Post-registration experience of nivolumab in advanced HCC

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INTRODUCTION

- Hepatocellular carcinoma (HCC) is a malignancy of high lethality and limited treatment options.
- Immune checkpoint inhibition against the PD-1 pathway has shown promising results.
- Anti-PD-1 antibody nivolumab is FDA-approved in sorafenib-experienced, advanced HCC.
- Post-registration data of treatment in a real-world setting is lacking.

AIM

- Evaluate the safety and efficacy of nivolumab using retrospective data from an international cohort outside the clinical trial setting.
- Establish basic information on patient outcomes and prognostic outlook to inform future clinical studies.

METHOD

- Patients receiving nivolumab were recruited from 8 tertiary referral centres from the US (n=226), Asia (n=47), and Europe (n=68).
- Nivolumab was administered intravenously at the dose of 3 mg/kg of body weight every 2 weeks. Dose modified based on toxicity.
- Evaluation of response followed the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, version 1.1.
- The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 were used to grade side effects.
- Demographic data were summarised with descriptive statistics.
- Nominal data were compared using Fischer's exact test or Chi-squared test.
- Overall and progression-free survival curves were calculated with the Kaplan-Meier method, and compared with the log-rank test with regards to clinically relevant variables using SPSS 25.0.

Baseline characteristic		N (%)			
Total		233 (100)	ECOG status	0	44 (28.0)
Age in years, median (IQR)		64 (56-69)		1	99 (63.1)
Gender	Male	184 (79.0)		2	11 (7.0)
	Female	49 (21.0)		3	2 (1.3)
Cirrhosis	Present	176 (75.5)	Portal vein thrombosis	Present	59 (37.6)
	Absent	57 (24.5)		Absent	98 (62.4)
Etiology	HCV	95 (40.8)	Extrahepatic spread	Present	66 (42.0)
	HBV	83 (35.6)		Absent	91 (58.0)
	Alcohol	29 (12.4)	Prior therapy	Surgery	65 (27.9)
	NASH	24 (10.3)		RFA	41 (17.6)
	Other	10 (4.3)		TACE	109 (46.8)
Child-Pugh class	A	158 (67.8)		TARE	66 (28.3)
	B	75 (32.2)		EBRT	23 (9.9)
Barcelona Clinic Liver Cancer stage	A	4 (1.7)	Therapy line	1	85 (36.5)
	B	23 (9.9)		2	130 (55.8)
	C	204 (87.8)		3	15 (6.4)
	D	2 (0.6)		4	3 (1.3)

Table 1 – Baseline characteristics of patients

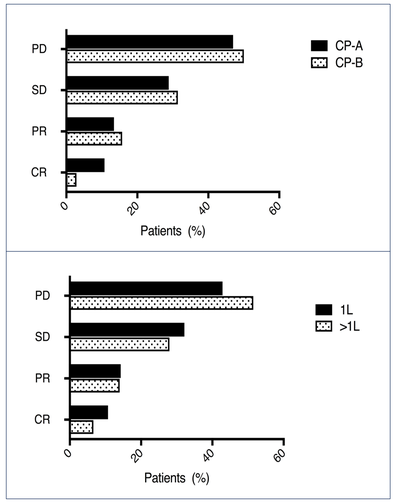

Figure 1 – Best response observed by Child-Pugh class and line of therapy. *No significant differences were observed in proportions of best responses when analysed by CP class (p=0.26, above top) and line of treatment (p=0.49, above bottom).*

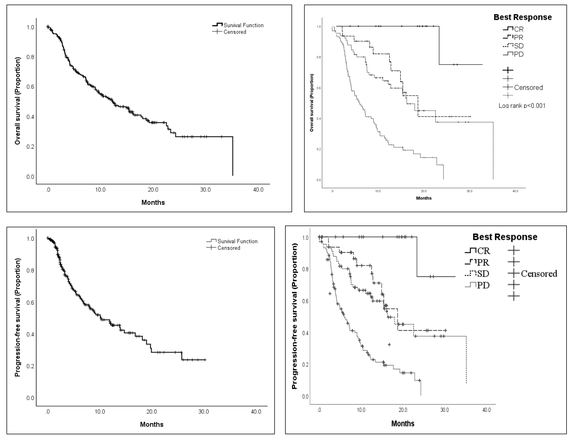

Figure 2 – Kaplan-Meier curves depicting median overall (OS) and progression-free survival (PFS). *Median OS was 12.2 months (95% CI 8.4-16.0)* ***(top left)****, and median PFS was 10.1 months (95% CI 6.1-14.2)* ***(bottom left)****. Both OS and PFS were significantly predicted by best objective response* ***(OS top right p<0.001, PFS bottom right p<0.001)****.*

Predictors of OS	Univariate HR (95% CI)	Multivariate HR (95% CI)
Child-Pugh class, B/A	1.95 (1.35-2.81)	2.30 (1.40-3.73)
Objective response CR+PR/ SD+PD	0.26 (0.18-0.39)	0.25 (0.12-0.54)
ECOG status	0.47 (0.22-0.99)	
Therapy line, 1 L/>1 L	0.68 (0.47-1.00)	
PVT, present/ absent	1.82 (1.13-2.94)	1.87 (1.15-3.05)
Predictors of PFS	**Univariate HR (95% CI)**	**Multivariate HR (95% CI)**
Barcelona Clinic stage, C+D/A+B	2.82 (1.46-5.44)	2.58 (1.33-5.01)
Objective response CR+PR/ SD+PD	0.26 (0.18-0.39)	0.20 (0.11-0.37)
Therapy line, 1 L/>1 L	0.60 (0.39-0.93)	0.60 (0.38-0.93)

Table 2 – Univariate and multivariate predictors of OS and PFS. *Variables which did not demonstrate significance were not included: AFP , cirrhosis, steroid use, ECOG status, extrahepatic spread.*

RESULTS

Efficacy

- Best response included ORR of 22.4% and DCR of 52.1%. A complete response was seen in 8.2%. No significant differences when analysed by salient characteristics (Fig 1).
- Median OS was 12.2 months (CI 8,4-16.0) and median PFS was 10.1 months (CI 6.1-14.2).Their univariate and multivariate predictors are shown in Table 2.

Safety

- Treatment-related toxicity was reported in 26.6% of patients, 6.4% being Grade 3 or above.
- Top 3 types were fatigue (46.8%), skin (33.9%), and liver toxicity (27.4%).
- No clinicopathologic features were found to predict toxicity (Figure 3).

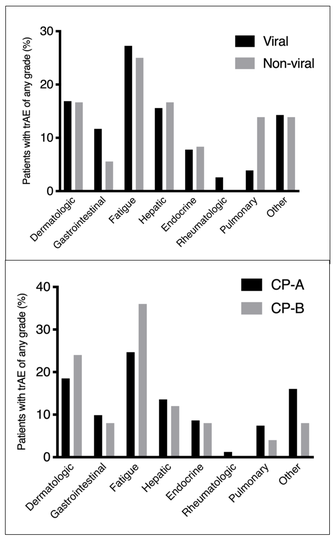

Figure 3 – The distribution of treatment-related adverse events (trAEs) of any grade in relation to etiology of chronic liver disease (viral versus non-viral, above) and CP class (below). *There was no significant difference between patients grouped by etiology of liver disease (p=0.07) and Child-Pugh class (p=0.61).*

CONCLUSIONS

- Nivolumab monotherapy is a deliverable treatment option in a real-world patient cohort, including patients with varying degrees of liver dysfunction and prior treatment.
- Measures of efficacy and safety of nivolumab therapy were comparable to clinical trial data.
- Longer survival was observed in patients achieving radiologic response to treatment.
- Although response rates were similar across Child-Pugh classes, OS was reduced in CP-B.
- The favourable response and toxicity observed in CP-B patients supports the case to investigate the use of nivolumab in this treatment-deprived patient population.

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