A phase 1b study of pembrolizumab following trans-arterial chemoembolization (TACE) in hepatocellular carcinoma (HCC): PETAL.

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Introduction

Trans-arterial chemoembolization (TACE) is standard of care for unresectable, non-metastatic hepatocellular cancer (HCC). The efficacy of TACE relies on the dual ischaemic and cytotoxic effect stemming from the sequential intra-arterial delivery of chemotherapy followed by direct occlusion of the arterial neo-vascular supply to the tumour; processes that may promote immunogenic cell death[1,2].

We hypothesised that TACE will prime adaptive immunity and enhance the efficacy of pembrolizumab (pembro), a programmed cell death-1 (PD-1) inhibitor.

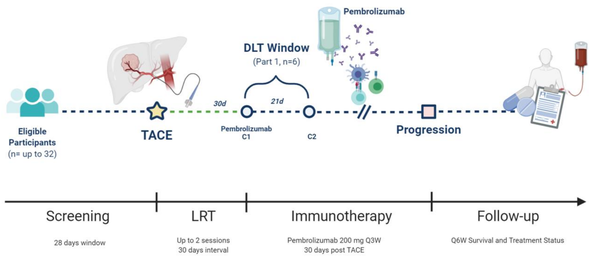
Aim

The purpose of this phase Ib study was to evaluate the safety of TACE followed by pembro, define preliminary activity and explore mechanisms of efficacy.

- **Primary endpoint**: To assess the safety and tolerability of pembrolizumab using National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4).
- **Secondary endpoint**: Assess preliminary activity of the combination with progression-free survival (PFS) based on RECIST v 1.1 criteria.
- **Exploratory endpoint**: Evaluate tumour and host determinants of response in tissue, blood and stool samples

Methods

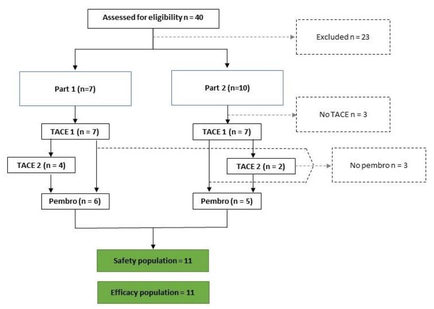
Up to 32 patients with intermediate-stage HCC were planned to receive up to 2 rounds of conventional or DEB-TACE with intra-arterial doxorubicin - followed by pembro 200 mg q3w 30-days post-TACE until disease progression or unacceptable toxicity for up to 1-year. Part 1 of the study featured a run-in of 6 patients observed with weekly laboratory assessments for the first 21 days to assess the safety of combined treatment and evaluate the emergence of dose-limiting toxicities (DLTs). To account for heterogeneity of patients with cirrhosis-related HCC, this included one CP B7 patient, all others were CP A. Part 2 of the study permitted expansion with up to 26 further patients.



Key Inclusion Criteria: Diagnosis of HCC (AASLD criteria), ≥1 measurable lesion by RECIST, previous TACE permitted provided untreated lesion, adequate organ function, Child-Pugh (CP) score ≤7, ECOG performance status 0-1, ineligible for resection or transplant.

Key Exclusion Criteria: Extrahepatic metastasis, systemic anticancer treatment for HCC, contraindication to TACE, recent major bleeding, hepatic encephalopathy, diuretic-refractory ascites, active autoimmune disease or other cancer, immunosuppression.

Fig 1. Study consort Diagram

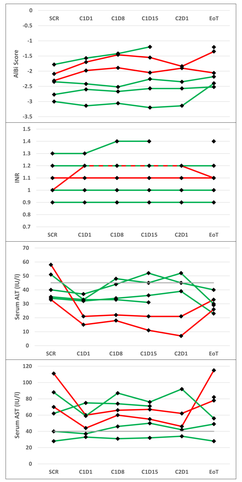


Characteristic	N (%)
Age median, range	67 (60-76)
Gender M F	9 (81) 2 (9)
Cirrhosis Present Absent	9 (81) 2 (9)
Etiology of Chronic Liver Disease Viral Non-viral	3 (28) 8 (72)
BCLC Stage A B	0 (0) 11 (100)
Child Pugh Score A5 A6 B7	7 (63) 3 (27) 1 (9)
AFP <400 ≥400	10 (90) 1 (10)
ECOG PS 0 1	6 (55) 5 (45)
Prior Therapy None RFA	9 (81) 2 (9)

Fig 2 (left): Study participant demographics. ***Fig 3*** (below): Treatment-related adverse events (trAE). No AEs above grade 2 were deemed treatment-related.

PATIENT ID	1	2	3	4	5	6	7	8	9	10	11	Overall Patient N (%)		
	NCI-CTC v. 4.0 (Maximum Grade)											1	2	≥3
Skin reactions	-	2	1	2	-	-	-	-	-	2	1	2 (18)	3 (27)	-
Diarrhoea / colitis	-	-	1	2	1	1	-	-	-	-	1	4 (36)	1 (9)	-
Constipation	-	2	-	-	-	-	-	-	-	-	-	-	1 (9)	-
Fatigue	-	2	1	1	-	-	-	1	-	1	-	4 (36)	1 (9)	-
Hepatitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thyroid disorders	-	-	-	-	-	-	-	-	2	-	-	-	1 (9)	-
Adrenal disorders	-	2	-	-	-	-	-	-	-	-	-	-	1 (9)	-
Shortness of breath	-	-	-	1	1	-	-	1	-	-	-	3 (27)	-	-
Cough	-	-	-	2	1	-	-	2	-	-	-	1 (9)	2 (36)	-
Other pulmonary disorders	-	-	-	-	-	2	-	-	2	-	-	-	2 (36)	-
Fever	-	-	-	1	-	-	-	-	-	-	-	1 (9)	-	-
Neuropathy	-	2	-	-	-	-	-	-	-	-	1	1 (9)	1 (9)	-
Mucositis	-	2	2	1	-	-	-	-	-	-	-	1 (9)	2 (18)	-
Dysgeusia	-	-	-	1	1	-	-	-	-	-	-	2 (18)	-	-
Hypertension	-	-	-	-	-	-	-	-	1	-	-	1 (9)	-	-
Infusion reactions	-	-	1	-	-	-	-	-	-	-	-	1 (9)	-	-
Thrombocytopenia	-	-	-	-	-	-	-	1	-	-	-	1 (9)	-	-
Proteinuria	-	-	-	-	-	-	-	-	1	-	-	1 (9)	-	-

Fig 4: Liver function in part 1 participants
Green: responders, Red: non-responders



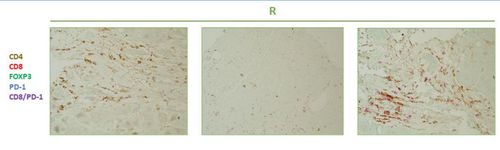


Fig 5 (left): Multiplex immunohistochemistry experiments on pre-treatment tissue samples characterising T-cell infiltrate in relationship with treatment response.

Fig 6 (below): Peripheral immune cell phenotyping using Mass Cytometry identifies dynamic changes in immune cells across study timepoints.

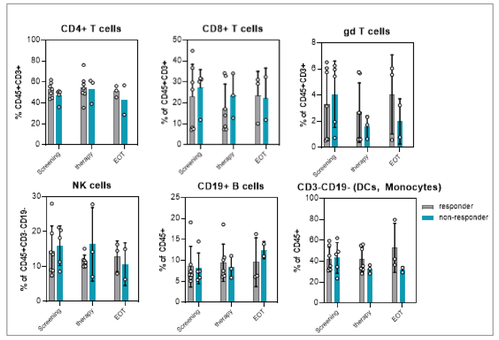


Fig 7 (below): 16s sequencing of stool DNA at baselines reveals differential composition of phyla in pre-treatment stool samples

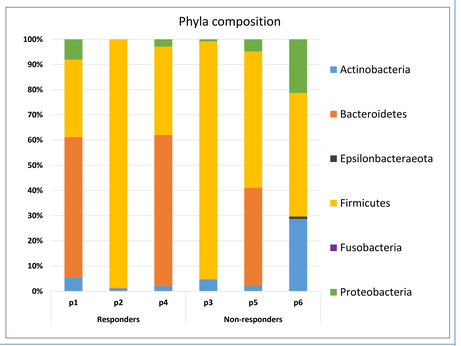
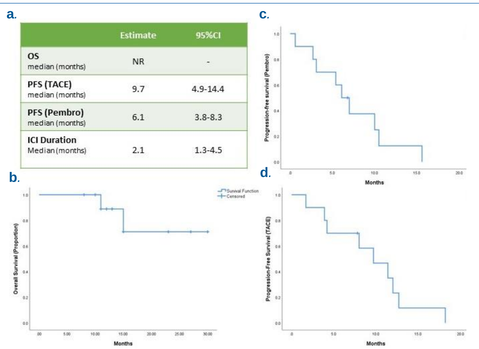


Fig 5: Patient survival. **a**. Survival summary and duration of treatment with pembro. **b-d** Kaplan-Meier (KM) plots of overall survival (OS - **b**), progression-free survival (PFS) from first dose of pembro (**c**) and PFS from TACE (**d**). **e**. Swimmer plot of PFS from TACE in 11 evaluable patients.

a.

	Estimate	95%CI
OS median (months)	NR	-
PFS (TACE) median (months)	9.7	4.9-14.4
PFS (Pembro) median (months)	6.1	3.8-8.3
ICI Duration Median (months)	2.1	1.3-4.5



Results

In total, 11 eligible patients received up to 2 rounds of TACE followed by pembro 200mg q3w 30 days post-TACE until unacceptable toxicity or disease progression. Study Part 1 was completed without documentation of dose-limiting toxicities from the combination of pembrolizumab following TACE.

Adverse events (AEs) of any grade potentially related to treatment occurred in 90% of patients, most commonly skin rash (45%) and fatigue (45%).

Median PFS was 9.7 months (95%CI 4.9-14.4) from TACE and 6.1 months (95%CI 3.8-8.3) from pembro initiation. In total, 7 of 11 (63%) patients demonstrated durable response to the combination, with > 100 days PFS from pembro initiation.

Reasons for discontinuation were disease progression (n=7), AEs (n=1), treatment-unrelated liver dysfunction (n=1, CP B7 patient), and withdrawal due to Covid-19 pandemic (n=2).

Conclusions

TACE followed by pembrolizumab had a tolerable safety profile with no evidence of dose limiting nor synergistic toxicity.

Alongside emerging efficacy data, this encourages the clinical development of the combination in Child-Pugh A patients.

Recruitment to study part II is currently ongoing.

Acknowledgements

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