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Liver tumours

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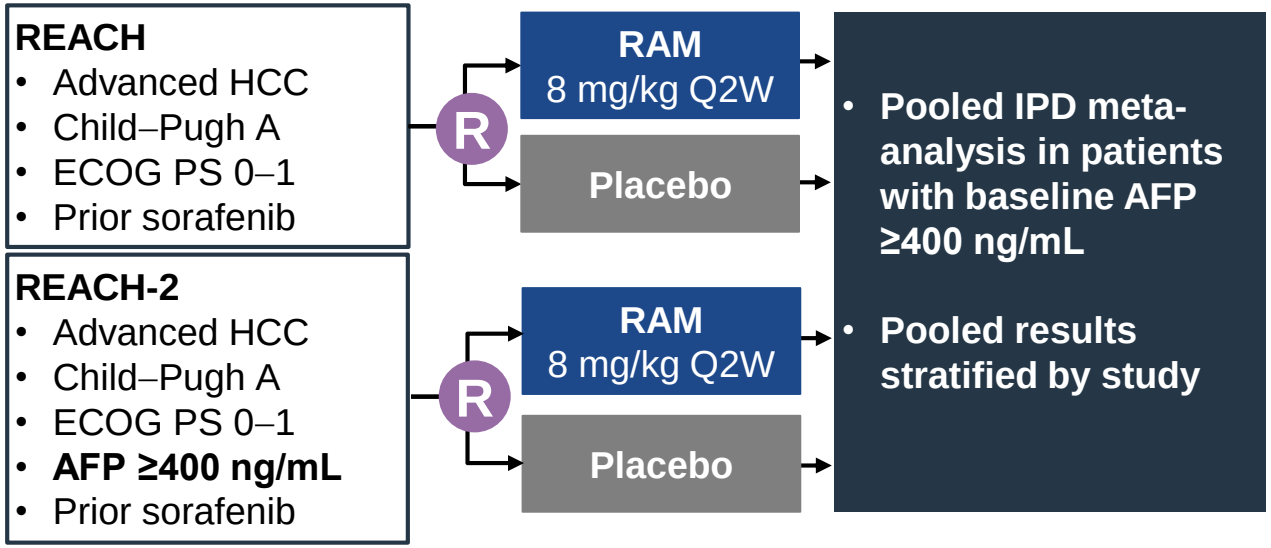
1. Therapy

Ramucirumab for patients with advanced hepatocellular carcinoma and elevated alpha-fetoprotein following sorafenib (REACH-2 and REACH): Outcomes by liver disease aetiology

BACKGROUND & AIMS

- REACH-2 and REACH, two global, randomized, blinded, placebo-controlled phase 3 trials, studied ramucirumab (RAM) in patients with advanced HCC following sorafenib
- REACH-2 enrolled patients with baseline AFP ≥400 ng/mL and met its primary endpoint of OS vs. placebo
- An exploratory analysis was conducted to investigate the efficacy and safety of RAM in patients with advanced HCC and AFP ≥400 ng/mL from REACH and REACH-2 by liver disease aetiology

METHODS



- Aetiology subgroups: hepatitis B, hepatitis C, other (e.g. significant alcohol use, steatohepatitis, cryptogenic cirrhosis)
- Survival was evaluated using the Kaplan–Meier method and Cox proportional hazard model*
- Clinical response rates were reported by treatment arms within each subgroup

*Aetiology subgroup-by-treatment interaction used the Wald test in the Cox model.

Galle P, et al. ILC 2019; GS-09

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Ramucirumab for patients with advanced hepatocellular carcinoma and elevated alpha-fetoprotein following sorafenib (REACH-2 and REACH): Outcomes by liver disease aetiology

RESULTS

- Patient populations were comparable between treatment arms in each aetiology subgroup
- A consistent treatment benefit for RAM vs. placebo (*Table*) was observed across aetiology subgroups (OS interaction; p=0.29)
- Grade ≥3 AEs were consistent with observations from both individual studies
  - Hypertension was the most frequent grade ≥3 AE

TABLE

Analysis population (RAM vs. placebo)	Hepatitis B, n=225 (RAM 124, placebo 101)	Hepatitis C, n=127 (RAM 76, placebo 51)	Other, n=190 (RAM 116, placebo 74)
OS median, months HR (95% CI)	7.7 vs. 4.5 0.74 (0.55, 0.99)	8.2 vs. 5.5 0.82 (0.55, 1.23)	8.5 vs. 5.4 0.56 (0.40, 0.79)
PFS median, months HR (95% CI)	2.7 vs. 1.4 0.55 (0.41, 0.74)	3.6 vs. 2.7 0.58 (0.39, 0.88)	2.8 vs. 1.6 0.57 (0.41, 0.79)
ORR, %	3.2 vs. 1.0	7.9 vs. 2.0	6.0 vs. 0.0
DCR, %	53.2 vs. 28.7	65.8 vs. 52.9	53.4 vs. 37.8

CONCLUSIONS

A treatment benefit with RAM was observed for patients with advanced HCC and baseline AFP ≥400 ng/ml, regardless of aetiology. RAM was well tolerated with a similar safety profile in all aetiology subgroups

Galle P, et al. ILC 2019; GS-09

Post-progression survival in patients with intermediate-stage hepatocellular carcinoma after receiving transarterial chemoembolization

BACKGROUND & AIMS

- Correlations between progression patterns and PPS in patients with advanced HCC treated with sorafenib have been reported[1]
  - Useful to understand prognosis of patients not responding to sorafenib
  - Useful in designing clinical trials
- **Aim:** To assess correlations between progression and PPS in patients with intermediate-stage HCC post-TACE

METHODS

- 437 patients* were enrolled between 2003–2016
- Radiological responses were evaluated according to mRECIST

RESULTS

Patient characteristics	
Male, %	76.4
Age, ≥73 years, %	42.6
Hepatitis B/C virus, %	11.7/66.6
Child–Pugh A, %	80.1

Clinical outcomes	
OS, median months (95% CI)	27.2 (23.7–30.7)
TTP, median months (95% CI)	4.3 (3.9–4.8)
Patients who progressed, n (%)	293 (67.0)
Intrahepatic growth, n (%)	145 (49.5)
New intrahepatic lesions, n (%)†	195 (66.5)
New extrahepatic lesions, n (%)	39 (13.3)

*With intermediate-stage HCC who received TACE as initial treatment; †≤3, n=129 (44.0%); 4–7, n=24 (8.2%); ≥8, n=42 (14.3%). 1. Reig M, et al. Hepatology 2013;58:2023–31.
Shima Y, et al. ILC 2019; PS-120

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Post-progression survival in patients with intermediate-stage hepatocellular carcinoma after receiving transarterial chemoembolization

RESULTS (Cont.)

- In patients with ≥8 NIH lesions, PPS was significantly lower than with 4–7 and ≤3 (p=0.002)
  - ≥8 lesions: 11.7 months (95% CI, 8.2–15.3 months)
  - 4–7 lesions, 17.7 months (95% CI, 11.5–24.0)
  - ≤3 lesions, 24.8 months (95% CI, 19.6–30.0)
- PPS in patients with NEH lesions was significantly lower than without NEH lesions (p<0.001)
  - With NEH lesions: 8.6 months (95% CI, 4.9–14.4)
  - Without NEH lesions: 24.5 months (95% CI, 20.4–28.5 months)
- Following multivariate Cox hazard analysis, ≥8 NIH lesions and NEH lesions were independent prognostic factors of PPS in patients with intermediate-stage HCC after receiving TACE

CONCLUSIONS Strong positive correlations are apparent between progression pattern and PPS in patients with intermediate-stage HCC after receiving TACE as initial treatment. These results may be beneficial for designing future clinical trials

A multicentric study on real-life impact of nivolumab in patients with hepatocellular carcinoma

BACKGROUND & AIMS

- Nivolumab was approved for HCC based on the Checkmate 040 trial[1]
- **Aim:** To describe the clinical/safety profile and outcomes of patients with HCC treated with nivolumab in routine practice

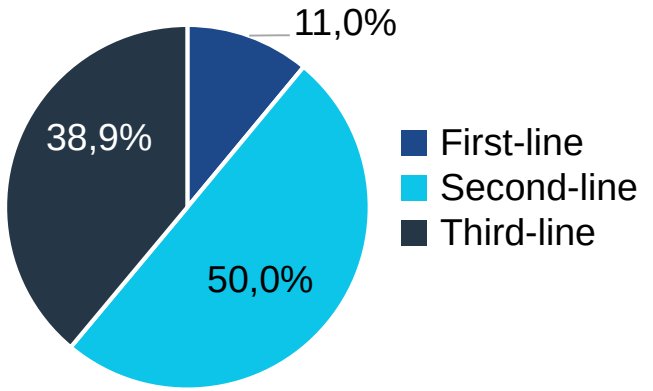
METHODS

- Retrospective, observational, multicentre study*
- Analyses
  - Clinical and laboratory data, previous treatments, adverse events, overall survival

RESULTS

- 118 patients received nivolumab
  - 76 as part of clinical trials
  - 42 outside clinical trials (*Figure*)
- In patients receiving second-line nivolumab
  - 50% CTP A
  - 40% CTP B
- 5 discontinued sorafenib due to AEs without radiologic progression
- Remaining patients
  - BCLCp-B (15%), BCLCp-C1 (35%) and BCLCp-C2 (25%)

Line of nivolumab treatment outside clinical trials†



1. El-Khoueiry AB, et al. Lancet 2017;389:2492–502.
*10 healthcare centres with multidisciplinary teams led by hepatologists;
†Sorafenib was 1st-line therapy in all patients receiving nivolumab 2nd- or 3rd-line;
Regorafenib was the 2nd-line therapy in 86% of the patients who received nivolumab as 3rd-line.
Gomes da Fonseca L, et al. ILC 2019; PS-137

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A multicentric study on real-life impact of nivolumab in patients with hepatocellular carcinoma

RESULTS (Cont.)

- Median follow-up and OS shown in table
- In the third-line nivolumab cohort*
  - 14/15 patients were treated following radiologic progression
    - 7.1%: BCLCp-B
    - 35.7%: C1
    - 57.2%: C2

- 18 (42.9%) patients presented 27 AEs
  - 7 (25.9%) AEs were grade III–IV
  - 1 was grade V‡
- Corticosteroids were required for the management of AEs in 5 (18.5%) patients
- 2 definitive discontinuations due to AEs
  - 1 rejection after liver transplantation
  - 1 ascites

TABLE

Since start of first-line, months (IQR)	Second-line nivolumab cohort	Third-line nivolumab cohort
Median follow-up	13.5 (8.5–26.9)	21.8 (16.9–27.1)
Median OS	28.8 (9.4–NE)	Not calculated†

CONCLUSION

- Safety profile consistent with clinical trials
- When evaluating OS data need to consider
  - Heterogeneity in progression
  - Need for nivolumab without presenting radiologic progression

*85.7% Child–Pugh A; 71.4% PS0 and 28.6% PS1;
†Owing to insufficient follow-up and number of events;
‡Rejection after liver transplantation.
Gomes da Fonseca L, et al. ILC 2019; PS-137

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PD-1 targeted immunotherapy in advanced hepatocellular carcinoma: Efficacy and safety data from an international multicenter real-world cohort

BACKGROUND & AIMS

- PD-1-targeted immunotherapy has shown promising results in phase 2 studies of HCC
- **Aim:** To evaluate safety and efficacy data from an international, multicentre, real-world cohort of patients with advanced HCC treated with nivolumab or pembrolizumab

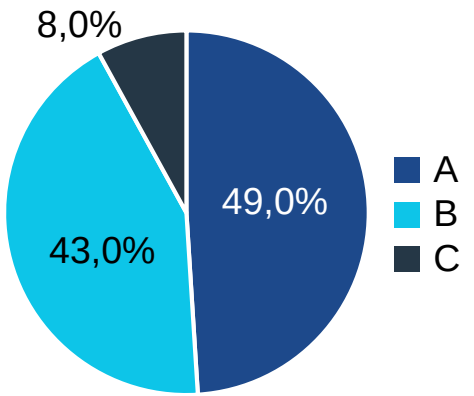
METHODS

- Data from 65 patients from Austria and Germany* were analyzed retrospectively
  - 34 treated with nivolumab
  - 31 treated with pembrolizumab

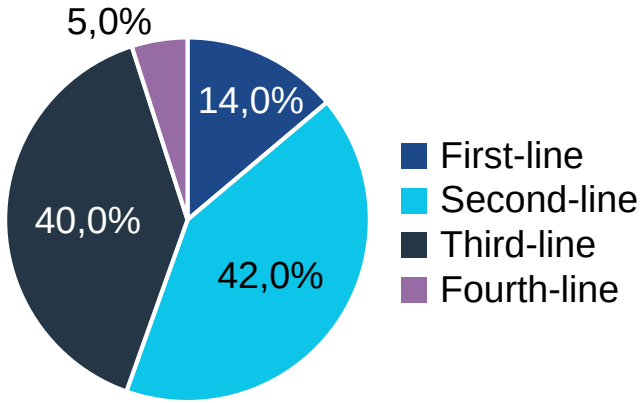
RESULTS

- Patient characteristics:

Child–Pugh class



Immunotherapy as systemic treatment



- 54 patients had ≥1 follow-up imaging to assess radiological response
- Overall response and disease control rates were 12% and 49%, respectively

*Data were from 6 centres; patients were treated between 10 July 2015 and 31 December 2018 (data cut-off).
Scheiner B, et al. ILC 2019; PS-138

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PD-1 targeted immunotherapy in advanced hepatocellular carcinoma: Efficacy and safety data from an international multicenter real-world cohort

RESULTS (Cont.)

- Time to progression and survival
  - Median TTP: 5.5 (95% CI, 3.5–7.4) months
  - Median PFS: 4.6 (95% CI, 3.0–6.2) months
  - Median OS: 11.0 (95% CI, 8.2–13.8) months
- Of 52 evaluable patients, 4 (8%) had hyperprogressive disease
- Most common adverse events were infections (n=7), rash (n=6), pruritus (n=3), fatigue (n=3), diarrhoea (n=3), and hepatitis (n=3)
- Efficacy and safety results were comparable between Child–Pugh A and B patients
  - Median OS was shorter in Child–Pugh B patients (8.6 vs. 16.7 months; p=0.065)
- No difference between patients receiving immunotherapy as 1st-/2nd-line vs. 3rd-/4th-line

CONCLUSIONS PD-1-targeted immunotherapy with nivolumab or pembrolizumab showed promising efficacy and safety in patients with advanced HCC, including those with Child–Pugh B and with intensive pre-treatment

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Scheiner B, et al. ILC 2019; PS-138

2. Clinical aspects except therapy

Multiplatform analysis of HCC tumours uncovers molecularly distinct subtypes

BACKGROUND & AIMS

- RPPA can measure multiple protein features in HCC, such as expression, protein modifications, and interaction with sample ligands
- **Aim:** To generate gene expression profile and proteomic data from HCC tumours and perform integrated analysis of both datasets

METHODS

- Data from 300 HCC tumours generated by expression microarrays and RPPA
- Supervised and unsupervised approaches applied to analyze proteomic and multiple genomic data
  - Somatic mutations, mRNA/miRNA expression, copy number alterations
- Integrated with proteomic data to uncover most correlated genomic alterations with functional products
- Clinical significance of identified key protein features validated in multiple independent HCC cohorts

RESULTS

- 3 HCC subtypes with distinct clinical outcomes
- One with strong mesenchymal characteristics
  - Low expression of epithelial markers, e.g. CDH1/CTNNB1
  - OS rate of this subtype lower than others (p=0.001)

Shin JH, et al. ILC 2019; PS-117

Multiplatform analysis of HCC tumours uncovers molecularly distinct subtypes

RESULTS (Cont.)

- Poor clinical outcomes of mesenchymal subtype were validated in multiple independent cohorts (>500 patients)
- Gene network analysis with integrated genomic/proteomic data revealed association of subtypes with currently available HCC treatments (e.g. sorafenib and immunotherapy)
- Multiple in-depth analysis of integrated data identified potential therapeutic target candidates for each subtype
  - Functional validation with cell lines demonstrated that some candidates are essential for growth and survival of HCC cells

CONCLUSIONS HCC can be classified into distinct subtypes by analyzing integrated genomic and proteomic data. These analyses identified potential therapeutic targets and their associated biomarkers. This study demonstrated the merit of integrated proteomic and genomic analysis to identify potential genetic drivers of HCC development

Shin JH, et al. ILC 2019; PS-117

HCV eradication in patients with hepatocellular carcinoma and cirrhosis improves tumour management and survival: The ANRS CO12 CirVir cohort

BACKGROUND & AIMS

- Assess impact of HCV eradication on:
  - HCC recurrence, liver decompensation, overall survival (OS) following curative treatment

METHODS

- Data were collected from 1,323 patients
  - With compensated cirrhosis*
  - Curatively treated for incidental HCC (resection or percutaneous ablation)
- Recruited 2006–2012 in 35 centres and followed up prospectively
  - SVR and HCC occurrence
- Primary outcomes
  - HCC recurrence, decompensation and OS from time of HCC treatment

RESULTS

- During a median FU of 67.5 months
  - 218 patients developed HCC
  - 128 received a curative procedure
- At HCC† diagnosis
  - Most patients were male (58.7%)
  - Mean age 63.9 years
  - 52.5% Child–Pugh A
- Attainment of SVR‡
  - Never: 71 patients (52.9%)
  - Before HCC occurrence: 27 patients (20.7%)
  - After HCC occurrence: 23 patients (18.1%)
- After a median 27.1 months post-HCC treatment
  - 55 (43.0%) experienced HCC recurrence
  - 48 (37.6%) patients died

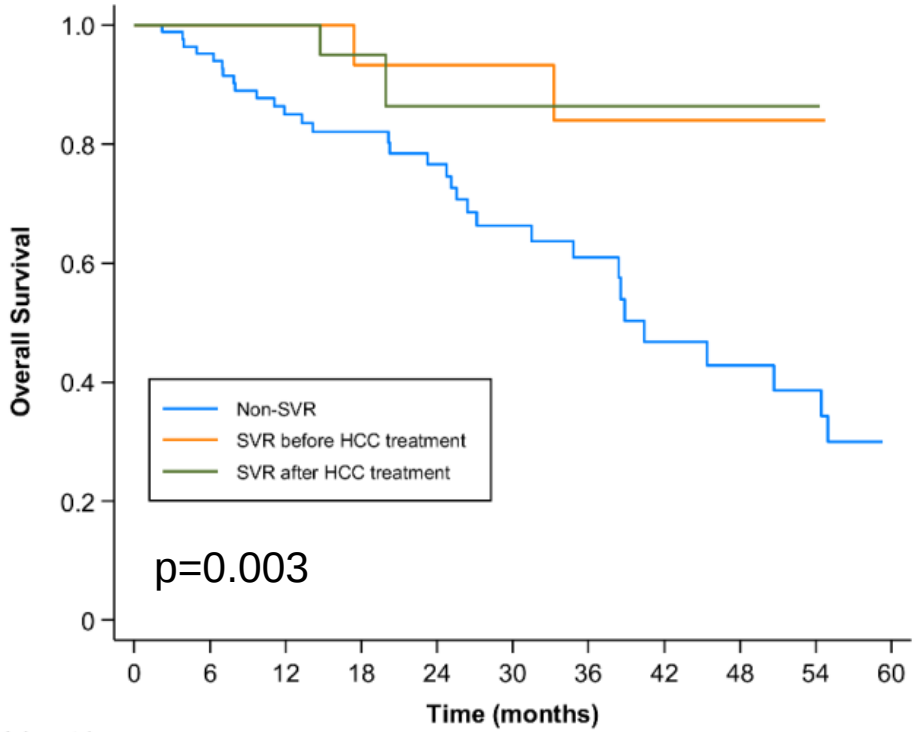
*Compensated Child–Pugh A biopsy-proven; †Mostly uninodular (75.7%), <20 mm (66.7%), and BCLC 0/A (93.7%); ‡Data missing in 7 patients.

Nahon P, et al. ILC 2019; PS-118

HCV eradication in patients with hepatocellular carcinoma and cirrhosis improves tumour management and survival: The ANRS CO12 CirVir cohort

RESULTS (Cont.)

- SVR did not significantly associate with reduced risk of HCC recurrence*
- In univariate (*Figure*) and multivariate analysis, SVR did associate with improved OS (HR=0.19 [0.07–0.48], p=0.001)
  - Survival benefit was explained by lower incidence of liver decompensation with SVR and higher rates of HCC recurrence re-treatment using sequential percutaneous ablation
- DAA intake associated with improved OS but not risk of HCC



Number at risk (events)																				
Non-SVR	85	(4)	78	(8)	63	(2)	50	(3)	39	(5)	27	(2)	21	(4)	13	(1)	10	(1)	9	(2)	5
SVR before HCC treatment	22	(0)	20	(0)	17	(1)	14	(0)	10	(0)	10	(1)	8	(0)	6	(0)	5	(0)	4	(0)	3
SVR after HCC treatment	29	(0)	27	(0)	27	(1)	15	(1)	4	(0)	3	(0)	3	(0)	3	(0)	2	(0)	2	(0)	1

CONCLUSIONS SVR is not associated with risk of HCC recurrence after a curative procedure in patients with cirrhosis. However, HCV eradication prevents potential liver function deterioration and improves OS by increasing HCC recurrence re-treatment

*Whether considering final SVR status (HR=0.94 [0.51; 1.73], p=0.84) or according to its time to achievement (before or after HCC emergence, global p=0.29).

Nahon P, et al. ILC 2019; PS-118

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3. Experimental and pathophysiology

Identification of a pan-γ-secretase inhibitor response signature for Notch-driven cholangiocarcinoma

BACKGROUND & AIMS

- Reports of Notch pathway reactivation in CCA are conflicting
- 40% of Notch-directed clinical trials are terminated or withdrawn
  - Improved guidelines for patient selection are required
- **Aim:** To identify a transcriptomic signature to predict pan-γ-secretase inhibitor (GSi) response across multiple patient cohorts, CCA models, and diverse cancer types

METHODS

- Transcriptomes were analyzed from 341 CCA patients
- Models of GSi sensitivity and resistance were identified from 13 CCA cell lines *in vitro*, followed by subcutaneous CCA xenograft models
- A responder signature was developed by transcriptome profiling of murine tumours
  - Tested for enrichment across diverse hydrodynamic models and patient subgroups
  - Pan-cancer analysis of the signature was also pursued in 9,409 patient tissues (31 cancer types) and 60 cancer cell lines

O'Rourke C, et al. ILC 2019; PS-044

Identification of a pan-γ-secretase inhibitor response signature for Notch-driven cholangiocarcinoma

RESULTS

- A *NOTCH*^{1high} CCA patient subgroup was identified
  - Distinct stromal infiltration and lymph node metastasis
- Extensive Notch network imbalance identified GS complex as an optimal therapeutic target
- HuCCT-1 and WITT cell lines identified as models of sensitivity and resistance, respectively
  - GSi pre-treatment: anti-neoplastic effects and 225-gene responder signature in the sensitive model
    - Enriched in intrahepatic vs. AKT-Ras-driven tumours ($p<0.001$) and in a subgroup of CCA patients ($P=0.0232$)
- Candidate GSi-responder patients characterized by unique intra-tumoural stromal reaction and signalling pathways, metastasis ($p=0.0078$) and cancer stemness ($p=0.0142$) signatures
- Pan-cancer analysis identified 41.9% cancers to harbour prospective GSi-responder patients
  - Nanomolar vs. micromolar sensitivity of 60 tumour lines to GSi with an AUC of 1

CONCLUSIONS This pan-GSi-responder signature may facilitate precision medicine application of Notch-directed therapy in CCA as well as prospectively across diverse malignancies. This is supportive of basket trial approaches using this theranostic signature

O'Rourke C, et al. ILC 2019; PS-044

HSD17B13 loss of function variant protects from hepatocellular carcinoma development in alcohol-related liver disease

BACKGROUND & AIMS

- Loss-of-function variant *HSD17B13* rs72613567 has been identified as protective in ALD and NAFLD
- **Aim:** To assess the impact of rs72613567 (TA) in European patients with HCC due to CLD

METHODS

HSD17B13 rs72613567, *PNPLA3* rs738409 and *TM6SF2* rs58542926 genotyped using case-control study design

Control: Healthy individuals (n=33,337)	Case: Patients with CLD and no HCC (n=2,206)	Case: Exploratory cohort: Patients with HCC (n=285)	Case: Validation cohort: Patients with HCC (n=824)
• From ExAC project	• Mean age 55 y • 69% male • 60% ALD • 24% hepatitis C • 11% NAFLD	• Mean age 65 y • 81% male • 35% ALD • 21% hepatitis C • 15% NAFLD	• Mean age 63 y • 83% male • 34% ALD • 25% hepatitis C • 17% NAFLD

Comparison of genotype distribution*

- *CLD vs. healthy individuals and HCC vs. CLD*

*Chi-square test and logistic regression; †Adjusted for age, sex, and fibrosis stage.

Yang J, et al. ILC 2019; PS-047

RESULTS

- TA allele carriers of *HSD17B13*
  - Less frequent in patients with CLD (39%, p<0.0001) and cirrhosis (38%, p<0.0001) vs. healthy individuals (47%)
  - Less frequent in patients with CLD due to chronic alcohol intake (40%; p<0.0001), CHC (39%, p=0.0002), and NAFLD (36%, p=0.0007) vs. healthy individuals (47%)
  - Suggests protective role of HSD17B13 rs72613567 in progression of CLD
  - Less frequent in patients with HCC due to ALD (*Figure A*), with protective effect remaining significant in multivariate analysis† (OR=0.6; p=0.005)
  - No association between HSD17B13 genotype and HCC risk in other aetiologies

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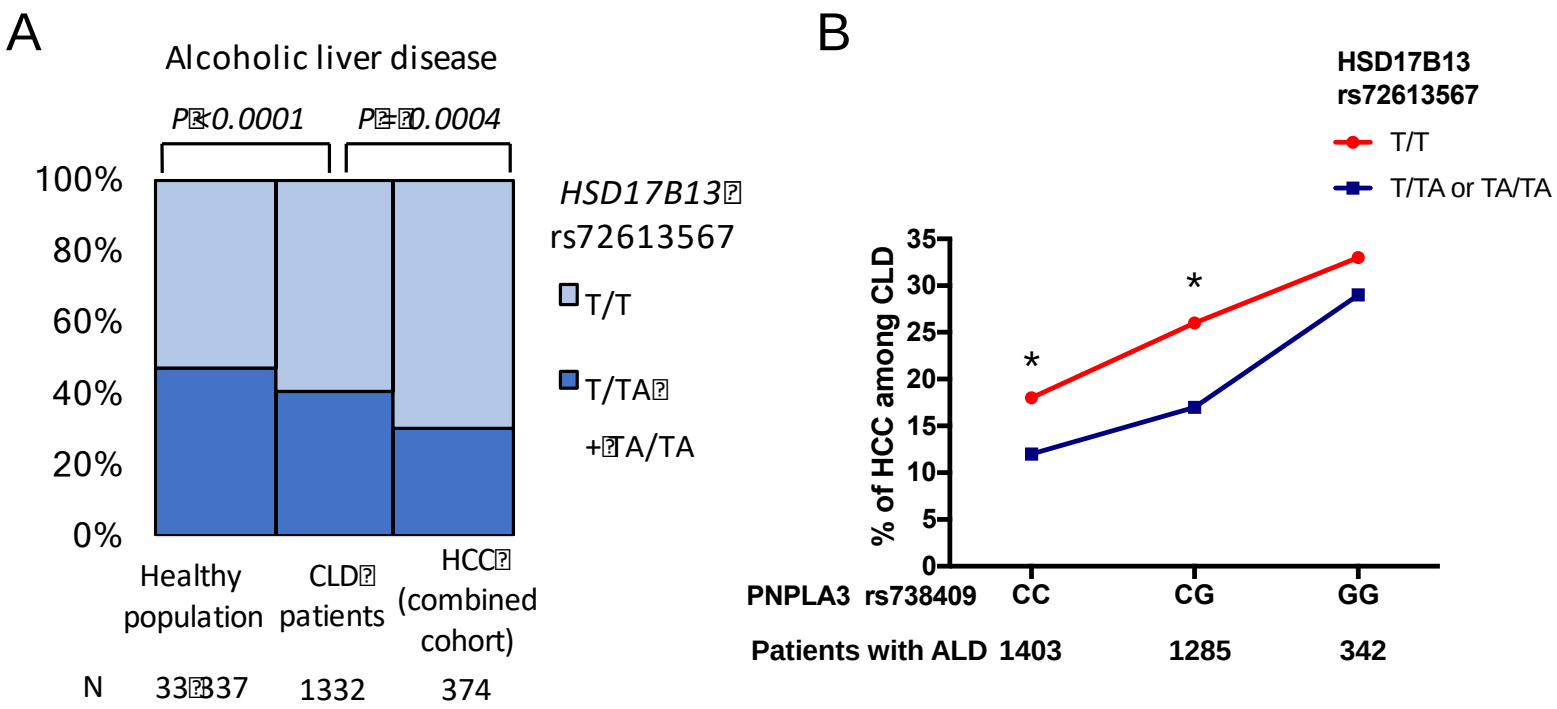
HSD17B13 loss of function variant protects from hepatocellular carcinoma development in alcohol-related liver disease

RESULTS (Cont.)

- *PNPLA3* rs738409* and *TM6SF2* rs58542926† both strongly associated with alcohol-related HCC risk
- *HSD17B13* rs72613567 TA allele reduced HCC risk in patients with ALD harbouring the at-risk *PNPLA3* rs738409 GC allele (OR=0.53; p=0.005; *Figure B*) but not in patients with the at-risk *TM6SF2* rs58542926 allele

FIGURE



CONCLUSIONS

The *HSD17B13* rs72613567 loss of function variant is protective of HCC development in patients with alcohol-related liver disease

*GC vs. CC: OR=1.8, p=0.0003, and GG vs. CC: OR=3.5, p=9.04e-09; †CT+TT vs. CC: OR=1.8, p=0.001.

Yang J, et al. ILC 2019; PS-047

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Definition of aneuploidy profiles and their impact on tumour progression and immune features in hepatocellular carcinoma

BACKGROUND & AIMS

- **Aneuploidy**, a cancer hallmark, includes **broad** whole chromosome- or arm-level somatic copy number alterations (sCNAs) and smaller **focal** sCNAs
- Pan-cancer studies suggest distinctive molecular/clinical traits are linked to either broad or focal sCNA loads,* with the former potentially interfering with tumour immune infiltrates
- **Aim:** To assess sCNA burdens in HCC to unveil associated clinical–molecular characteristics and immune profiles

METHODS

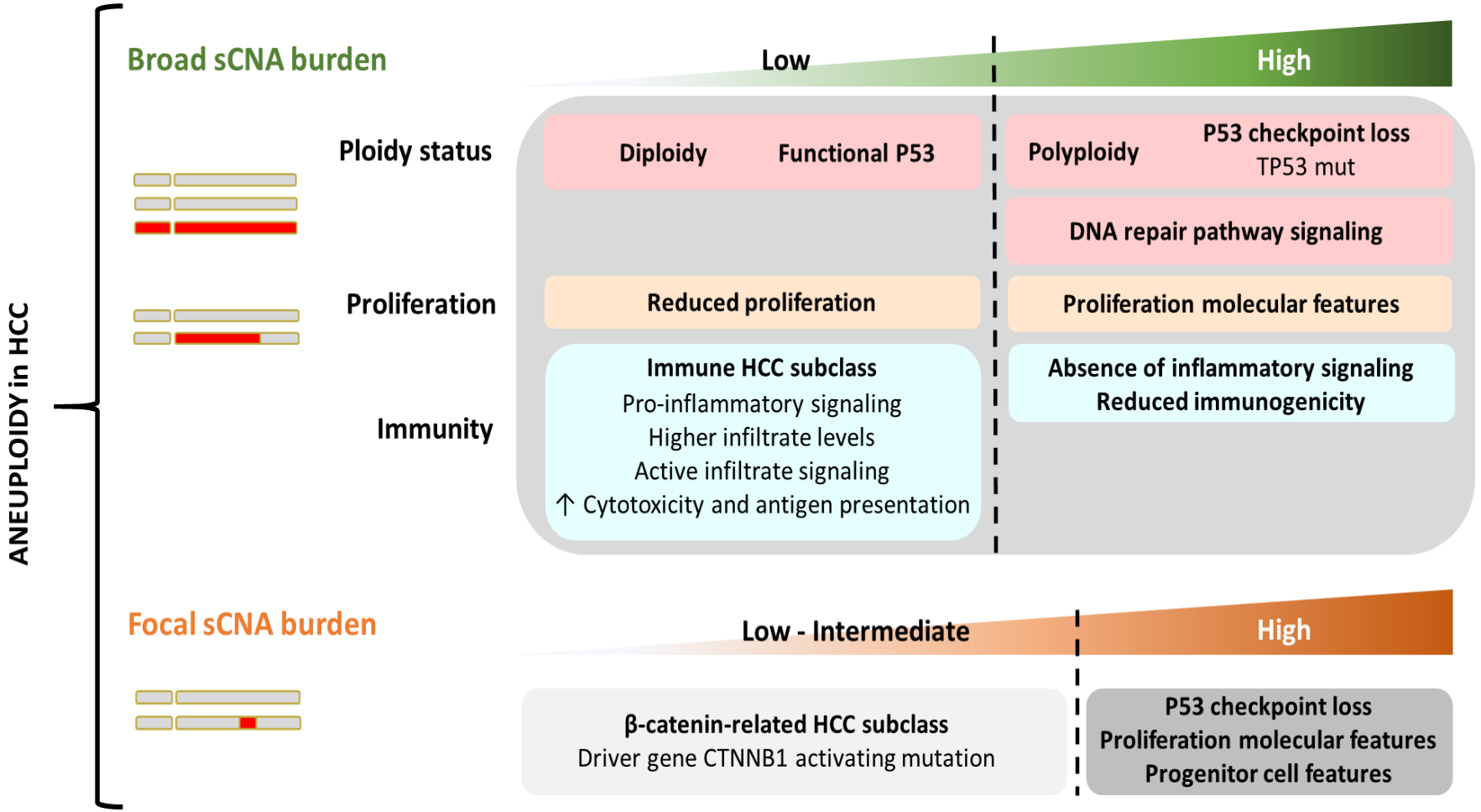
- 520 paired tumour/adjacent surgically resected HCC samples:
  - 150 discovery cohort (HEPTROMIC); 370 validation cohort (TCGA)
- Tumour ploidy and sCNAs extracted from SNP array data using ASCAT and SAAS-CNV
  - **Broad** and **Focal sCNA Scores** based on sCNA number, amplitude and length were created to assess **sCNA loads** in each sample
  - Scores were integrated with gene expression profiling, clinical–pathological data and composition of the tumour immune infiltrate, determined using the tools ESTIMATE and Immunophenoscore

*Alterations spanning ≥50% (broad) and <50% (focal) of a chromosome arm.

Esteban-Fabró R, et al. ILC 2019; PS-048

Definition of aneuploidy profiles and their impact on tumour progression and immune features in hepatocellular carcinoma

RESULTS



CONCLUSIONS

Tumours with chromosomal stability, defined by low burdens of broad copy number alterations, are enriched in the immune class of HCC. Proposed Broad sCNA Score capturing chromosomal stability might enable identification of those patients responding to immune checkpoint inhibitors

Esteban-Fabró R, et al. ILC 2019; PS-048

4. Acute liver failure and drug induced liver injury

Liver enzyme elevations and hepatotoxicity in patients treated with checkpoint inhibitor immunotherapy

BACKGROUND & AIMS

- Common liver immune-related AEs (LirAEs) resulting from CPi immunotherapy are poorly characterized
- **Aim:** To better understand the causes of liver enzyme elevation (LEE), frequency of LirAEs and the resulting impact on patient management

METHODS

Aug 2012–Dec 2018
Patients from phase 1/2 clinical trials (Tumor Immunotherapy Program*)

↓

Clinical records reviewed for patients with clinically significant LEE (ALT/AST >3x ULN and/or bilirubin >1.5x ULN)

RESULTS

Patient demographics	Patients (%) treated with CPi (N=472)
Therapy type	
Anti-PD-1	65.2
Combination CPi	6.1
Clinically significant LEE	21.6
Diagnostic evaluation	
Liver imaging	71.6
HBV/HCV serology	16.7
Autoimmune serology	13.7
Liver biopsy	2.9
LEE attributed to	
Disease progression	54.9
Other drugs/toxins	6.9
Surgery	4.9
Other	16.7
LirAE	16.7 of LEE (3.6% of total cohort)

*At the Princess Margaret Cancer Centre, Toronto, Canada.

Cunningham M, et al. ILC 2019; PS-139

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Liver enzyme elevations and hepatotoxicity in patients treated with checkpoint inhibitor immunotherapy

RESULTS (Cont.)

- LirAE associated with
  - Prior CPi exposure (in 41.2% of patients with vs. 15.4% without LirAE; p=0.011)
  - Other irAEs (in 76.5% of patients with vs. 19.2% without LirAE; p=<0.001)
- 15/17 patients with LirAE received steroids and liver enzymes normalized after a median of 37 days (IQR 21–52). 4 patients received further CPi with recurrent LirAE in 1 patient

Variable	Patients (N=472)
Follow-up, median (IQR)	7.5 months (3.6–16.2)
Total disease progression, n (%) Patients with LirAE (%) Patients without (%)	421 (89.2) 52.9 86.7 p=0.001
Death, n (%)	292 (61.9)
Death due to complications from LirAE	0

CONCLUSIONS

LEE may be unrelated to cancer/CPi. LirAEs were more common in patients with previous CPi exposure and other irAEs. Lower incidence of disease progression seen in those with LirAE

Cunningham M, et al. ILC 2019; PS-139