Progression patterns and clinical outcomes following immune checkpoint inhibition for hepatocellular carcinoma (HCC): a multi-institutional international study.

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) are revolutionising the treatment algorithm of patients with advanced hepatocellular carcinoma (HCC)[1]. They are available in clinical practice, either alone or in combinations across different treatment lines[2].

Different approaches are available after progressive disease (PD): continuation of ICI, treatment switching to tyrosine kinase inhibitors (TKi) and cessation of systemic therapy. Evidence to guide clinician decision at progression is mainly empirical or inferred from experience with other cancers.

Different patterns of disease progression are known to influence survival after treatment with sorafenib; development of a new extrahepatic lesion is associated with poorer survival[3], but little is known about progression patterns and post-progression outcomes following ICI in HCC.

AIMS

We sought to determine the clinical characteristics of HCC patients treated with ICI, comparing those who received post-progression therapy to those who did not.

We aimed to identify whether different patterns of progression are associated with differential post-progression survival (PPS) after ICI treatment in HCC.

We also sought to describe clinician attitudes towards continuation of ICI beyond treatment progression and treatment switching to TKi, and appraise relative PPS.

METHODS

From an international consortium of 13 tertiary-care referral centres located in Europe, USA and Asia, we screened 472 consecutive HCC patients treated with ICIs between 2017 & 2021, including only those who experienced PD at data cut-off.

We first compared the baseline clinical features of patients who did not receive any post-progression anti-cancer treatments to those who did.

We then performed univariable and multivariable analyses using the Cox proportional model to evaluate PPS according to several clinical characteristics including the patterns of radiological progression, as previously defined[2]: intrahepatic growth (IHG), new intrahepatic lesion (NIH), extrahepatic growth (EHG), new extrahepatic lesion (NEH) and new vascular invasion (nVI).

We evaluated PPS of those continuing ICI beyond PD vs those who did not with a Kaplan Meier model.

RESULTS

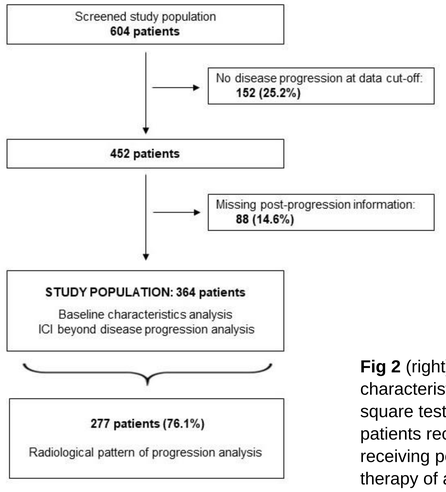

Fig 1 (above). Study consort diagram

Fig 2 (right). Cohort clinical characteristics, with chi-square tests between patients receiving and not receiving post-progression therapy of any kind

Baseline Characteristic	*Overall N=364 (%)*	*Patients receiving post-progression therapy N=199 (54.7%)*	*Patients not receiving post-progression therapy N=165 (45.3%)*	*Chi-square*
Age (years: median (range)) < 70 ≥ 70	66 (25-86) 247 (67.9) 117 (32.1)	66 (25-86) 139 (69.8) 60 (30.2)	67 (39-86) 108 (65.6) 57 (34.5)	P = 0.3721
Gender Male Female	290 (79.7) 74 (20.3)	159 (79.9) 40 (20.1)	131 (79.4) 34 (20.6)	P = 0.9052
ECOG-PS 0 1 2	203 (55.8) 149 (40.9) 12 (3.3)	124 (62.3) 74 (37.2) 1 (0.5)	79 (47.9) 75 (45.5) 11 (6.7)	**P = 0.0005**
Cirrhosis Absent Present	114 (31.3) 250 (68.7)	65 (32.7) 134 (67.3)	49 (29.7) 116 (70.3)	P = 0.5441
Viral or Non-viral HCC Non-viral HCC HBV and/or HCV infection	157 (43.1) 207 (56.9`)	84 (42.2) 115 (57.8)	73 (44.2) 92 (55.8)	P = 0.6973
Child-Pugh Class A B	268 (73.6) 96 (26.4)	153 (76.9) 46 (23.1)	115 (69.7) 50 (30.3)	P = 0.1219
BCLC Stage A B C	13 (3.6) 48 (13.2) 303 (83.2)	5 (2.5) 32 (16.1) 162 (81.4.)	8 (4.8) 16 (9.7) 141 (85.5)	P = 0.1140
AFP (ng/ml), <400 >400	203 (57.8) 148 (42.2)	110 (55.6) 88 (44.4)	93 (60.8) 60 (39.2)	P = 0.3260
Unknown	13	1	12	
Prior Treatment for HCC Resection Trans-arterial chemoembolization Sorafenib	115 (31.6) 182 (50.0) 193 (53.0)	75 (37.7) 105 (52.8) 99 (49.7)	40 (24.2) 77 (46.7) 94 (57.0)	**P = 0.0061** P = 0.2474 P = 0.1700
Treatment Line First systemic line Second systemic line Beyond second systemic line	160 (44.0) 155 (42.6) 49 (13.5)	93 (46.7) 78 (39.2) 28 (14.1)	67 (40.6) 77 (46.7) 21 (12.7)	P = 0.3546
Immunotherapy Regime Anti- PD(L)-1 monotherapy Anti-PD(L)-1 + CTLA-4 combination Anti-PD(L)-1 + TKI combination Atezolizumab/bevacizumab	292 (80.2) 23 (6.3) 32 (8.8) 17 (4.7)	175 (87.9) 9 (4.5) 7 (3.5) 8 (4.0)	117 (70.9) 14 (8.5) 25 (15.1) 9 (5.5)	**P = 0.0005**

Fig 3 (below). Univariable and multivariable analysis of PPS in ICI-treated HCC

Variable	*Post progression survival (PPS)*			
	N° of patients	Univariable analysis *HR (95% CI); p-value*	*N° of patients*	Multivariable analysis *HR (95% CI); p-value*
ICI Beyond PD Yes vs No	364	0.62 (0.45-0.86); p = 0.0048	267	0.67 (0.46-0.97); p = 0.0382
Post-progression TKi Yes vs No	364	0.51 (0.39-0.66); p < 0.0001		0.52 (0.37-0.72); p = 0.0001
IHG Yes vs No	277	1.64 (1.21-2.22); p = 0.0013		1.38 (0.98-1.95); p = 0.0582
NIH Yes vs No	*277*	0.80 (0.57-1.13); p = 0.2116		1.01 (0.70-1.43); p = 0.9715
EHG Yes vs No	277	0.98 (0.74-1.31); p = 0.9245		1.15 (0.85-1.55); p = 0.3377
NEH Yes vs No	*277*	1.05 (0.76-1.43); p = 0.7594		1.12 (0.80-1.56); p = 0.5004
nVI Yes vs No	*277*	2.15 (1.38-3.35); p = 0.0007		2.07 (1.31-3.28); p = 0.0019
ECOG-PS at disease progression 2 vs 0-1	*341*	2.71 (2.05-3.58); p < 0.0001		2.26 (1.56-3.25); p < 0.0001
ICIs treatment line First vs Non-first	364	1.03 (0.81-1.31); p = 0.8040		0.85 (0.63-1.13); p = 0.2747

Fig 4 (right). Kaplan-Meier curves of PPS in HCC patient treated with ICI. Patients in red continued ICI post-progression, patients in blue did not

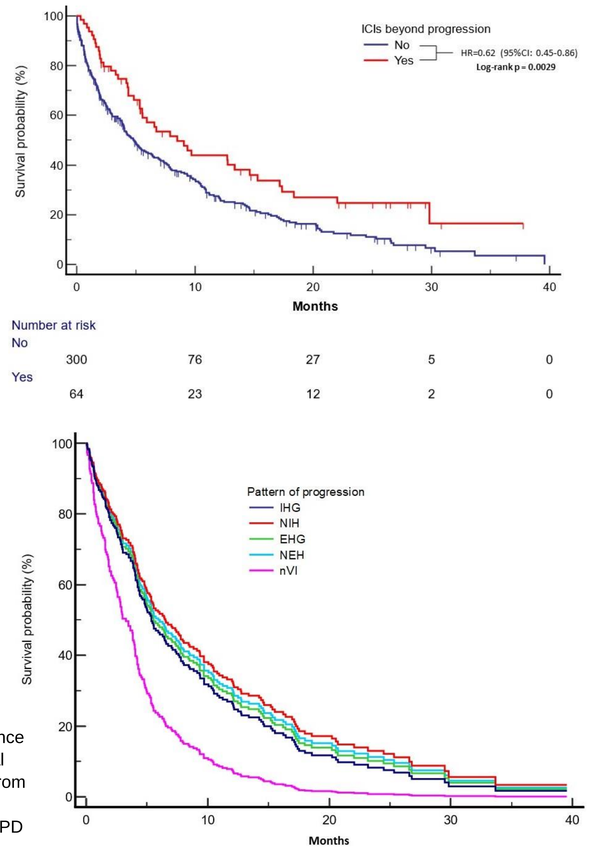

Fig 5 (right). Cox regression survival probability plot for PPS according to presence of a given radiological pattern of progression (whole study population). Individual participants typically progress with multiple patterns. Each curve was obtained from separates multivariable models and superimposed, incorporating ECOG-PS at disease progression (0-1 vs ≥ 2), ICI treatment line (1st vs non-1st), ICI beyond PD and post-progression TKis as adjusting factors

CONCLUSIONS

- In our study 73% of patients received anti-cancer therapy after progression on ICI
- Patients with better ECOG PS, and patients with history of liver resection were more likely to receive post-ICI therapy
- Presence of nVI and IHG predict for poorer post-progression survival
- Continuation of ICI beyond PD is frequent in routine practice and is associated with a prolonged PPS, independent of radiological pattern of disease progression and receipt of subsequent line anti-cancer therapy
- Treatment switching to a TKi at progression is also is associated with prolonged PPS

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