109P: DNA damage repair in biliary tract cancer: a new target for precision medicine?

I.A. Mavroeidi[1,2], T.M. Reissig[1,2] S. Kalbourtzis[2,4,] , S. Kasper-Virchow [1,2], S.T. Liffers[2,3], T. Herold[2,4] J. Treckmann[4], H.U. Schildhaus[2,3] M. Schuler[1,2], J.T. Siveke [1,2,3]

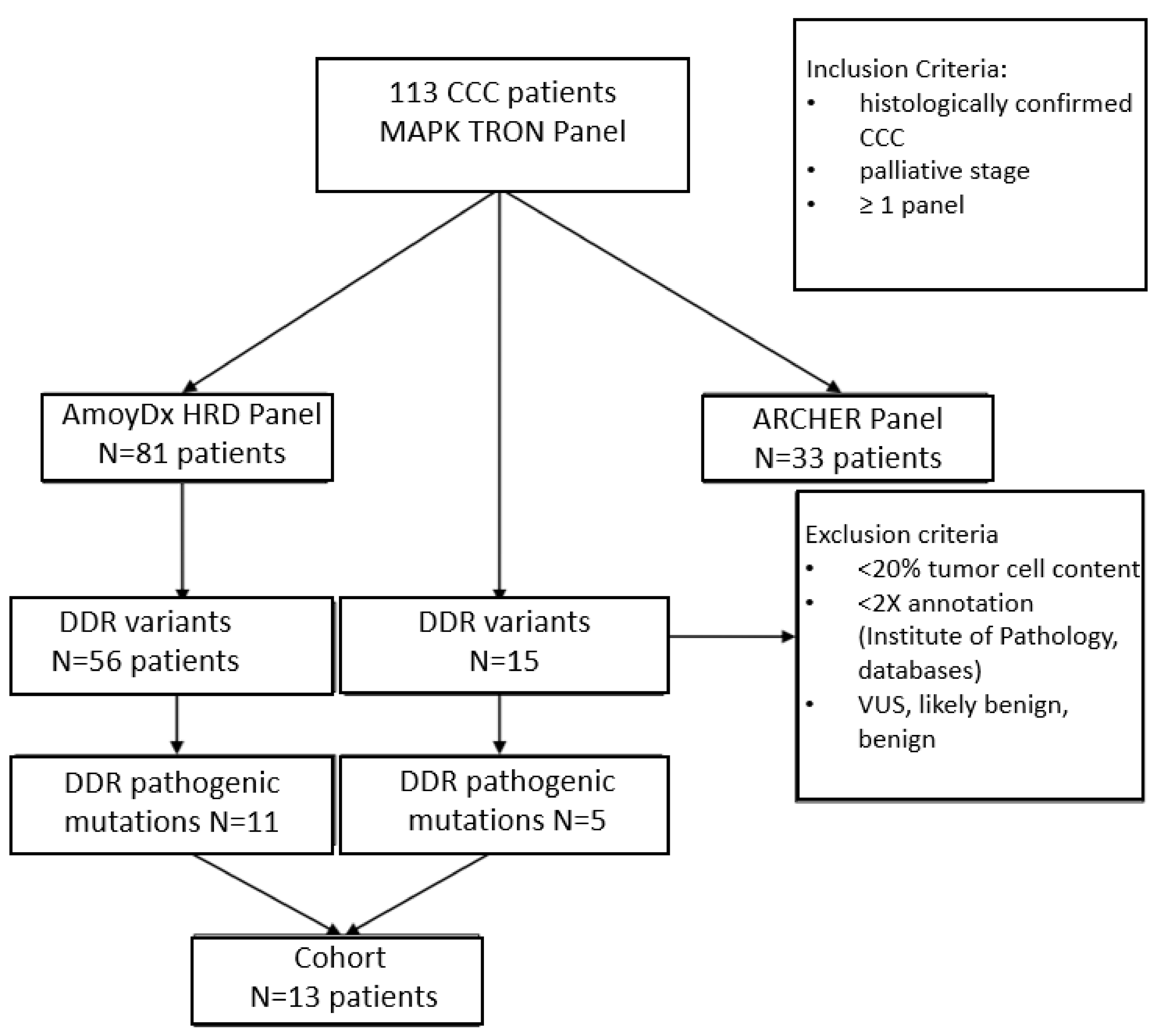
1. Department of Medical Oncology, West German Cancer Center, University Hospital Essen, 2. German Cancer Consortium (DKTK), Partner Site University Hospital Essen , 3. Bridge Institute of Experimental Tumor Therapy, West German Cancer Center, University Hospital Essen ,
4. Institute of Pathology German Cancer Center, University Hospital Essen,Germany, 5. Department of General- Visceral and Transplantation Surgery,University Hospital Essen, Germany.

INTRODUCTION

Biliary tract cancers (BTC) are a relatively rare tumor entity showing a high mortality rate and heterogeneity in terms of clinical and molecular features. Aim of this work is the molecular characterisation of a BTC cohort in a single comprehensive cancer institute focusing on genomic alterations of DNA damage repair (DDR) genes, which are less evaluated in BTC.

METHODS

- Retrospective analysis of the clinical course and mutation status of patients with locally advanced or metastatic BTC treated at the West German Tumour Centre of the University Hospital Essen between the years 2016 and 2022.
- Microsatellite instability (MSI) / DNA mismatch repair (MMR) status was determined by immunohistochemistry and DNA sequencing.
- Gene variants were assessed using two targeted DNA-based assays (MAPK-TRON customized NGS panel, 47 genes; AmoyDx HRD Focus panel, 32 genes) and an RNA fusion assay (FusionPlex CTL panel [Archer]).
- 113 patients received the MAPK-TRON NGS (next generation sequencing) panel (96%), while 81 were also analysed with the HRD (homologous recombination deficiency) focus panel (72%). 59 patients were analysed as for MSI Status and 33 patients with ARCHER panel.
- Time in first palliative regime till disease progression (Time to Event =TET), overall survival (OS) and secondary clinical endpoints were analysed statistically and correlated using the long-rank test with mutation status and treatment data.

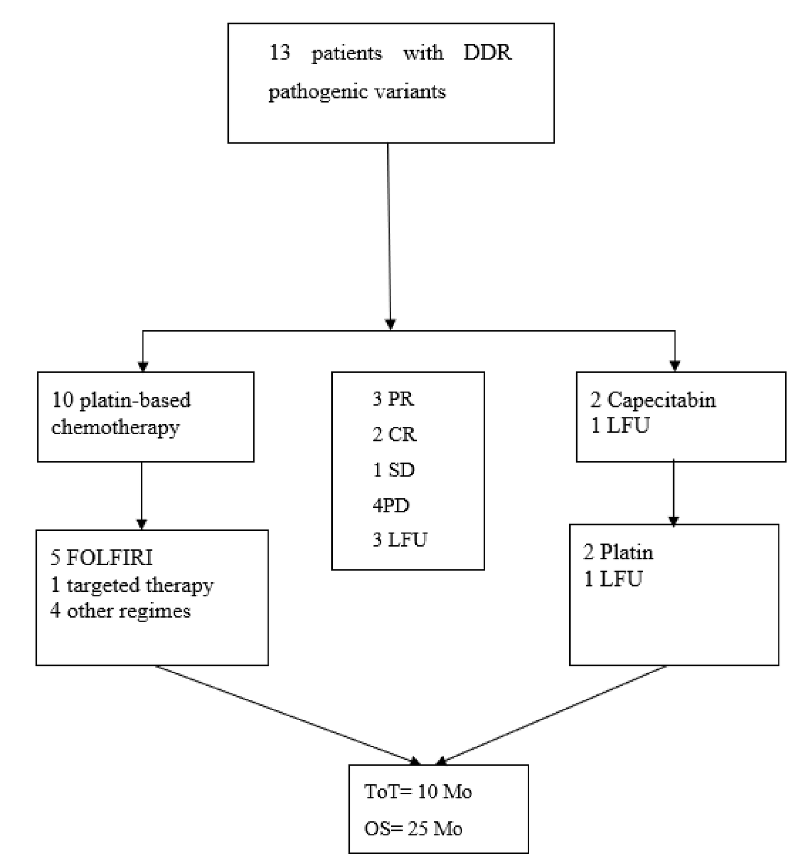

113 CCC patients
MAPK TRON Panel
Inclusion Criteria:
• histologically confirmed CCC
• palliative stage
• ≥ 1 panel
AmoyDx HRD Panel
N=81 patients
ARCHER Panel
N=33 patients
Exclusion criteria
• <20% tumor cell content
• <2X annotation (Institute of Pathology, databases)
• VUS, likely benign, benign
DDR variants
N=56 patients
DDR variants
N=15
DDR pathogenic mutations N=11
DDR pathogenic mutations N=5
Cohort
N=13 patients

Consort diagram of the project focusing on the DDR-mutated sub-cohort.

RESULTS

- Equal distribution between both sexes.
- Median age 60 years (minimum 26 years, maximum 82 years).
- Till last observation date (30.04.2022), 80 patients were deceased.
- Histology: 73 intrahepatic (64.6%), 19 perihilar (16.8%), 14 distal cholangiocarcinomas (12.4%), and 7 gallbladder carcinomas (6.2%).
- 46 patients (40%) presented distant metastases by first diagnosis with statistical significantly worsened OS (HR=1,9, p=0.01; 95% CI=1.13-3.14).
- 70% (80/113) of patients were in the 1.line treated with a platinum-containing chemotherapy
- TP53 (33/113, 29.2%), KRAS (25/113, 22.1%), IDH1/2 (18/113, 16%), PIK3CA (8/113, 7%), and BRAF (6/113, 5.3%) were identified as the most frequently mutated genes.

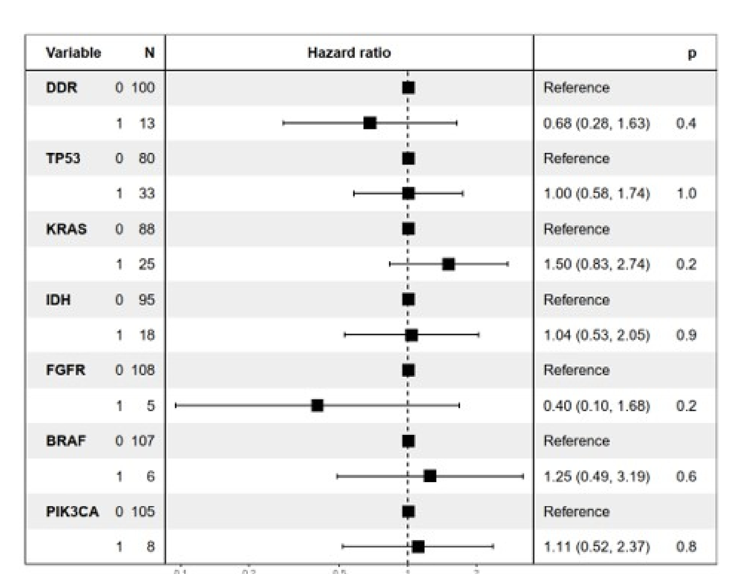
Patients	Characteristics
Age (Median, years)	60 (26-82)
Sex, n (%)	
men	53 (47%)
women	60 (53%)
Histology, n (%)	
ICC	73 (64.6%)
PCC	19 (16.8%)
ECC	14 (12.4%)
GBC	7 (6.2%)
UICC, n (%)	
A	6 (5%)
B	26 (23%)
C	19 (17%)
D	58 (51.3%)
T, n (%)	
1	13 (11.5%)
2	44 (39%)
3	19 (16.8%)
4	12 (10.4%)
N, n (%)	
0	33 (29.2%)
1	38 (33.4%)
2	2 (0.2%)
3	3 (0.3%)
M, n (%)	
0	59 (52%)
1	
• synchronous	49 (43.4%)
• metachronous	42 (37%)
G grading, n (%)	
1	4 (4%)
2	55 (48.7%)
3	43 (38%)

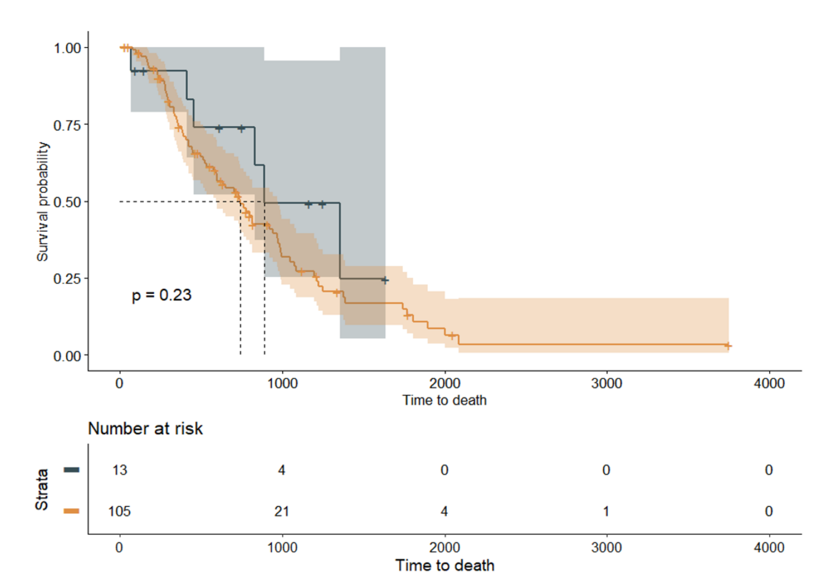

13 patients with DDR pathogenic variants
10 platin-based chemotherapy
3 PR
2 CR
1 SD
4PD
3 LFU
2 Capecitabin
1 LFU
5 FOLFIRI
1 targeted therapy
4 other regimes
2 Platin
1 LFU
ToT= 10 Mo
OS= 25 Mo

Molecular subgroups	ToT (Mo)	OS (Mo)
DDR	**10.1 (6.6; 13.5)**	**25 (13.7; 38.8)**
IDH1/2	**13 (11.1; 18.6)**	18.9 (11.2; 26.9)
FGFR2	5.5 (3.7; 8.4)	**41.5 (20.7; 43.1)**
KRAS	7.4 (2.8; 9.7)	12.8 (10.2; 20.3)
BRAF	**9.3 (6.8; 11.2)**	**24.2 (11.9; 27.2)**
TP53	5.9 (2.8; 8.7)	19.1 (8; 27.3)
PIK3CA	6.7 (6.1; 7.9)	**29.8 (12.9; 39.1)**
Cohort	8.8 (4.8; 11.6)	19.9 (10; 32,5)

Right:
Above: Clinical characteristics of the studied cohort.
Below: Forest plot for OS separated by molecular subgroup for the whole cohort and the patients who received platinum-containing 1st line chemotherapy separated by molecular subgroup. Hazard ratio (HR), 95% CI and p-value are given in the right column.

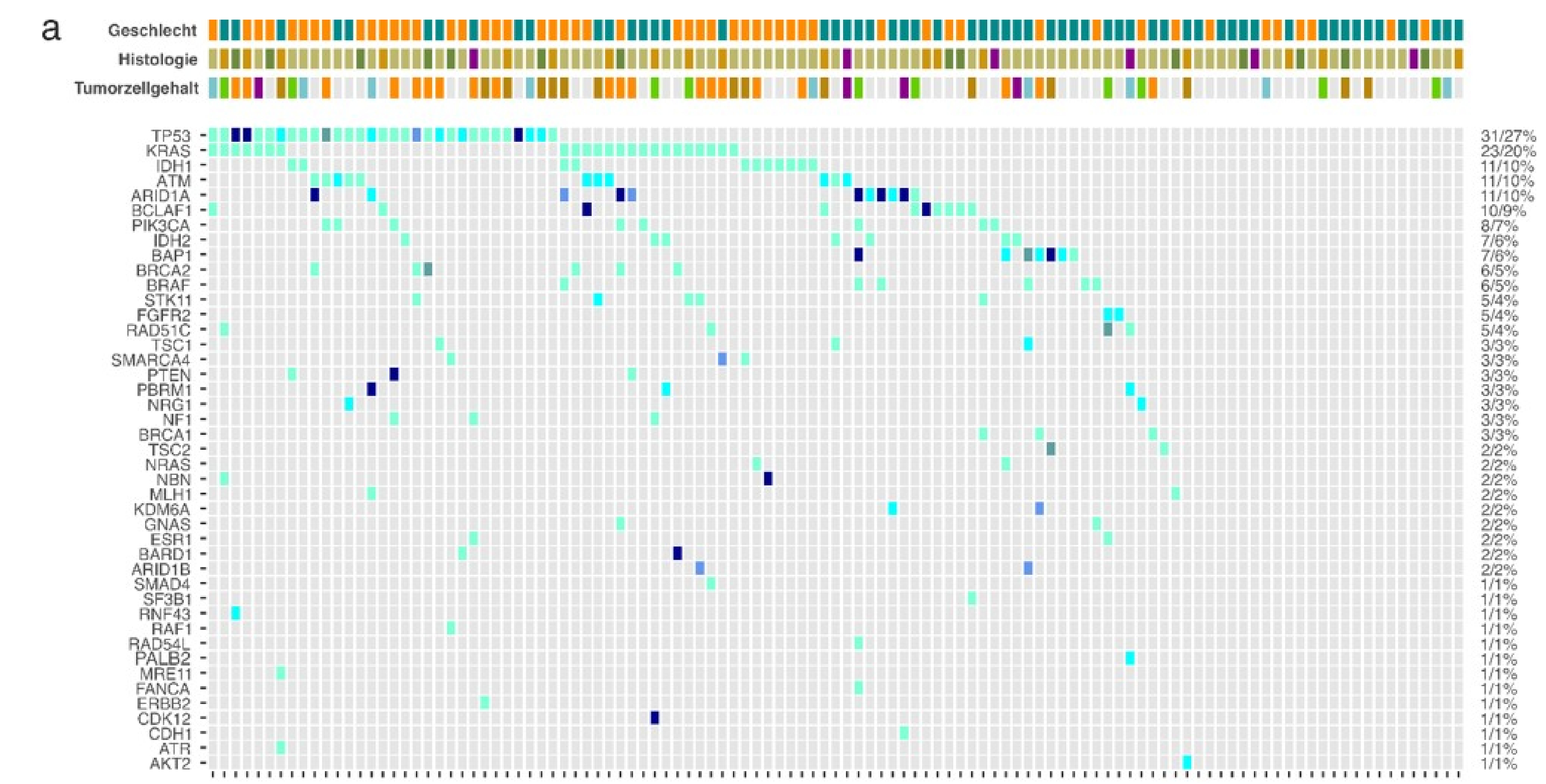
Left:
Above: Therapy regimes for the DDR mutated subgroup
Below: Kaplan Meier curve for the DDR mutated subgroup

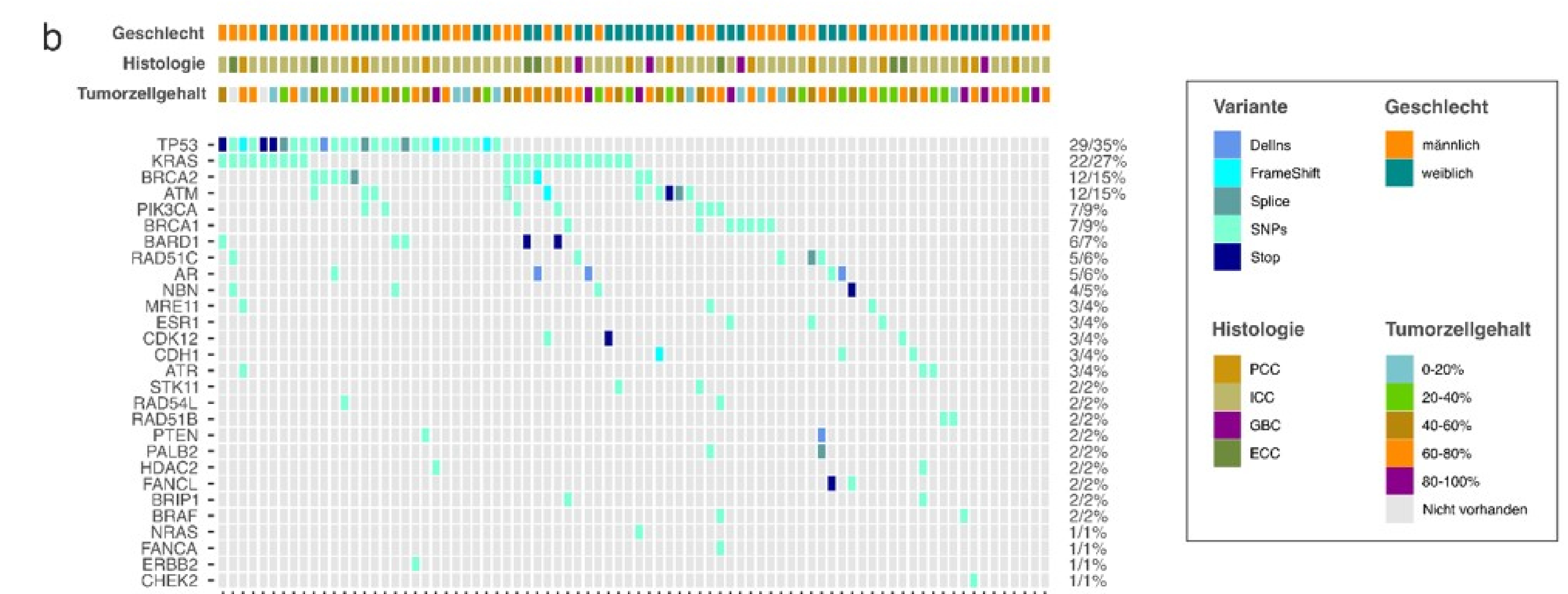

Variable N Hazard ratio p
DDR 0 100 Reference
1 13 0.68 (0.28, 1.63) 0.4
TP53 0 80 Reference
1 33 1.00 (0.58, 1.74) 1.0
KRAS 0 88 Reference
1 25 1.50 (0.83, 2.74) 0.2
IDH 0 95 Reference
1 18 1.04 (0.53, 2.05) 0.9
FGFR 0 108 Reference
1 5 0.40 (0.10, 1.68) 0.2
BRAF 0 107 Reference
1 6 1.25 (0.49, 3.19) 0.6
PIK3CA 0 105 Reference
1 8 1.11 (0.52, 2.37) 0.8


Survival probability
p = 0.23
Time to death
Number at risk
Strata
13 4 0 0 0
105 21 4 1 0

RESULTS

- In addition, one patient with dMMR status (deficient MMR status, 1/59, 1.7%) and 5 cases with FGFR2 fusions (5/33, 15%, with different fusion partners) were identified.
- The HRD focus panel detected pathogenic alterations in genes of the DDR pathways in 11 patients (11/81, 13.5%). 2 more patients were included by identifying pathological DDR mutations according to the MAPK-TRON panel.
- The most commonly mutated were **ATM** (8/13), **BRCA2** (1/13), **RAD51C** (1/13), **PALB2** (1/13), **NBN** (1/13) and **BRIP1** (1/13).
- The patients with DDR mutations showed a weak but coherent benefit in all primary endpoints (OS, TET, OS after platinum therapy). BRAF and PIK3CA mutated subgroups showed a weak benefit too.


a
Geschlecht
Histologie
Tumorzellgehalt
TP53 31/27%
KRAS 23/20%
IDH1 11/10%
ATM 11/10%
ARID1A 11/10%
BCLAF1 10/9%
PIK3CA 8/7%
IDH2 7/6%
BAP1 7/6%
BRCA2 6/5%
BRAF 6/5%
STK11 5/4%
FGFR2 5/4%
RAD51C 5/4%
TSC1 3/3%
SMARCA4 3/3%
PTEN 3/3%
PBRM1 3/3%
NRG1 3/3%
NF1 3/3%
BRCA1 3/3%
TSC2 2/2%
NRAS 2/2%
NBN 2/2%
MLH1 2/2%
KDM6A 2/2%
GNAS 2/2%
ESR1 2/2%
BARD1 2/2%
ARID1B 2/2%
SMAD4 1/1%
SF3B1 1/1%
RNF43 1/1%
RAF1 1/1%
RAD54L 1/1%
PALB2 1/1%
MRE11 1/1%
FANCA 1/1%
ERBB2 1/1%
CDK12 1/1%
CDH1 1/1%
ATR 1/1%
AKT2 1/1%


b
Geschlecht
Histologie
Tumorzellgehalt
TP53 29/35%
KRAS 22/27%
BRCA2 12/15%
ATM 12/15%
PIK3CA 7/9%
BRCA1 7/9%
BARD1 6/7%
RAD51C 5/6%
AR 5/6%
NBN 4/5%
MRE11 3/4%
ESR1 3/4%
CDK12 3/4%
CDH1 3/4%
ATR 3/4%
STK11 2/2%
RAD54L 2/2%
RAD51B 2/2%
PTEN 2/2%
PALB2 2/2%
HDAC2 2/2%
FANCL 2/2%
BRIP1 2/2%
BRAF 2/2%
NRAS 1/1%
FANCA 1/1%
ERBB2 1/1%
CHEK2 1/1%
Variante
DelIns
FrameShift
Splice
SNPs
Stop
Geschlecht
männlich
weiblich
Histologie
PCC
ICC
GBC
ECC
Tumorzellgehalt
0-20%
20-40%
40-60%
60-80%
80-100%
Nicht vorhanden

DISCUSSION

Biliary tract cancers with a homologous recombination deficiency (HRD) were seen in 11.5% of the cases studied and may be a relevant subgroup for targeted therapies, i.e. PARP inhibition
Larger cohorts are needed (i) to confirm the findings of our preliminary data and (ii) investigate therapies targeting HRD genes
DDR-deficient CCC patients showed a potential advantage in OS and ToT and represent a potential subgroup that benefits from platinum-containing treatment strategies.

Disclosures:

No conflicts of interest.

Created with BioRender Poster Builder