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MEETING SUMMARY
ASCO 2019, Chicago, USA

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HIGHLIGHTS ON HCC

DISCLAIMER

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RESULTS OF KEYNOTE-240: PHASE III STUDY OF PEMBROLIZUMAB VS BSC FOR 2ND-LINE THERAPY IN ADVANCED HCC

Finn et al. ASCO 2019 abstract #4004

BACKGROUND: COMPROMISE IN IMMUNE FUNCTION PROMOTES HCC DEVELOPMENT

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PRECLINICAL AND CLINICAL DATA INDICATE HCC IS AN ATTRACTIVE TARGET FOR IMMUNE CHECKPOINT INHIBITION

Inflammatory Response	• Cytokine profile favors Th2 response • Recruitment of tumor associated macrophages (TAMS) • Expansion on myeloid derived suppressor cells • Impaired antigen presentation and dendritic cell function
HCC Immune Escape	• Decreased expression MHC 1 • T-regs recruitment to tumor microenvironment • High levels of lymphocytes expressing PD1 • T-cell exhaustion (PD-1, TIM3, LAG) • Presence of TILs with blunted type-1 T-cell profiles
HCC Immune Response	• Multiple tumor associated antigens identified: AFP, TERT, MAGE-A, NY-ESO-1 • Anti-PD1 therapy can control HCC in preclinical models

Harding JJ, et al. Cancer 2016;122:367-77

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; MAGE-A, Melanoma Antigen Gene A; MHC 1, Major histocompatibility complex 1; PD-1, programmed cell death protein 1; TERT, Telomerase Reverse Transcriptase; TILs, Tumor-infiltrating lymphocytes; Tregs, T Regulatory Cells

BACKGROUND

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REPRODUCIBLE ANTI-TUMOR OF ANTI-PD1 THERAPY IN HCC IN REPORTED PHASE I/II AND 2 SINGLE ARM STUDIES

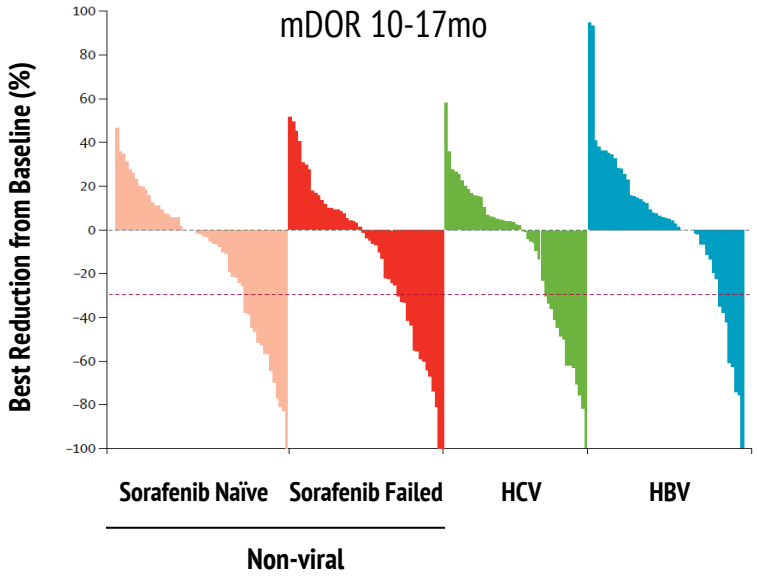
Nivolumab

CheckMate 040

N=262

ORR = 15-20%

mDOR 10-17mo



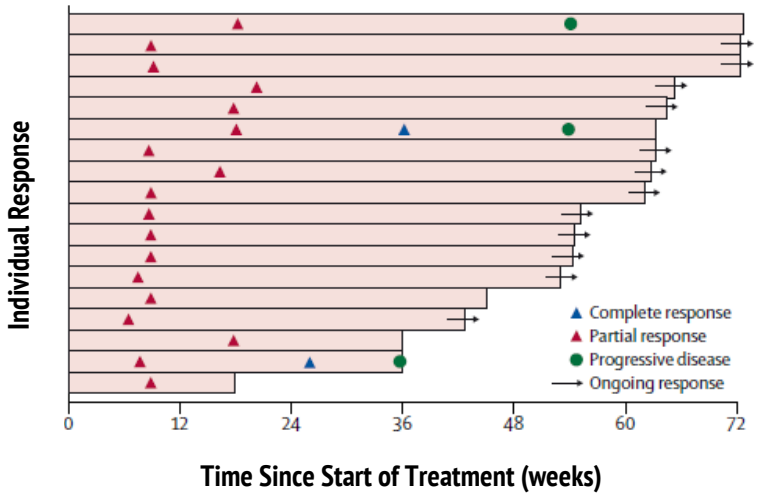
Pembrolizumab

KEYNOTE-224

N=104

ORR = 17%

mDOR = not reached



Preliminary data for durvalumab and other anti-PD1/L1 MoAs indicate similar efficacy across drug class

El-Koureiy AB, et al. Lancet 2017;389:2492-502. Zhu AX, et al. Lancet Oncol 2018;19:940-52.

ORR, overall response rate; mDOR, median duration of response; MoA, mechanism of action; PD-1, programmed cell death protein 1

KEYNOTE-240: RANDOMIZED, DOUBLE-BLIND, PHASE III PEMBROLIZUMAB VERSUS BEST SUPPORTIVE CARE WHO FAILED/INTOLERANT PRIOR SORAFENIB

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Key Eligibility Criteria

- Pathologically/radiography confirmed HCC
- Progression on/intolerance to sorafenib
- Child-Pugh A
- BCLC-B /C
- ECOG 0-1
- Measurable disease per RECIST v 1.1

R
2:1

N=413

Pembrolizumab 200mg q3 weeks + BSC

Saline-placebo q3 weeks + BSC

Stratification Factors

- Geographic Region
- Macro-vascular Invasion
- AFP level (≥200 vs <200ng/mL)

Endpoints

- Primary: OS and PFS

AFP, alpha-fetoprotein; BCLC, Barcelona Clínic Liver Cancer; BSC, best-supportive care; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; OS, overall survival; PFS, progression-free survival; q, every; RECIST, Response Evaluation Criteria in Solid Tumours

Finn RS, et al. Abstract #4004 Presented at ASCO 2019

KEYNOTE-240: RESULTS SUMMARY AND KEY POINTS

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- Pembrolizumab is tolerable with similar safety profile seen in earlier studies
- Pembrolizumab; ORR 18.3% (95% CI 14.0–23.4) vs. BSC 4.4 (1.6–9.4%)
- PFS Pembro 3.0 vs. BSC 2.8 months (HR 0.775 95% CI 0.609–0.987, p=0.186) not reaching pre-specified statistical significance; apparent tail of PFS curve with longer follow up
- OS Pembro 13.9 vs. BSC 10.6 months (HR 0.781 95% CI 0.611–0.998, p=0.0238) not reaching pre-specified statistical significance
- **Co-primary endpoints of PFS and OS were not met. Reason for failure of study to confirm an OS advantage include statistical design, underestimation of OS for BSC group, and that ~50% of the study population going on to a 3rd line treatment that may have confounded the OS endpoint. PFS may not be an ideal endpoint for immunotherapy**
- **Further data are required to understand the activity and use of immune checkpoint inhibitors in HCC. Data are awaited from an ongoing study of pembrolizumab of similar design in Asia (KEYNOTE-394) as well as the front-line study evaluating nivolumab vs. sorafenib in advanced HCC patients (CHECKMATE-459)**

CI, confidence interval; BSC, best-supportive care; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Finn RS, et al. Abstract #4004 Presented at ASCO 2019

RANDOMIZED, OPEN-LABEL, PERIOPERATIVE PHASE II STUDY EVALUATING NIVOLUMAB ALONE OR NIVOLUMAB PLUS IPILIMUMAB IN PATIENTS WITH RESECTABLE HCC

Kaseb et al. ASCO 2019 abstract #4098

NIVOLUMAB + IPILIMUMAB COMBINATION THERAPY IN PATIENTS WITH ADVANCED HCC: RESULTS FROM CHECKMATE 040

YAU ET AL. ABSTRACT #4012.

Yau et al. ASCO 2019 abstract #4012

PRELIMINARY EFFICACY DATA FOR CTLA-4 AND PD1/PD-L1 IN HCC WAS ALSO PRESENTED AT THE MEETING

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	Checkmate-040		
	NIVO1/IPI3 Q3W (n=50)	NIVO3/IPI1 Q3W (n=49)	NIVO3 Q2/IPI1 Q6W (n=49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
DCR, % (95% CI)	54 (39–68)	43 (29–58)	49 (34–64)
mOS, mo (95% CI)	23 (9–NA)	12 (8–15)	13 (7–33)
12-mo OS rate, % (95% CI)	61 (46–73)	56 (41–69)	51 (36–64)
24-mo OS rate, % (95% CI)	48 (34–61)	30 (18–44)	42 (28–56)

- Subset of Checkmate-040 assessed Ipilimumab and Nivolumab at 3 different schedules
- Preliminary data indicate a ~30% response rate across cohorts as well as favorable OS in this population
- AEs occur at a higher rate than seen previously with nivolumab alone
- Another study (abstract 4098) evaluated the same combination in the neoadjuvant setting and reported 4 of 14 evaluable patients with pathologic CRs
- Multiple ongoing studies are testing anti-PD-1 therapy with TKIs, ICIs, and other novel targets

AEs, adverse events; CI, confidence interval; CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DCR, disease control rate; HCC, hepatocellular carcinoma; HR, hazard ratio; ICIs, immune checkpoint inhibitors; ipi, ipilimumab; mo, months; mOS, median overall survival; NA, not available; nivo, nivolumab; ORR, overall response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed-death ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; TKIs, tyrosine kinase inhibitors

Yao T, et al. Abstract #4012 Presented at ASCO 2019; Kaseb AO, et al. Abstract #4098 Presented at ASCO 2019

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