European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

18th October 2023

Johan Hamrin & Irene Schmid

Immunotherapy for recurrence of FL-HCC

Moderation: Małgorzata Krawczyk

Funded by the European Union's EU4Health Programme

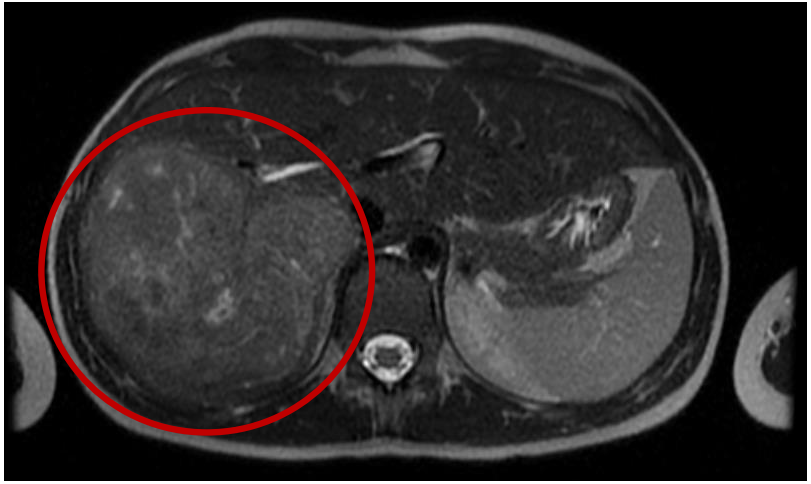
COI declaration

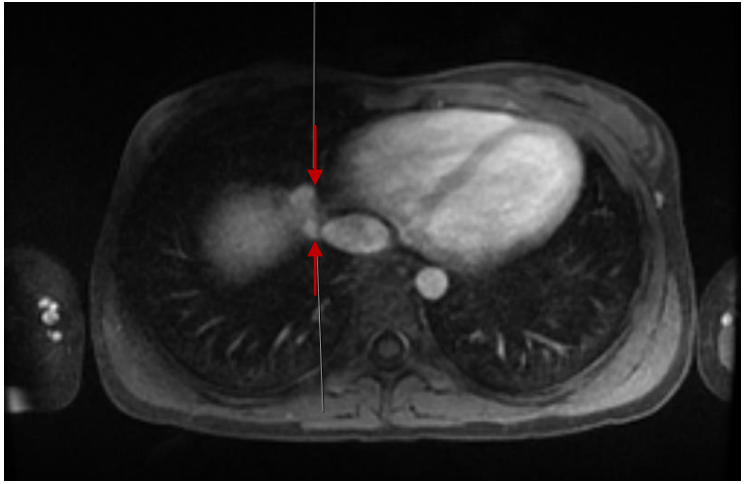
- Dr Johan Hamrin: nothing to declare
- Prof Irene Schmid: nothing to declare

Primary diagnosis

- 12-year old girl with prior history of asthma, obesity in childhood (7 years of age), now normal weight.
- Presented end of January 2020 with increasing symptoms of fever, diarrhea and abdominal pains over a period of 2-3 months
- Elevated inflammatory tests (CRP, SR, normal blood counts, slightly elevated liver enzymes including LDH)
- An abdominal CT-scan ordered from GPs office revealed a suspected tumor originating from the liver

Initial imaging





Normal AFP levels.

Question 1

- Which diagnosis do you suspect?
  - Hepatoblastoma?
  - Hepatocellular carcinoma?
  - Tumor of biliary origin?
  - Other non-hepatic primary tumor?

Pathology & Staging

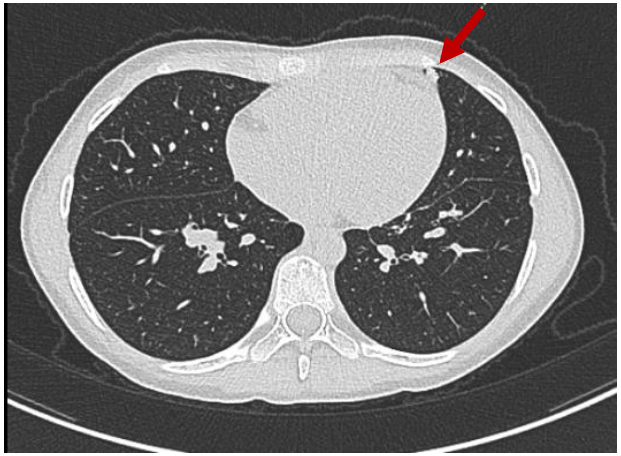
- Hepatocellular carcinoma, fibrolamellar variant (FL-HCC)

- PRETEXT II. Lymph node involvement, no other metastases. Annotation factors (VPEFR) negative.

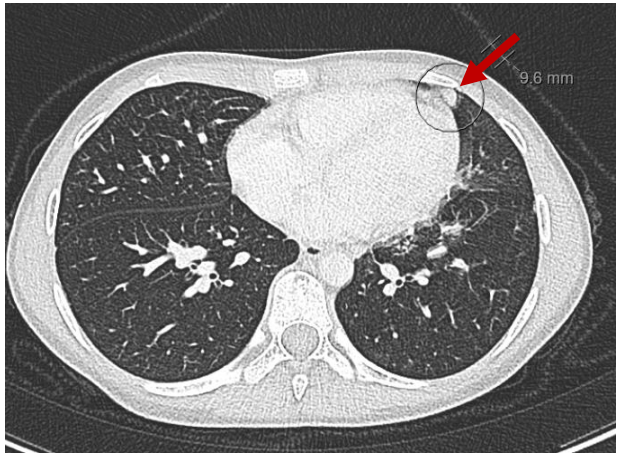
Primary treatment

- Primary surgery 18th February 2020 with resection of liver (right lobe) and 20 abdominal lymph nodes (mostly paraoartal) and one above the diaphragm.
- Histology from surgery: Confirmed FL-HCC in otherwise healthy liver. 5/21 removed lymph nodes with metastases. Radical resection.
- Post-operative complication: chylothorax (cytology without malignant cells)
- Post-operative chemotherapy: PLADO (Cis/Doxo) x4 with Sorafenib
- End of treatment: June 2020

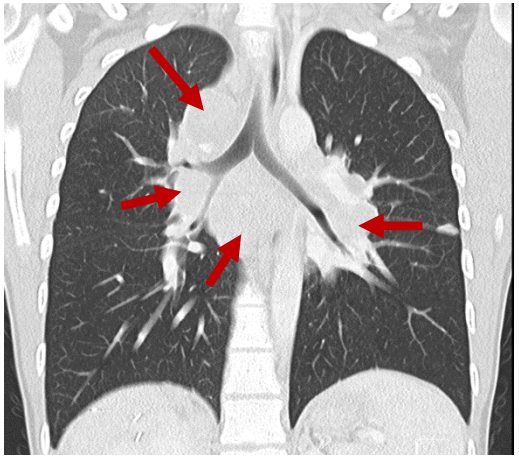
October – December 2020



November 2020



December 2020



December 2020

- Initially asymptomatic.
- By December: Subfebrile, loss of stamina during exercise, some light pain in her right hip

Recurrence

- CT-led biopsy of suspected lung metastases early December 2022: inflammatory cells, no malignant cells.
- MRI without sign of local recurrence in abdomen. Avascular necrosis of right caput femoris.
- Mediastinoscopy with biopsy of mediastinal lymph nodes in late December confirms recurrent metastasis of FL-HCC. INFORM results pending.
- Thorax surgeons: Mediastinal metastases not radically resectable, lung metastases would be.

Treatment?

1. Conventional chemotherapy with GEMOX, perhaps with another multikinase inhibitor
2. Immunotherapy given to adult patients with HCC: PD1-inhibitor combined with VEGF-inhibitor?

Question 2

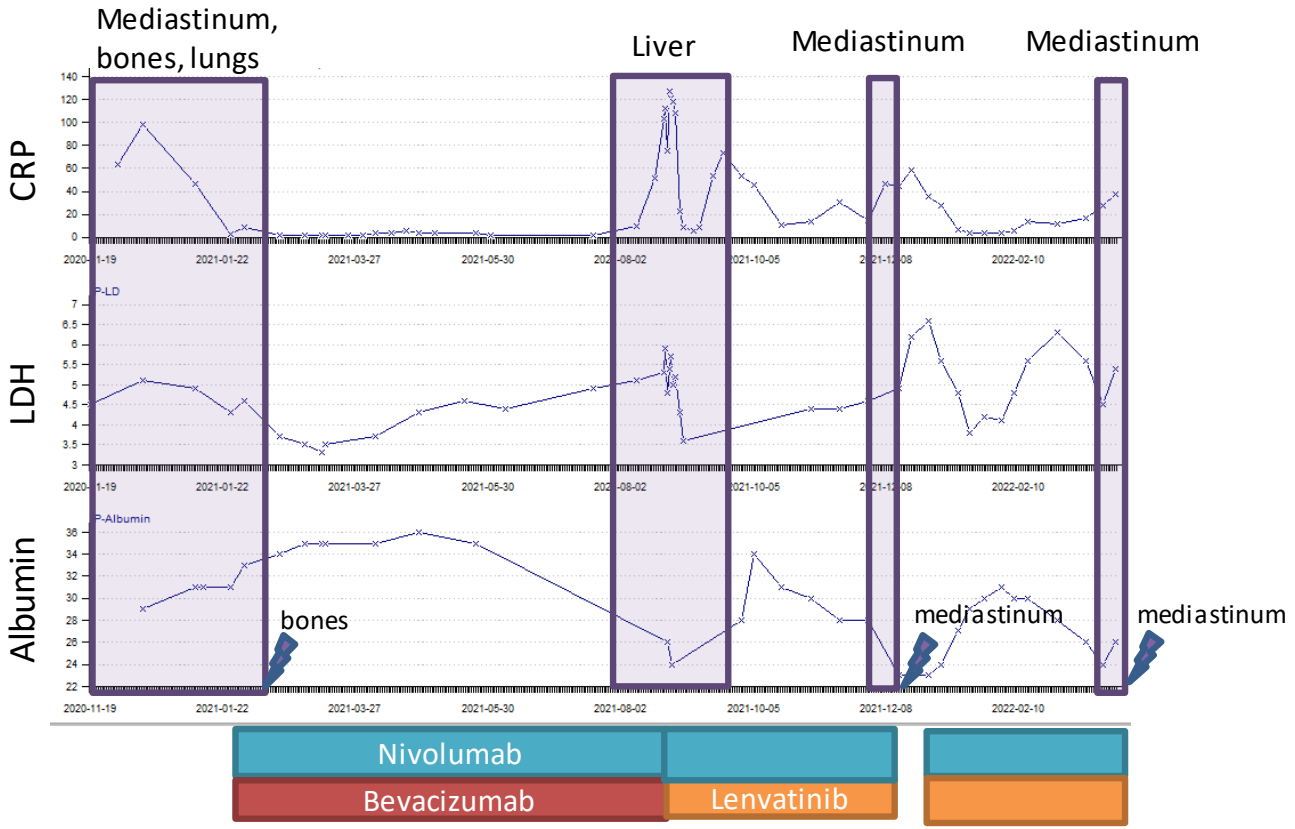
- What would you have chosen?

1. GEMOX +/- other MKI
2. Immunotherapy: PD1-inhibitor with VEGF?

Therapy at recurrence

- Nivolumab (3mg/kg) 14-day intervals + Bevacizumab (15mg/kg) on 21-day intervals.
- Rationale:
  - Clearly highly chemo-resistant tumor
  - High price on QoL with GEMOX
  - INFORM results: DNJAB1:PRKACA fusion (genetic signature of FL-HCC) with PD-L1 overexpression. Low-priority recommendation (7/8) to consider treatment with PD1/PD-L1 inhibitor.
  - Parallel case with advanced FL-HCC progressing under conventional therapy (PLADO/GEMOX +S), but responding to Nivolumab + Lenvatinib (MKI)

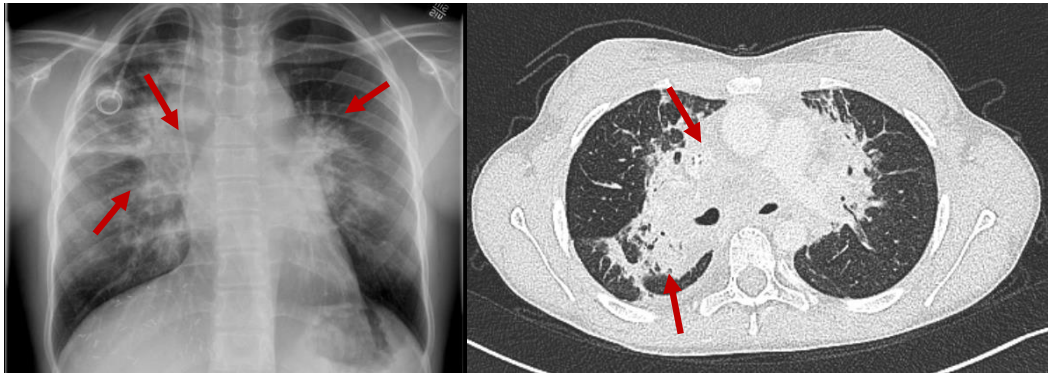
Treatment response



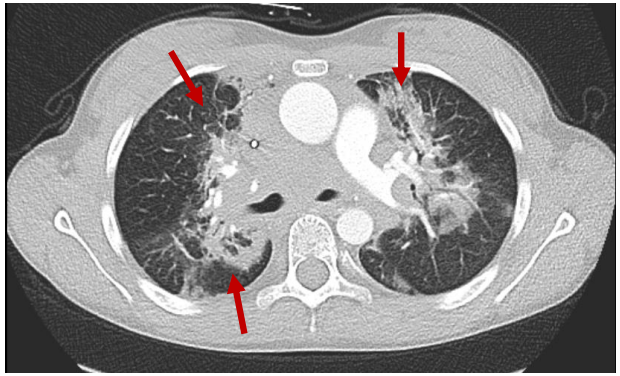
Continued therapy?

- March 2022: Continued progression on PD-1 inhibitor combinations: 1st with VEGF-inhibitor, later on MKI and short-lived clinical responses to radiation treatments (palliative doses 4Gyx5).
- Discussed options:
  - Stop oncologic treatment
  - Escalate immunotherapy to combined checkpoint inhibition: PD1-inhibotor with CTL4-inhibitor (Nivolumab + Ipilimumab)

ICI combination therapy



Pred



May 2022: Two weeks after first dos of Nivo + Ipi
ICI-associated pneumonitis

Early june 2022: Clinical improvement, partial resolution of infiltrates.

ICI combination therapy

- From mid-June 2022: Worsening of coughing/fever, progressive dyspnoea
- Passed away end of June

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DISCUSSION

Co-funded by the European Union's Health Programme

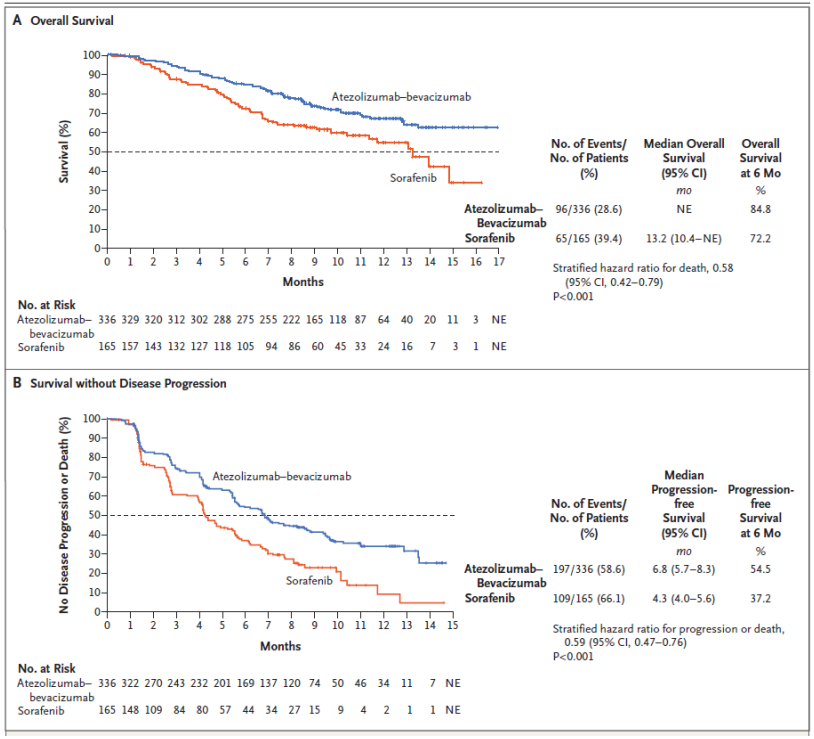
FL-HCC Background

- 1-6% of all primary liver tumors in whole population
- Median age at disease presentation 21 years, two incidence peaks: first age 10-30 years, second 60-70 years
- Not associated with liver disease/cirrhosis, but sometimes associated with FNH
- Genetic signature DNJAB1-PRKACA
- Low tumor mutational burden and PD-L1 expression
- Limited effect of conventional chemotherapy

Take home messages

- FL-HCC is a rare disease with limited guidance regarding treatments for advanced stages/disease recurrence
- Mainstay of treatment is radical resection
- Immunotherapy and palliative radiation provided 18 months with stable disease with very little side-effects

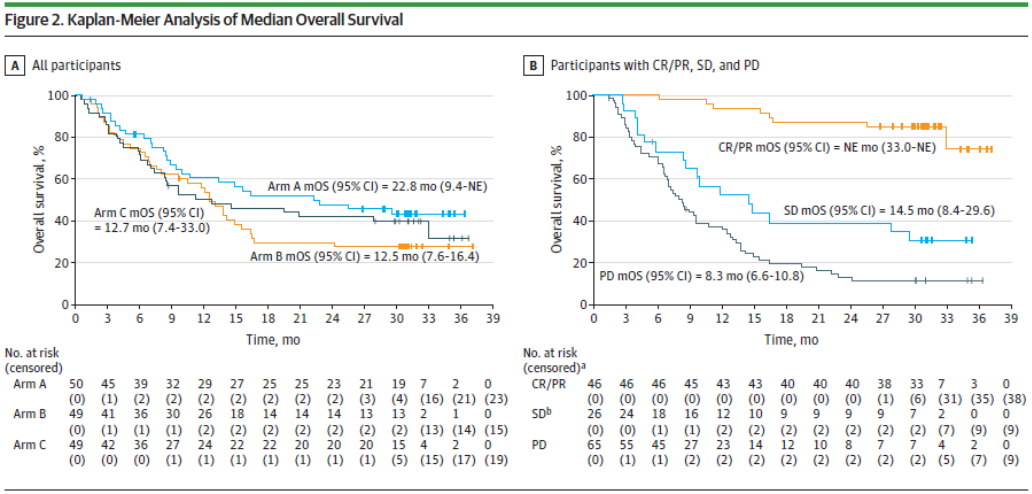
Atezolizumab - Bevacizumab



- IMbrave150 phase III RCT
- 336 adults with unresectable HCC, no previous treatment
- Randomized in 2:1 ratio
- OS at 12 months 67% vs 55%
- Progression-free survival: 6.8 months vs 4.3 months

- FL-HCC an exclusion criteria

Nivolumab + Ipilimumab



- CheckMate040 RCT, phase I/II
- Patients with unresectable HCC or with disease progression/intolerance to Sorafenib
- Arm A: Nivo 1mg/kg + Ipi 3mg/kg
- Arm B: Nivo 3mg/kg + Ipi 1mg/kg
- Arm A+B: Nivo+Ipi every 3 weeks, 4 doses, then Nivo every 2 weeks
- Arm C: Nivo 3mg/kg every 2 weeks + Ipi 1mg/kg every 6 weeks.

- FL-HCC an exclusion criteria

- mOS: 22.8 months in arm A, approx 12.5 months in arm B+C
- Accelarated approval in USA as second-line treatment for HCC

ICIs for FL-HCC

- Retrospective study of 19 patients with advanced stage FL-HCC receiving ICI therapy outside a clinical trial
- 80% of patients had prior systemic treatment, previous ICI an exclusion criteria
- Response evaluated according to RECIST 1.1
- Median TMB 1.85 mut/MB (0 – 6 mut/MB) -> LOW
- PD-L1 expression: negative (<1%) in 11/11

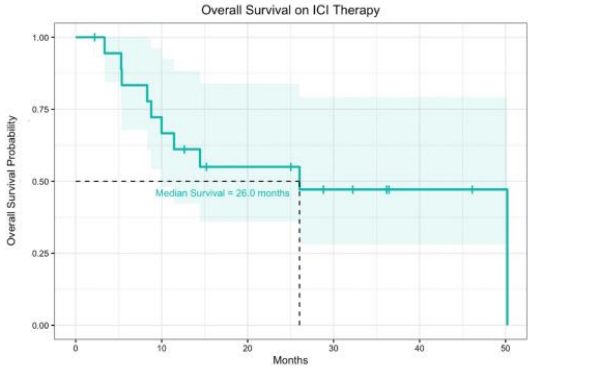


Figure 3. Overall survival of 19 patients with FLC treated with ICI therapy. Of 19 patients, 15 received ICIs alone and 4 received ICIs in combination with other therapies. The shaded region represents the 95% confidence interval.

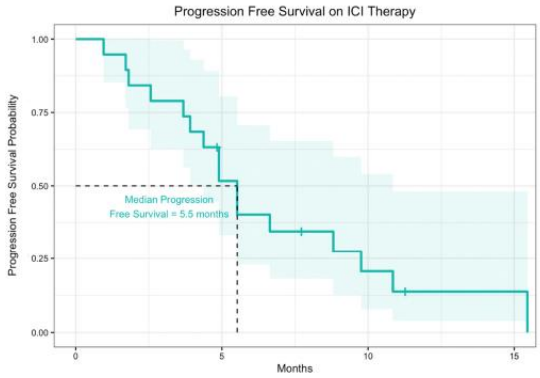


Figure 2. Progression free survival of 19 patients with FLC treated with ICI. Of 19 patients, 15 received ICIs alone and 4 received ICIs in combination with other therapies. The shaded region represents the 95% confidence interval.

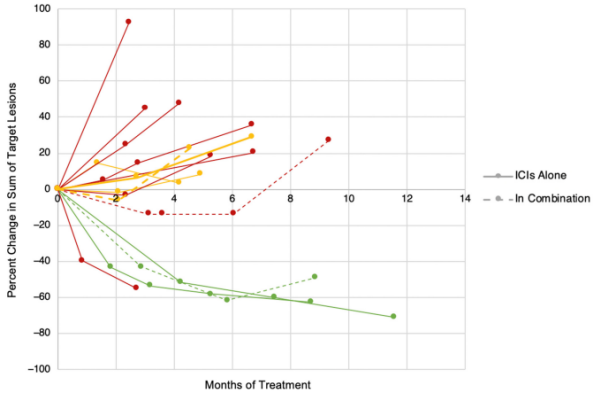


Figure 1. Percent change in sum of target lesions over time for patients with FLC treated with ICI therapy by RECIST 1.1 Criteria. Green = PR, Yellow = SD, Red = PD.

Considerations

Pros	Cons
Overall good response to immunotherapy. Increased inflammatory response associated with progression.	Therapeutic effect of immunotherapy already exhausted?
Side effects of immunotherapy: Patienta so far: very few: acne, rhinitis According to literature single PD1-inhibitor: 74% immunmediated toxicity, 14% grade >3	Combined immunotherapy side effects (literature): 90% immunmediated toxicity 55% >grade 3
Immunotherapies with better evidence have now been exhausted	Very little evidence on combined check-point inhibitors in children (approved in US for adults with HCC)
Good clinical condition: able to sustain possible side-effects	Side-effects even more detrimental to quality of life
Patient and family motivated to attempt further treatment	
Hospital advisory board for 'unproven therapies approved'	