Optimizing Treatment Strategies: Immunotherapy in Combination with Local Therapy for Hepatocellular Carcinoma

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Financial disclosures

None

Objectives

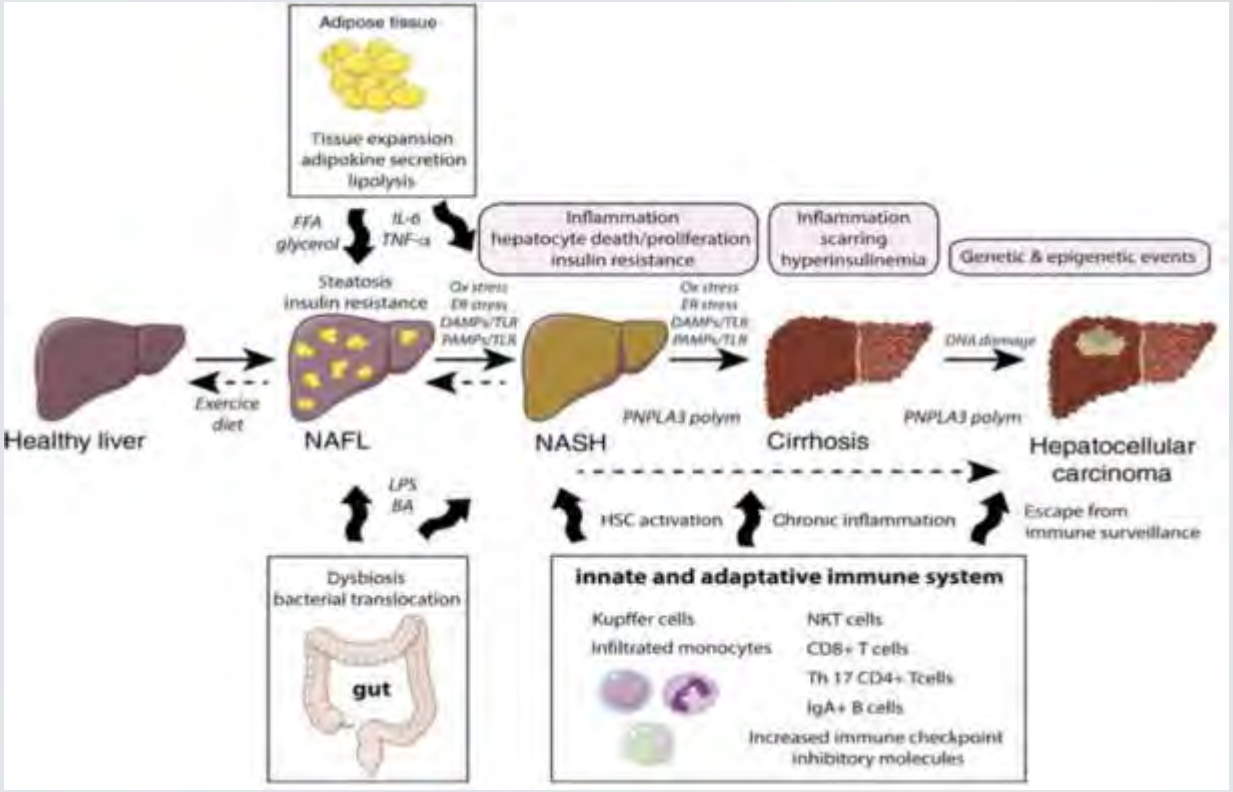
- Overview of treatment of unresectable HCC
- Systemic therapy landscape in HCC
- Clinical trials supporting combined approach with local and immunotherapy
- Future directions

Introduction

- Third leading cause of cancer related death globally
- Most common primary liver cancer
- Arises in a background of chronic liver disease including chronic viral hepatitis, alcohol associated liver disease and NASH
- Unfortunately, associated with one of the lowest five-year survival rates at 21%
- Challenges in treatment – Management varies based on tumor burden, liver function, comorbidities and performance status

Cancer Statistics, 2023. *CA Cancer J. Clin.*

Pathogenesis



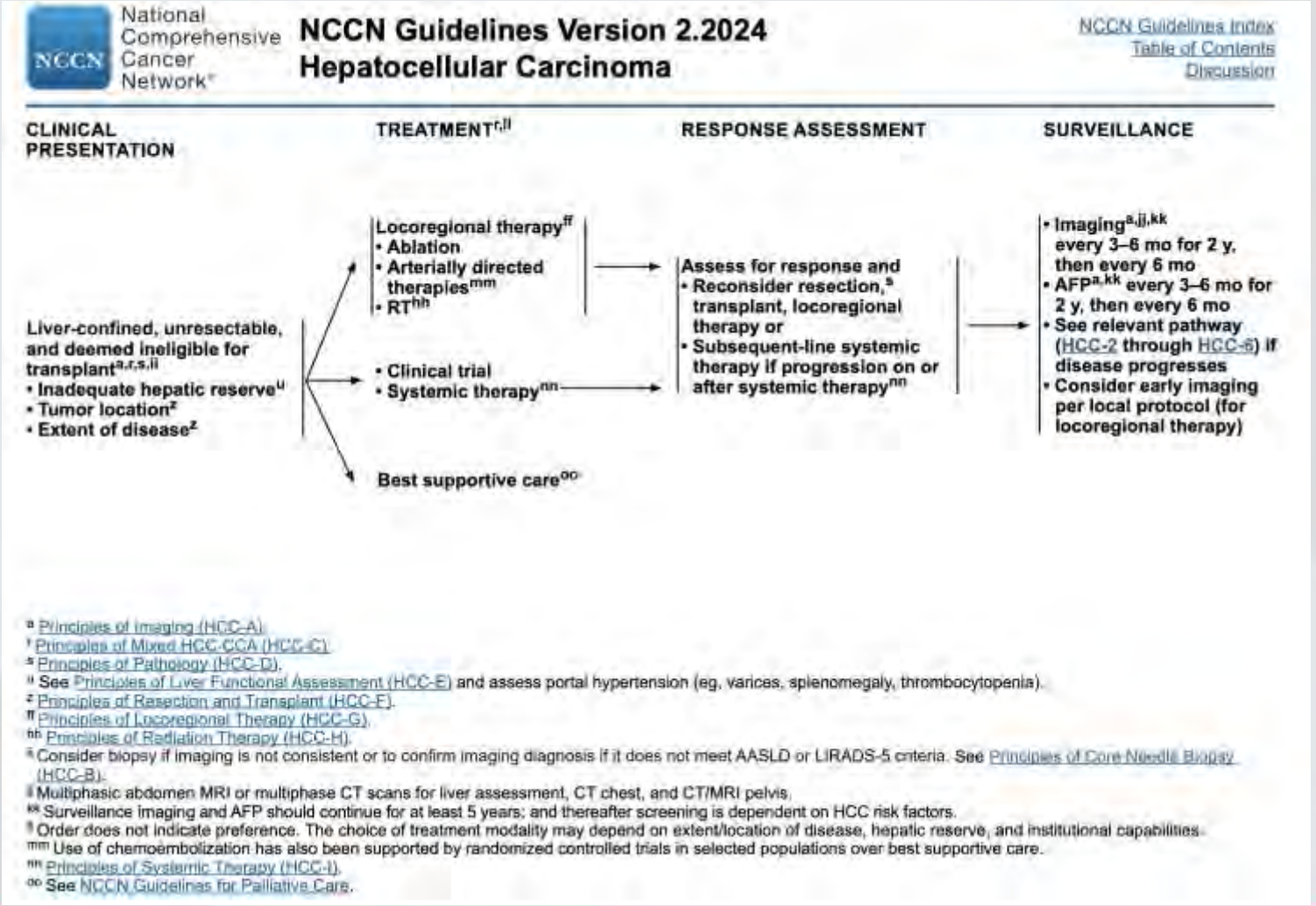
Current treatment landscape

Surgical Options: Liver resection and transplantation

Systemic Therapies: immune checkpoint inhibitors/Targeted therapies

Local Therapies: Ablation, transarterial chemoembolization (TACE), radioembolization, SBRT

Nccn guidelines for unresectable HCC



National Comprehensive Cancer Network

NCCN Guidelines Version 2.2024
Hepatocellular Carcinoma

NCCN Guidelines Index
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Discussion

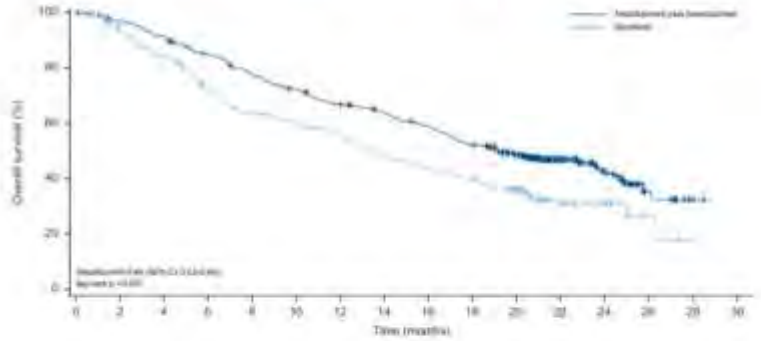
CLINICAL PRESENTATION	TREATMENT[r,ll]	RESPONSE ASSESSMENT	SURVEILLANCE
Liver-confined, unresectable, and deemed ineligible for transplant[a,r,s,ll] • Inadequate hepatic reserve[u] • Tumor location[z] • Extent of disease[z]	Locoregional therapy[ff] • Ablation • Arterially directed therapies[mm] • RT[hh] • Clinical trial • Systemic therapy[nn] Best supportive care[oo]	Assess for response and • Reconsider resection,[s] transplant, locoregional therapy or • Subsequent-line systemic therapy if progression on or after systemic therapy[nn]	• Imaging[a,jj,kk] every 3–6 mo for 2 y, then every 6 mo • AFP[a,kk] every 3–6 mo for 2 y, then every 6 mo • See relevant pathway (HCC-2 through HCC-6) if disease progresses • Consider early imaging per local protocol (for locoregional therapy)

[a] Principles of Imaging (HCC-A).
[r] Principles of Mixed HCC-CCA (HCC-C).
[s] Principles of Pathology (HCC-D).
[u] See Principles of Liver Functional Assessment (HCC-E) and assess portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
[z] Principles of Resection and Transplant (HCC-F).
[ff] Principles of Locoregional Therapy (HCC-G).
[hh] Principles of Radiation Therapy (HCC-H).
[ll] Consider biopsy if imaging is not consistent or to confirm imaging diagnosis if it does not meet AASLD or LIRADS-5 criteria. See Principles of Core Needle Biopsy (HCC-B).
[jj] Multiphasic abdomen MRI or multiphase CT scans for liver assessment, CT chest, and CT/MRI pelvis.
[kk] Surveillance imaging and AFP should continue for at least 5 years; and thereafter screening is dependent on HCC risk factors.
[ll] Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.
[mm] Use of chemoembolization has also been supported by randomized controlled trials in selected populations over best supportive care.
[nn] Principles of Systemic Therapy (HCC-I).
[oo] See NCCN Guidelines for Palliative Care.

First line systemic therapy

Current standard of care in the Western world

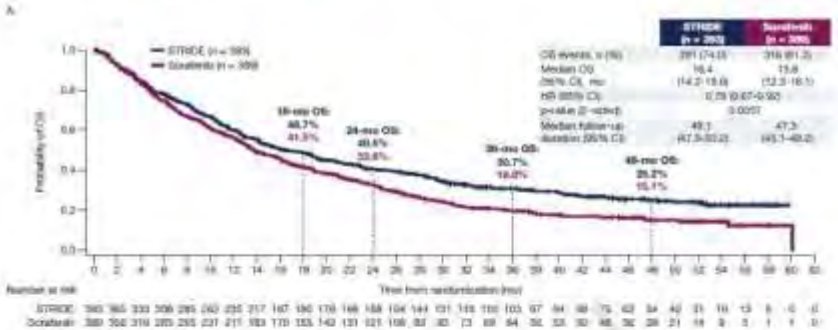
Atezolizumab-bevacizumab



Improvement of OS, PFS, ORR, QOL over sorafenib

Cheng, J Hep 2022

Durvalumab-tremelimumab



Improvement of OS, ORR, QOL over sorafenib

Sangro, Ann Oncol 2024

Systemic therapy – how do you choose first line?

What work up should be done at the start

Images with 4 phases for liver and chest imaging

Liver function – Child Pugh score

How to optimize atezolizumab-bevacizumab

EGD – risk of bleeding with bevacizumab

Varices – Beta blockers>ligatures

Criteria for selection for atezolizumab/bevacizumab versus durva tremilimumab

Contraindication to bev – recent bleeding/thrombosis/active wound

Subsequent line therapy – how do you choose?

- Several subsequent-line therapy options for disease progression following first-line systemic therapy
- However, there are no comparative data to define optimal treatment after first-line systemic therapy.
- Targeted therapy options include regorafenib (for C-P Class A HCC), cabozantinib (for C-P Class A HCC), lenvatinib (for C-P Class A HCC), and sorafenib (for C-P Class A or Class B7 HCC). Regorafenib and cabozantinib are category 1 options
- Checkpoint inhibitor options include nivolumab monotherapy, pembrolizumab monotherapy, and combination therapy with nivolumab and ipilimumab

Challenges with immunotherapy alone

- Moderate response rates
- Immune tolerance in the TME

Rationale for combination therapies

- Synergistic effects
- Median PFS for patients treated with TACE remains 7-8 months
- TACE may prime the tumor microenvironment for immunotherapy and anti VEGF therapy via neoantigen release and ischemia
- Immunogenic cell death induced by local therapies

Clinical trials and studies for combination local/targeted therapies

- **Emerald 1** – TACE +/- systemic therapy
- **NRG/RTOG 1112** – SBRT for HCC with sorafenib
- **Launch trial** - Lenvatinib vs Lenvatinib + TACE

ASCO Gastrointestinal Cancers Symposium

EMERALD-1: a Phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization

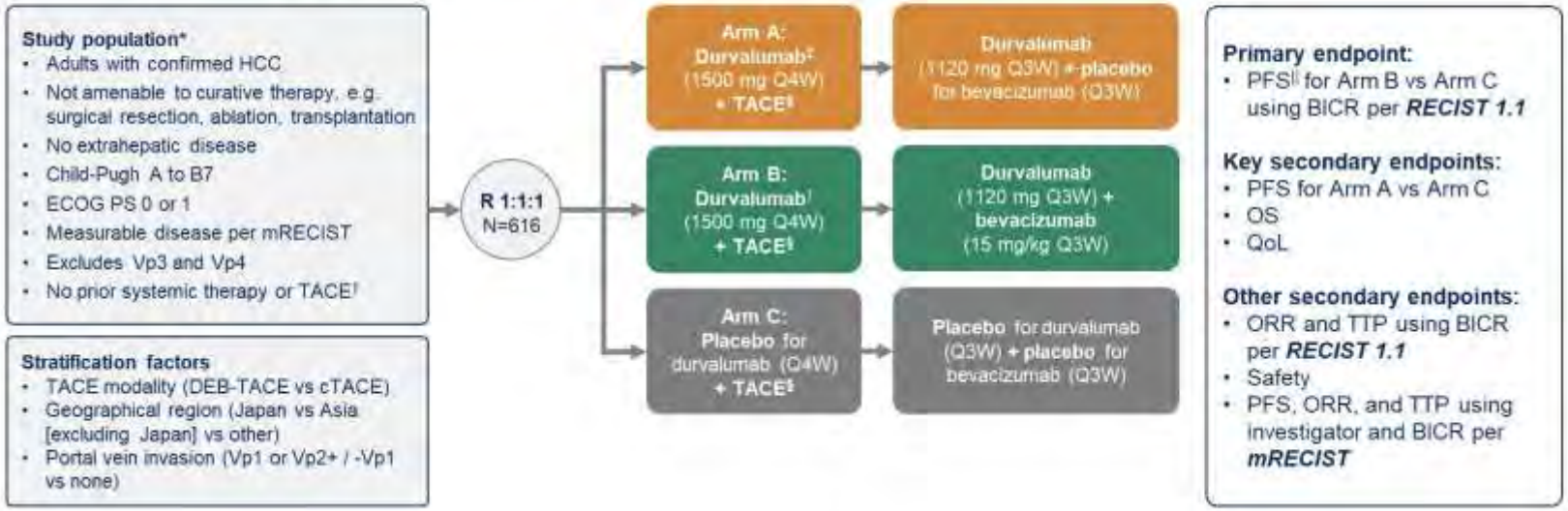
Riccardo Lencioni*[1], Masatoshi Kudo[2], Joseph Erinjeri[3], Shukui Qin[4], Zhenggang Ren[5], Stephen L Chan[6], Yasuaki Arai[7], Jeong Heo[8], Anh Mai[9], Jose Escobar[10], Yamil Alonso Lopez Chuken[11], Jung-Hwan Yoon[12], Won Young Tak[13], Tanita Suttichaimongkol[14], Mohamed Bouattour[15], Shi-Ming Lin[16], Magdalena Żotkiewicz[17], Stephanie Udoye[18], Gordon J Cohen[18], **Bruno Sangro***[19]

Design

- Double blind phase 3 study
- Embolization eligible unresectable HCC
- Child Pugh A to B7
- ECOG 0-1

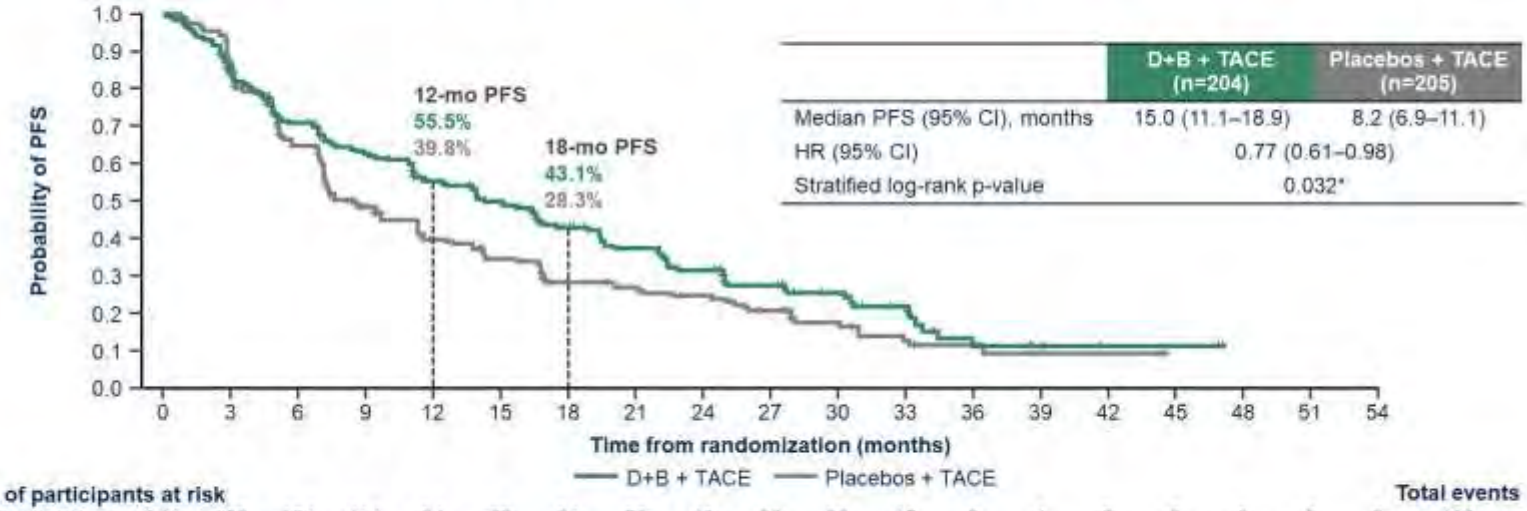
EMERALD-1 study design

EMERALD-1 was a global, double-blind, placebo-controlled Phase 3 study



PFS with D+B + TACE versus placebos + TACE: primary endpoint

Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

No. of participants at risk																				Total events
D+B + TACE	204	162	134	114	94	82	64	53	43	32	23	15	6	4	2	2	0	0	0	136
Placebos + TACE	205	159	121	81	62	51	39	35	32	24	15	10	5	2	2	0	0	0	0	149

Median (range) duration of follow-up in censored participants: D+B + TACE 16.7 (0.03–47.1) months; Placebos + TACE 16.5 (0.03–44.3) months. **Median (95% CI) duration of follow-up** in all participants using the reverse Kaplan-Meier method: D+B + TACE 22.2 (16.7–27.5) months; Placebos + TACE 20.3 (16.7–30.4) months. PFS was assessed by BICR (RECIST v1.1).

*The threshold of significance for this analysis was 0.0435 based on the α spend at the PFS interim analysis (2.27%) and the actual number of events at PFS final analysis.

B, bevacizumab; BICR, blinded independent central review; CI, confidence interval; D, durvalumab; HR, hazard ratio; mo, months; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.

- First global phase 3 study to demonstrate statistically significant PFS benefit
- ORR Consistent across key clinical subgroups
- Safety profile was manageable and consistent with known safety profile of TACE and ICI

Launch trial

- Advanced/unresectable HCC\RCT,
- Phase III study in China
- Randomized to Lenvatinib + TACE (n = 170) or lenvatinib alone (n = 168).
- Median OS of 17.8 months for the combination versus 11.5 months for lenvatinib alone (HR, 0.45; *P* < .001). The median PFS was 10.6 and 6.4 months, respectively

Combination of RT and ICI

- Timing and sequencing is crucial for maximizing therapeutic synergy
- This is unclear
- Administering immunotherapy before radiation therapy aims to prime the immune system, enhancing the recognition of tumor antigens released during subsequent radiation therapy.
- Radiation therapy can modulate the tumor microenvironment, enhancing the expression of molecules such as PD-L1, thus providing a rationale for the subsequent introduction of immunotherapeutic agents like PD-1/PD-L1 inhibitors

NRG/RTOG 1112 – SBRT for HCC with sorafenib

- Randomized Phase 3 study
- Recurrent HCC unsuitable for surgery/ablation or TACE
- Child Pugh A
- 1:1 to either Sorafenib 400mg BID or SBRT (27.5 to 50 Gy in 5 fractions) with sorafenib 200mg BID increased to 400mg BID after 28 days
- Primary end point was OS

RTOG study

- 292 patients
- Accrual closed early since SOC for systemic therapy changed around this time
- 193 patients accrued, multisite
- median OS was improved from 12.3 mo. (90% CI 10.6, 14.3) with S to 15.8 mo. (90% CI 11.4-19.2) with SBRT/S (HR=0.77, 1-sided p=0.0554)
- Median PFS was improved from 5.5 mo. (95% CI 3.4-6.3) with S to 9.2 months (95% CI 7.5-11.9) with SBRT/S (HR=0.55, 95% CI 0.40-0.75, 2-sided p=0.0001)
- Compared to Sorafenib alone, SBRT improved OS & PFS in patients with HCC, with no observed increase in AEs, and a strong suggestion for QOL benefit at 6 months

Ongoing trials

Trial	Randomization	End point
LEAP –012	TACE vs TACE + pembrolizumab/lenvatinib	End point PFS/OS
EMERALD 3	TACE versus TACE + durvalumab/tremilimumab +/- lenvatinib	PFS
EMERALD Y-90	TARE + durvalumab/bevacizumab	PFS
ROWAN	TARE + durvalumab+ tremilimumab	ORR
REPLACE	TACE/TARE + pembrolizumab/regorafenib	PFS

Challenges and considerations

- **Patient Selection**
  - Identifying patients who may benefit most from combination therapy
- **Safety and Toxicity**
  - Managing adverse effects from combination treatments
- **Cost and Accessibility**
  - Economic considerations in combining therapies

Future directions

- Integration of locoregional therapies with systemic therapy is undergoing a rigorous investigation
- potential to revolutionize HCC treatment and could significantly alter the treatment paradigm in the future
- However, the optimal timing for such combination therapy remains undetermined.
- Development of precise biomarkers and prognostic models is imperative to select the most suitable patients for these therapies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