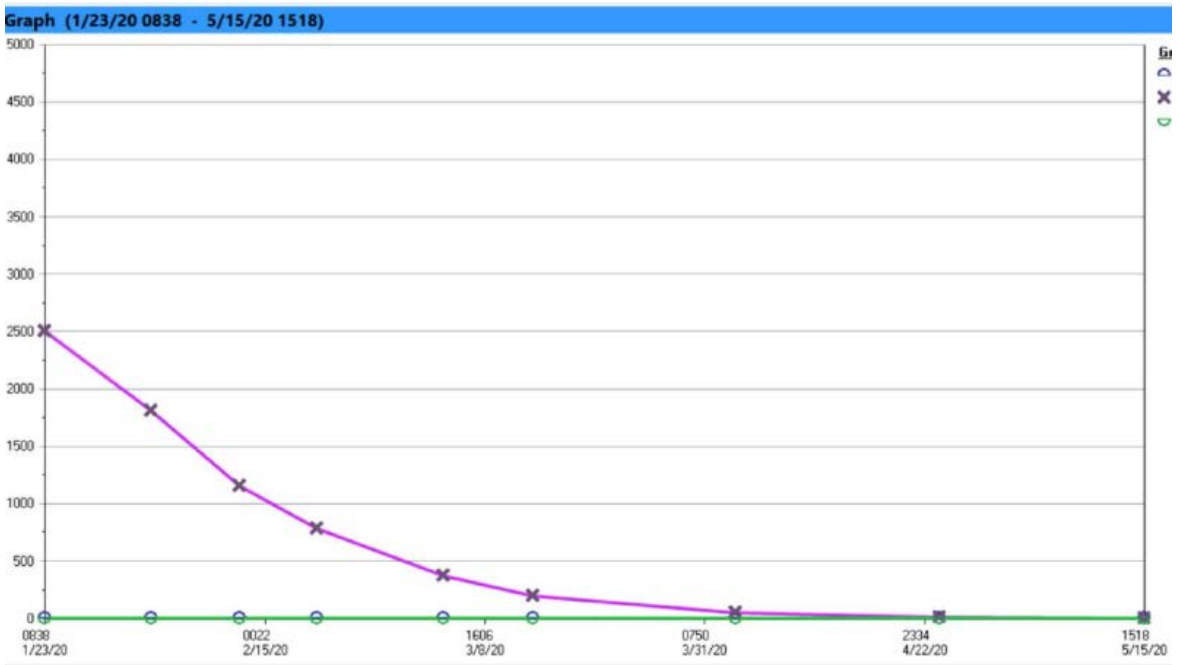
- Have discussion, pt with very advanced HCC with invasion into the RA
- CP A6/ B7 (from ascites)
- Needs a response and quickly
- Start len 12 mg + pembro Feb 2020
- T bili slowly rises, peaking at 4.6 in March

and len held, wt loss

- AFP rapidly declines
- T bili starts falling and len resumed at

4 mg then titrated to 8 mg

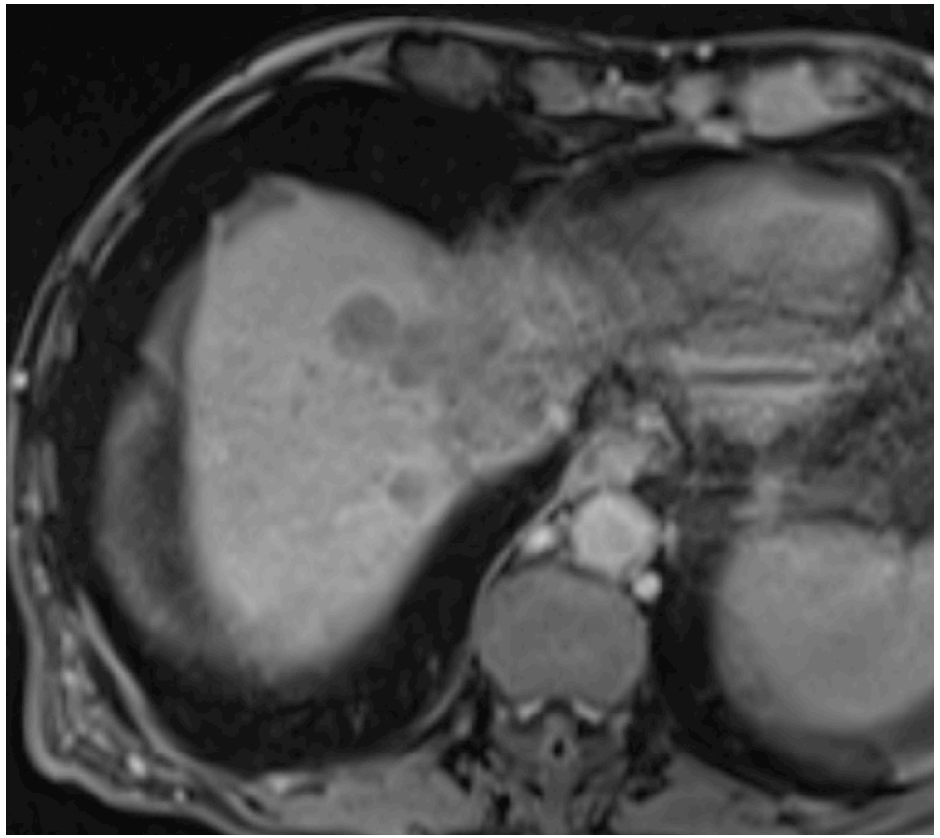
AFP over time



Courtesy of Richard S Finn, MD

Case: Len/pembro for first-line advanced HCC, continued

- Overall improving energy, decreased ascites, stopped using walker
- Reimaged May 2020 after C5 pembro
  - Significant response
- Ongoing response, 2021



Courtesy of Richard S Finn, MD