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Integrating systemic and liver-directed therapy: oncologist's perspective

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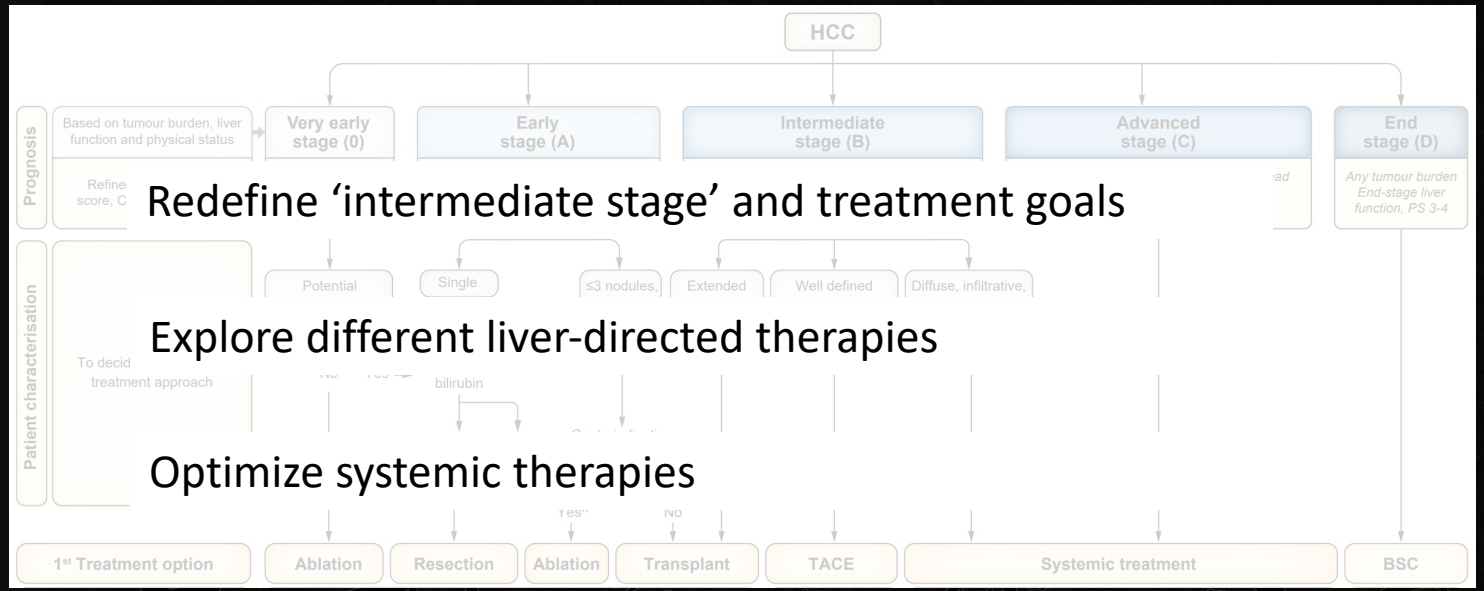


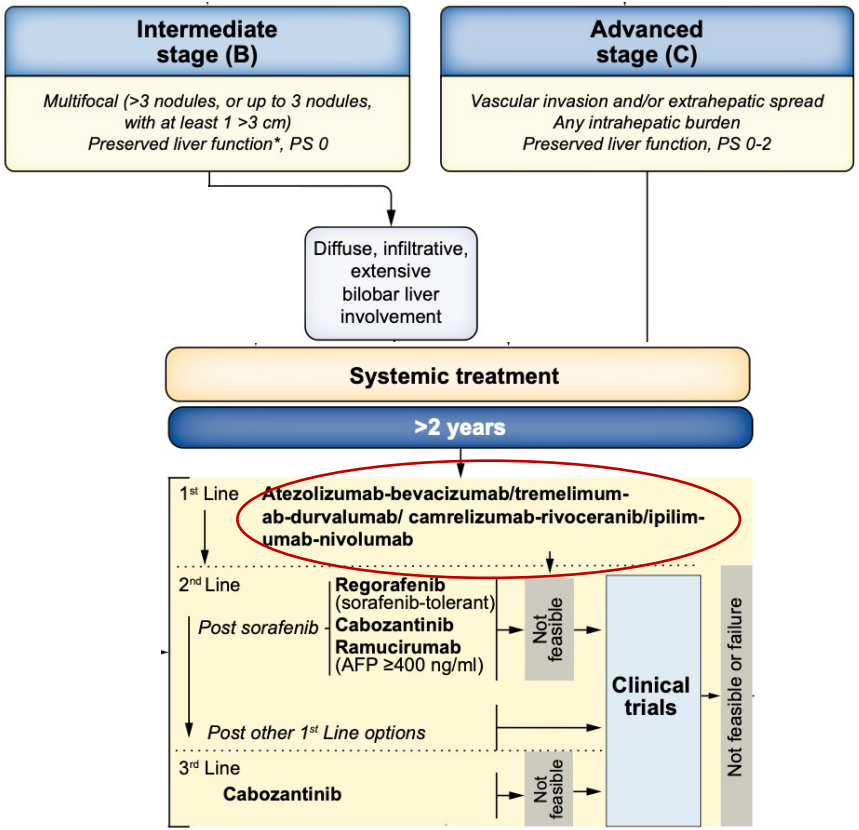
Conflict of interest disclosure

Research funding: National Science and Technology Council (Taiwan), Bristol-Myers Squibb/ ONO, Eureka Therapeutic, GoldenBiotech (Taiwan), IPSEN, Roche

Advisory board: AstraZeneca

Honorarium/ consultation: AstraZeneca, Bristol-Myers Squibb/ONO, Eisai, MSD, Roche

Redefine ‘intermediate stage’ and treatment goals (1)



ORIGINAL ARTICLE

N Engl J Med 2020

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*

Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study

Lancet 2023

Shukui Qin*, Stephen L. Chan*, Shanzhi Gu, Yuxian Bai, Zhenggang Ren, Xiaoyan Lin, Zhendong Chen, Weidong Jia, Yongdong Jin, Yobing Guo, Xiaohua Hu, Zhiqiang Meng, Jun Liang, Ying Cheng, Jianping Xiong, Hong Ren, Fang Yang, Wei Li, Yajin Chen, Yong Zeng, Alexander Sultanbaev, Monika Pappas-Simon, Margarytis Psatsko, Daniil Melki, Dmitriy Ponomarenko, Yurii Osypchuk, Ivan Sinelnikov, Tsai-Sheng Yang, Xiao Liang, Chunxia Chen, Linna Wang, Ann-Lii Cheng†, Ahmed Kaseb†, Arndt Vogel†, for the CARES-310 Study Group†

Summary

Background Immunotherapy with immune checkpoint inhibitors combined with an anti-angiogenic tyrosine-kinase inhibitor (TKI) has been shown to improve overall survival versus anti-angiogenic therapy alone in advanced solid tumours, but not in hepatocellular carcinoma. Therefore, a clinical study was conducted to compare the efficacy and safety of the anti-PD-1 antibody camrelizumab plus the VEGFR2-targeted TKI rivoceranib (also known as apatinib) versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma.

NEJM Evidence

Published June 6, 2022
NEJM Evid 2022; 1 (8)
DOI: 10.1056/EVIDoa2100070

ORIGINAL ARTICLE

Tremelimumab Plus Durvalumab in Unresectable Hepatocellular Carcinoma

NEJM Evid 2022

Ghassan K. Abou-Alfa, M.D., M.B.A.,[1,2] George Lau, M.D., F.R.C.P.,[3] Masatoshi Kudo, M.D., Ph.D.,[4] Stephen L. Chan, M.D.,[5] Robin Kate Kelley, M.D.,[6] Junji Furuse, M.D., Ph.D.,[7] Wattana Sukeepaisarnjaroen, M.D.,[8] Yoon-Koo Kang, M.D., Ph.D.,[9] Tu Van Dao, M.D., Ph.D.,[10] Enrico N. De Toni, M.D., Ph.D.,[11] Lorenza Rimassa, M.D.,[12,13] Valeriy Breder, M.D., Ph.D.,[14] Alexander Vasiliev, M.D.,[15] Alexandra Heurgué, M.D.,[16] Vincent C. Tam, M.D.,[17] Kabir Mody, M.D.,[18] Satheesh Chinadoni Thungappa, M.D.,[19] Yuriy Ostapenko, M.D.,[20] Thomas Yau, M.D.,[21] Sergio Azevedo, M.D.,[22] María Varela, M.D., Ph.D.,[23] Ann-Lii Cheng, M.D., Ph.D.,[24] Shukui Qin, M.D., Ph.D.,[25] Peter R. Galle, M.D., Ph.D.,[26] Sajid Ali, M.D.,[27] Michelle Marcovitz, Ph.D.,[27] Mallory Makowsky, Pharm.D.,[27] Philip He, Ph.D.,[27] John F. Kurland, Ph.D.,[27] Alejandra Negro, Ph.D.,[27] and Bruno Sangro, M.D., Ph.D.,[28] for the HIMALAYA Investigators*

Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): an open-label, randomised, phase 3 trial

Lancet 2025

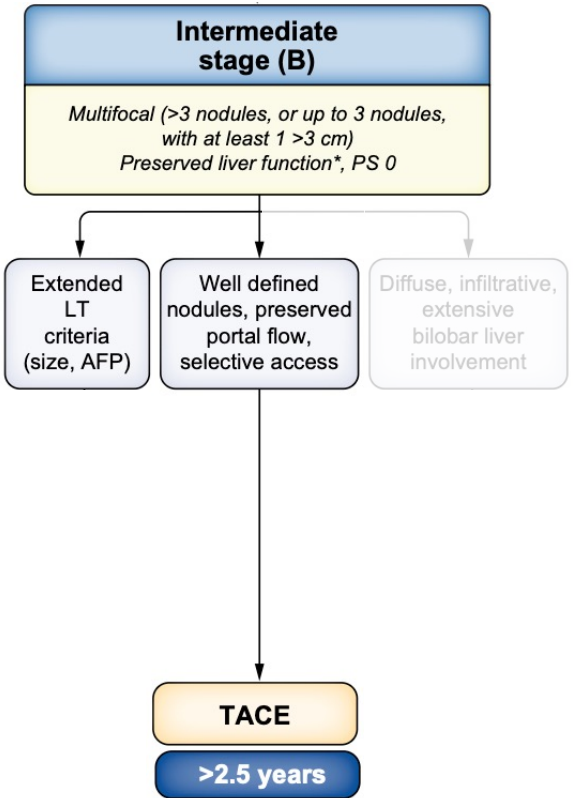
Thomas Yau*, Peter R Galle*, Thomas Decaens, Bruno Sangro, Shukui Qin, Leonardo G da Fonseca, Hatim Karachiwala, Jean-Frederic Blanc, Joong-Won Park, Edward Gane, Matthias Pinter, Ana Matilla Peña, Masafumi Ikeda, David Tai, Armando Santoro, Gonzalo Pizarro, Chang-Fang Chiu, Michael Schenker, Aiwu He, Hong Jae Chon, Joanna Wojcik-Tomaszewska, Gontran Verset, Qi Qi Wang, Caitlyn Stromko, Jaclyn Neely, Prianka Singh, Maria Jesus Jimenez Exposito, Masatoshi Kudo, on behalf of the CheckMate 9DW investigators

Treatment goal: prolong survival

Roles of liver-directed therapy:

- improve liver tumor control
- treat (oligo)metastases

Redefine ‘intermediate stage’ and treatment goals (2)



‘Oncological resectability’

The Japan Liver Cancer Association and Japanese Society of Hepato-Biliary-Pancreatic Surgery Expert Consensus

R	BR1	BR2
Single (no size limit)		
Multinodular: 2-3 nodules, each ≤3cm	Multinodular: status between R and BR2	Multinodular: >5 nodules, and/or any nodule >5cm
Vp0-1 Vv0-1 B0-1	Vp2-3 Vv2 B2-3	Vp4 Vv3 B4
	*Localized Extrahepatic spread	Extrahepatic spread

Akahoshi K, et al. *Liver Cancer* 2024; 13: 579-89

Treatment goal: improve curability

Roles of liver-directed therapy:

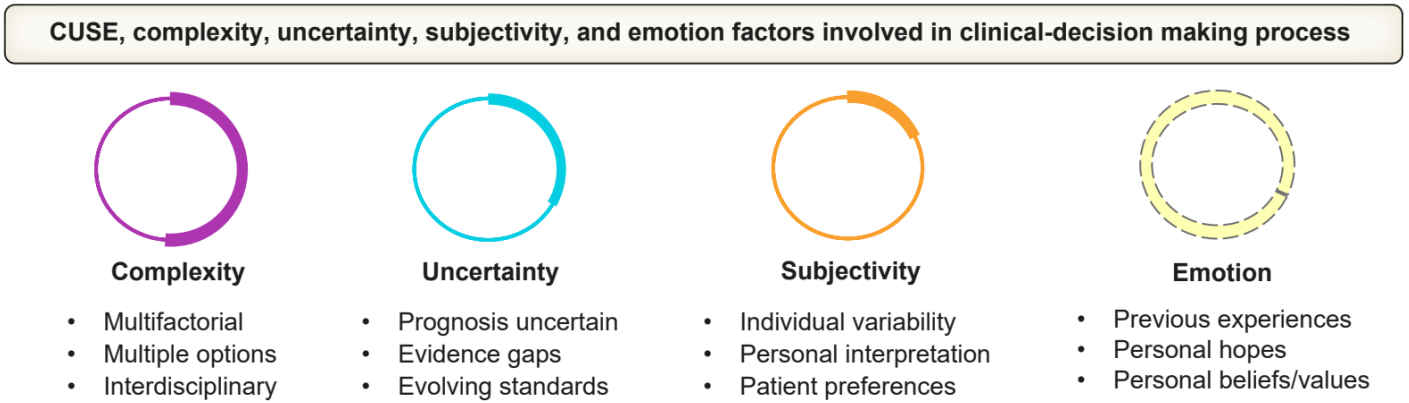
- increase objective tumor response
- maintain safety

In the BCLC framework

Reig M et al. *J Hepatol* 2026;84:631-654

- Downsizing, downstaging and conversion approach through loco-regional treatment
- Downsizing, downstaging and conversion approach with systemic treatment

'The concept of a conversion approach – using systemic or combined treatment to achieve potential cure after major response – remains unproven and is categorised as an alternative sequence in BCLC 2026.'



What if systemic therapy is good enough?
the case for non-small cell lung cancer

anti-PD1/ anti-PDL1 based

4- 6 weeks before surgery

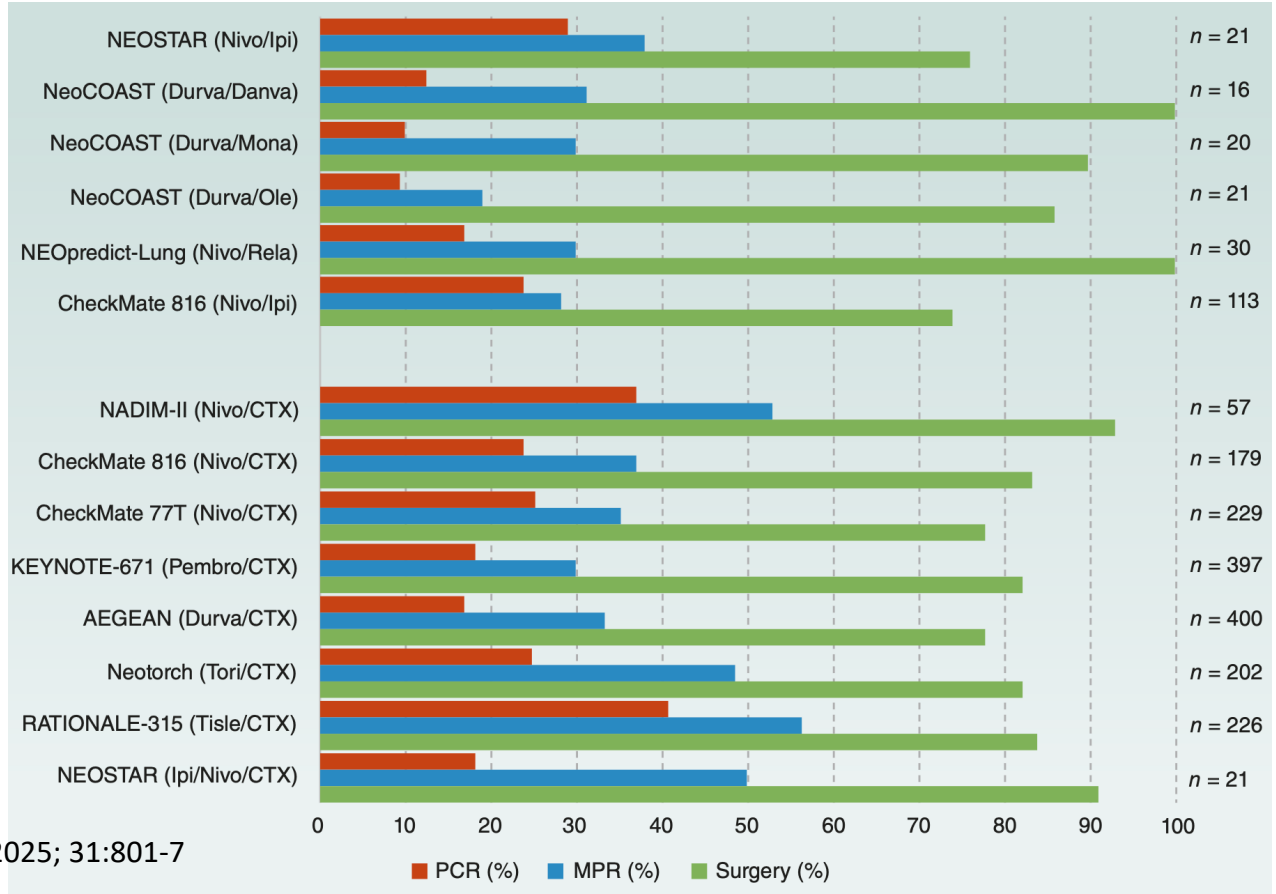
Study	Agent(s)	Preoperative ICI
Forde and colleagues	Nivolumab	2 × 3 mg/kg every 2 weeks
LCMC3	Atezolizumab	2 × 1,200 mg every 3 weeks
NEOSTAR	Nivolumab	3 × 3 mg/kg every 2 weeks
	Ipilimumab	1 × 1 mg/kg
NeoCOAST	Durvalumab	1 × 1,500 mg
	+ Oleclumab	2 × 3,000 mg every 2 weeks
	+ Monalizumab	2 × 750 mg every 2 weeks
	+ Danvatirsen	3 + 4 × 200 mg every week
NEOpredict-Lung	Nivolumab	2 × 240 mg every 2 weeks
	Relatlimab	2 × 80 mg every 2 weeks
CheckMate 816	Nivolumab	3 × 3 mg/kg every 2 weeks
	Ipilimumab	1 × 1 mg/kg

Shuler M. *Clin Cancer Res* 2025; 31:801-7

What if systemic therapy is good enough?
the case for non-small cell lung cancer

Immunotherapy

Immunotherapy + chemotherapy



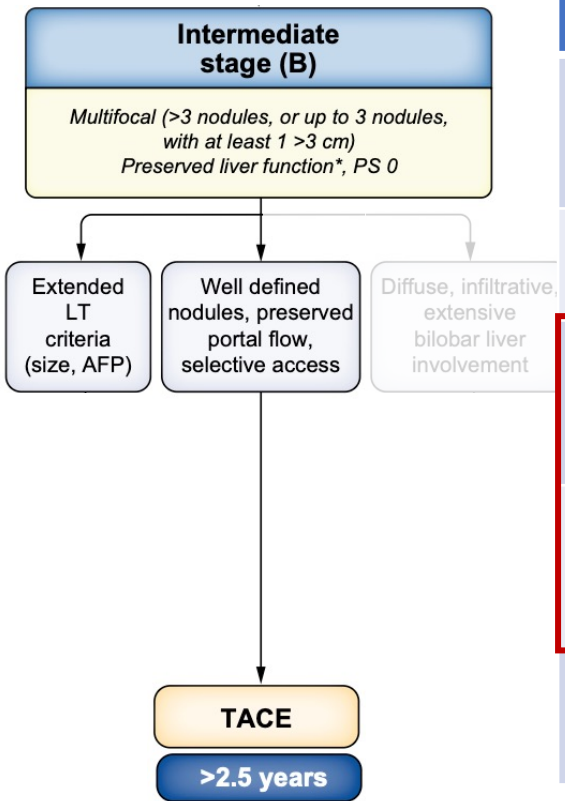
Shuler M. *Clin Cancer Res* 2025; 31:801-7

		Anti-PD1/ anti-PD-L1 (ICI)+ targeted agents (anti-angiogenic)		Anti-PD1/ anti-PD-L1 + anti-CTLA4 (duo – ICI)	
		Atezolizumab (anti-PD-L1)+ bevacizumab (anti-VEGF)	**Camrelizumab (anti-PD1) + rivoceranib (MKI)**	**Durvalumab (anti-PD-L1) + Tremelimumab (anti-CTLA4)**	**Nivolumab (anti-PD-1)+ Ipilimumab (anti-CTLA4)**
Trial		**IMbrave150[1,2]**	**CARES-310[4]**	**HIMALAYA[3]**	**CheckMate-9DW[5]**
Control arm		**sorafenib**	**sorafenib**	**sorafenib**	**Lenvatinib (80%) sorafenib (20%)**
Overall survival	Hazard ratio	**0.66** 95% CI (0.52-0.85)	**0.62** (0.49-0.80)	**0.78** (0.65–0.93)	***0.79*** *(0.65-0.96)*
	Median (months)	**19.2 vs. 13.4**	22.1 vs. 15.2	16.4 vs. 13.8	*23.7 vs. 20.6*
Progression-free survival	Hazard ratio	**0.65** (0.53-0.81)	**0.52** (0.41-0.65)	**0.90** (0.77–1.05)	***0.87*** *(0.72-1.06)*
	Median (months)	**6.9 vs. 4.3**	**5.6 vs. 3.7**	**3.8 vs. 4.1**	**9.1 vs. 9.2**
Response rate (RECIST 1.1)		**30.0%**	**25.0%**	**20.1%**	**36.1%**
mFollow-Up (months, range)		15.6 (N/A)	14.5 (9.1 – 18.7)	33.2 (31.7 to 34.6)	35.2 (26.8-48.9)

ICI: immune checkpoint inhibitor
MKI: multi-kinase inhibitor

1. Finn RS, et al. N Engl J Med. 2020;382(20):1894-1905. 2. Cheng AL, et al. J Hepatol. 2022;76(4):862-873. 3. Abou-Alfa GK, et al. NEJM Evid. 2022;1(8):EVIDoa2100070. 4. Qin S, et al. Lancet 2023; 402:1133-46. 5. Yau T, et al. Lancet 2025; 405;1851-64

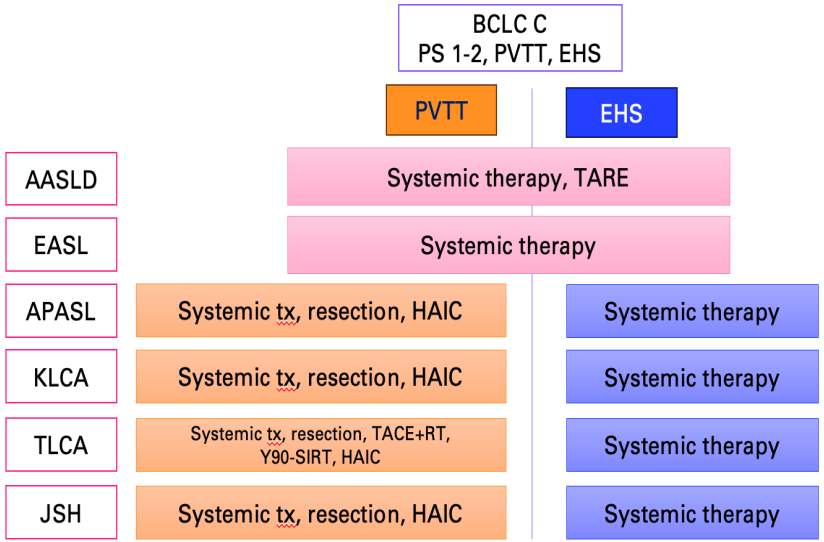
Is TACE a good partner?



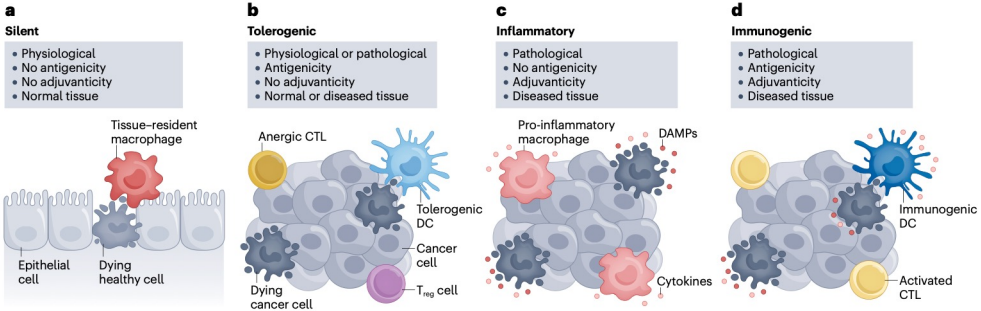
	EMERALD-1	LEAP-012	TALENTACE	EMERALD-3	Cam + Rivo
Regimen (patient no.)	A: Durva + Placebo (207) B: Durva + Bev (204)	Pembrolizumab + Lenvatinib (237)	Atezolizumab + Bev (171)	A: STRIDE + Len (293) B: STRIDE (175)	Camrelizumab + Rivoceranib (214)
Control (patient no.)	TACE (205)	TACE (243)	TACE (171)	TACE (292)	TACE (209)
PFS HR (95% C.I.) (months)	**0.77** (0.61-0.98) 15.0 (A) vs. 8.2 (TACE)	**0.66** (0.51-0.84) 14.6 vs. 10.0	**0.64** (0.50-0.82) 10.32 vs. 6.37	**0.70** (0.57-0.86) 13.0 (A) vs. 9.8 (TACE)	**0.73** (0.56-0.96) 11.1 vs. 8.3
OS HR (95% C.I.) (months)	Not reported	**0.80** (0.57-1.11)	Immature	**0.84** (0.65-1.09) 39.5 (A) vs. 34.7 (TACE)	Immature
ORR (RECIST)	A: 44% B: 41% C: 30%	46.8% vs. 33.3%	49.1% vs. 33.9%	A: 38.9% B: 40.8% C: 27.0%	60.3% vs. 45.5% (mRECIST)

1. Sangro B,,et al. *Lancet*. 2025;405(10474):216-232 (EMERALD-1). 2. Kudo M, et al. *Lancet*. 2025;405:203-215 (LEAP-012). 3. Dong J, et al. *Ann Oncol 2025; 36 (suppl 1): S62 (TALENTACE). 4.* Abou-Alfa G, et al. *J Clin Oncol* 2026; 44 (suppl): LBA4000 (EMERALD-3). 5. Jia W, et al. *J Clin Oncol* 2026; 44 (suppl): 4001 (camrelizumab + rivoceranib)

Multi-disciplinary management for HCC: synergize



Combining liver-directed therapy with immunotherapy for HCC: Inducing '**immunogenic cell death**'



Adapted from Iwamoto H et al. *Clin Mol Hepatol* 2023;29:593-604

Galluzzi L, et al. *Nat Rev Drug Discov* 2024; 23: 445-60

Combining systemic and local therapies:

Hepatic arterial infusional chemotherapy (HAIC)

Author (year)	Patients	Treatment (patient no.)	OS (mon)	PFS (mon)	ORR (%)
Kudo (2018)	Not suitable for surgery, ablation, TACE; Child score ≤ 7	Sorafenib + HAIC (cisplatin + 5FU) (102)	11.8	4.8	36
		Sorafenib (103)	11.5	3.5	18
He (2019)	Portal vein invasion (+), Child A	Sorafenib + HAIC (oxaliplatin + 5FU + leucovorin) (125)	**13.37**	**7.03**	**40.8**
		Sorafenib (122)	7.13	2.60	2.5
Zheng (2022)	Vp3/ Vp4 portal vein invasion, Child A	Sorafenib + HAIC (oxaliplatin + 5FU + leucovorin) (32)	**16.3**	**9.0**	**41**
		Sorafenib (32)	6.5	2.5	3
Lyu (2022)	Not suitable for surgery, ablation, TACE; Child score ≤ 7	HAIC (oxaliplatin + 5FU + leucovorin) (130)	**13.9**	**7.8**	**31.5**
		Sorafenib (132)	8.2	4.3	1.5
Li (2022)	Liver tumor ≥ 7 cm, no vascular invasion, Child A	HAIC (oxaliplatin + 5FU + leucovorin) (159)	**23.1**	**9.6**	**73**
		TACE (epirubicin + lobaplatin)(156)	16.1	5.4	28

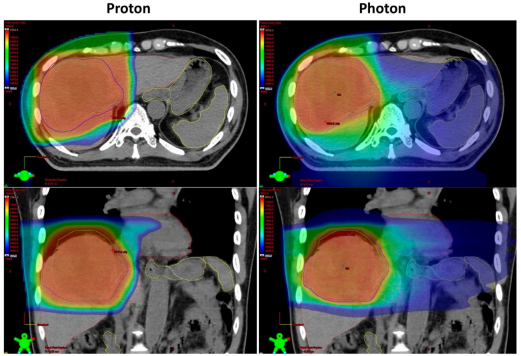
Combination with liver-directed therapy

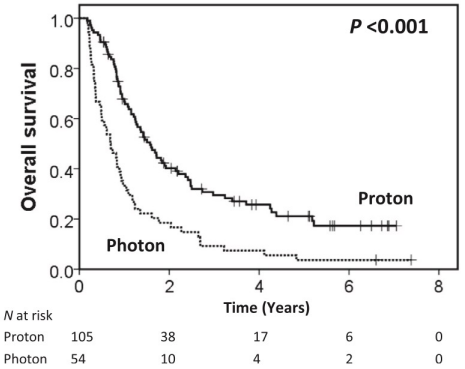
CLINICAL INVESTIGATION

Clinical and Dosimetric Results of Proton or Photon Radiation Therapy for Large (>5 cm) Hepatocellular Carcinoma: A Retrospective Analysis

Rodney Cheng-En Hsieh, MD, PhD,[*,†,‡,§] Ching-Hsin Lee, MD,[*] Hsiao-Chieh Huang, MS,[*] Shu-Wei Wu, PhD,[*] Chen-Yu Chou, MS,[*] Sheng-Ping Hung, MD,[*] Chao-Wei Lee, MD,[‖] Sunil Krishnan, MD,[¶] Bhanu Prasad Venkatesulu, MD,[#,**] Jin-Chiao Lee, MD,[‖] Yung-Chih Chou, MD,[*,††] Kun-Ming Chan, MD,[‖] Po-Ting Lin, MD,[‡‡] Wei-Chen Lee, MD,[‖] Chen-Chun Lin, MD,[‡‡] Shen-Yen Lin, MD,[§§] and Ji-Hong Hong, MD, PhD[*]

Int J Radiat Oncol Biol Phys 2024; 118: 712-24



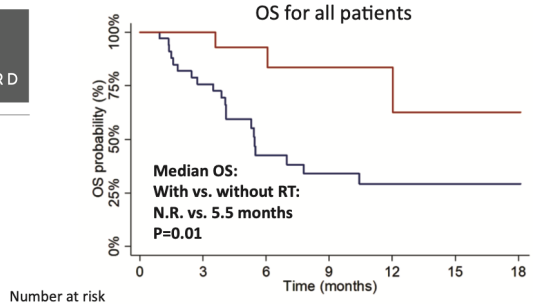


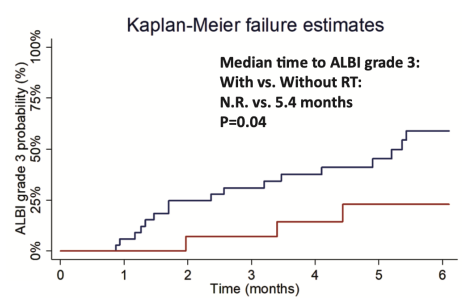
The Oncologist, 2024, **29**, e922–e931
https://doi.org/10.1093/oncolo/oyae048
Advance access publication 26 March 2024
Original Article

OXFORD

Concurrent Atezolizumab Plus Bevacizumab and High-Dose External Beam Radiotherapy for Highly Advanced Hepatocellular Carcinoma

Chung-Wei Su[1,2], Wei Teng[1,2], Eric Yi-Liang Shen[2,3,4], Bing-Shen Huang[2,3], Po-Ting Lin[1,2], Ming-Mo Hou[2,5], Tsung-Han Wu[2,6], Din-Li Tsan[2,3], Chia-Hsun Hsieh[2,5,7], Ching-Ting Wang[2,8], Pei-Mei Chai[2,8], Chun-Yen Lin[1,2], Shi-Ming Lin[1,2], Chen-Chun Lin[2,9,*]





Summary: how to synergize in HCC MDT