63P – Intrahepatic Cholangiocarcinoma (iCCA) Genomic Findings with High versus Low Tumor Mutational Burdens

Tin-Yun Tang[1], Jeffrey S. Ross[2,3], Jordi Rodon Ahnert[1], Milind Javle[1]

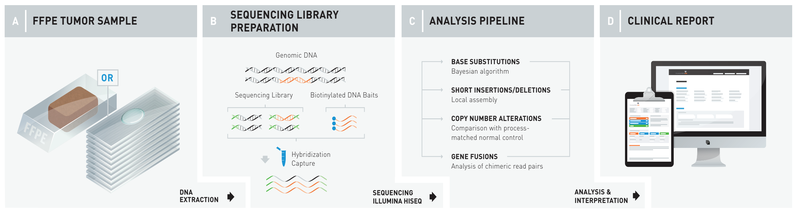
[1]The University of Texas MD Anderson Cancer Center, [2]Upstate Medical University, [3]Foundation Medicine Inc.

Background

Less than 5% of intrahepatic cholangiocarcinomas (iCCA) are tumor mutational burden-high (TMB-H), defined as ≥10 mut/Mb. The genomic landscapes of TMB-H versus TMB-low (TMB-L), defined as < 10 mut/Mb, have not been contrasted. Ongoing interest in the development of combination immunotherapy strategies make characterizing the genomic landscape of TMB-H iCCAs clinically relevant.

Methods

3,317 cases of iCCA underwent comprehensive genomic profiling with the FoundationOne CDx assay. Prevalence of different genomic alterations in cases with TMB-H were compared against TMB-L using Fischer's exact test.



- ≥50 ng DNA extracted from 40 µm of FFPE sections
- Sequencing performed for up to 324 cancer-related genes and introns from 28 genes commonly rearranged in cancer
- Hybrid capture-based sequencing using adaptor ligation-based libraries
- Mean coverage depth >600X
- Tumor mutational burden (TMB) calculated from 0.83-1.14 Mb sequenced DNA
- PD-L1 expression was measured by IHC (Dako22C3)

Results

127 (3.9%) of 3,190 cases were TMB-H and of these cases 32.6% were TMB ≥ 20 mut/Mb. Compared to TMB-L cases, microsatellite instability (MSI) was higher in TMB-H (35.5% v 0.1%, *p*<.0001), as was high (≥50%) PD-L1 IHC staining (8.9% v 2.9%, *p*=0.47) and mutations in potential immunotherapy biomarkers *PBRM1* (17.5% v 10.7%, *p*=.028) and *STK11* (10.3% v 2.8%, *p*=.0001). TMB-H cases have lower frequencies of previously identified iCCA drivers such as *FGFR2* fusions (0.8% v 8.2%, *p*=.0006), *IDH1* mutations (1.6% v 14.0%, *p*<.0001) and *IDH2* mutations (0% v 4.3%, *p*=.01). *ERBB2* non-amplification structural variants are also increased (5.6% v 1.1%, *p*=.0009) in TMB-H. Mutations in genes with roles in genomic stability were increased with *TP53* (61.9% v 34.1%, *p*<.0001) and *ARID1A* (38.9% v 17.8%, *p*<.0001). TMB-H cases had higher mutations in *BRCA2* (7.9% v 2.2%, *p*=.0008) and *ATM* (7.9% v 3.1%, *p*=.008), but not *BRCA1* (2.4% v 0.8%, NS). In contrast, TMB-L cases have higher incidences of *CDKN2B* (22.3% v 9.5%, *p*=.0003) and *MTAP* mutations (15.4% v 7.1%, *p*=.008).

Table 1: Genomic Differences between TMB Low and High iCCA

Clinical and Genomic Findings in Low (< 10 mutations/Mb) and High (≥ 10 mutations/Mb) Intrahepatic Cholangiocarcinoma			
	TMB < 10 Mutations/Mb	TMB ≥ 10 mutations/Mb	Significance
Number of Cases	3,190	127	
Males/Females	50%/50%	47%/53%	NS
Median age (range) years	66 (18-89+)	65 (26-88)	
GA/tumor	4.01	8.72	<.0001
Cell Cycle and Survival Regulators			
CDKN2A	30.2%	34.2%	NS
CDKN2B	22.3%	9.5%	=.0003
TP53	34.1%	61.9%	<.0001
TERT	7.9%	10.3%	NS
ARID1A	17.8%	38.9%	<.0001
RAS/RAF Pathway Genes			
KRAS	20.1%	14.3%	NS
KRAS G12C	1.0%	0.8%	NS
BRAF	4.7%	6.4%	NS
TK Growth Factor Receptor Genes			
EGFR	2.2%	2.4%	NS
ERBB2 (amp/sv mut)	3.4%/1.1%	3.2%/5.6%	NS/=.0009
FGFR2 (total/fusions)	10.8%/8.2%	4.0%/0.8%	=.011/=.0006
Metabolism Genes			
IDH1	14.0%	1.6%	<.0001
IDH2	4.3%	0%	=.01
MTAP	15.4%	7.1%	=.008
PIK3CA-MTOR Pathway Genes			
PTEN	2.7%	4.0%	NS
NF1	1.9%	16.7%	<.0001
TSC1	0.9%	2.4%	NS
PIK3CA	6.1%	15.9%	=.0001
MMRD Genes			
BRCA1	0.8%	2.4%	NS
BRCA2	2.2%	7.9%	=.0008
ATM	3.1%	7.9%	=.008
IO Drug Biomarkers			
PBRM1	10.7%	17.5%	=.028
STK11	2.8%	10.3%	=.0001
MDM2	4.0%	3.2%	NS
MSI High	<0.1% (3,138 cases)	35.5% (110 cases)	P<.0001
Median TMB	2.5	15	
Mean TMB	2.3	20.1	P<.0001
TMB≥10 mut/Mb	0%	100%	
TMB≥20 mut/Mb	0%	32.6%	
PD-L1 Low Positive	21.6% (1,118 cases)	22.2% (45 cases)	
PD-L1 High Positive	2.9%	8.9%	

Figure 1: Long Tail Plot of Genomic Alterations in iCCA with TMB ≥ 10 mut/MB

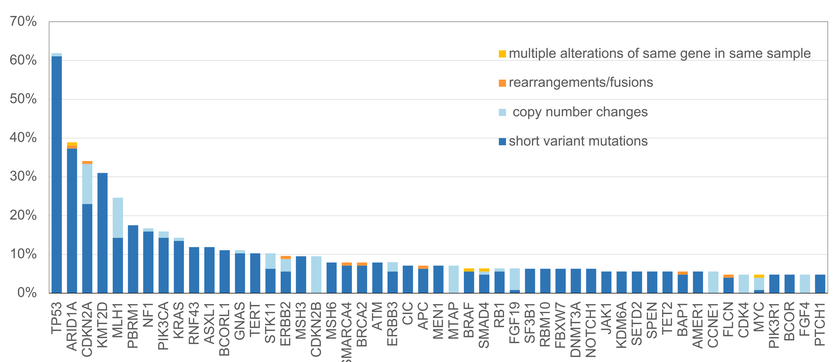
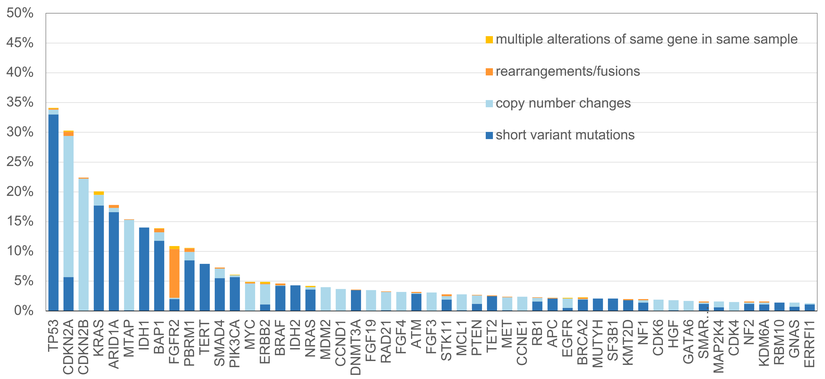
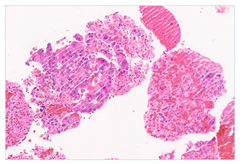


Figure 2: Long Tail Plot of Genomic Alterations in iCCA with TMB < 10 mut/Mb





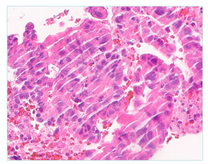


Figure 3: Fine needle aspiration biopsy of peri-portal lymph node. Imaging showed a large infiltrating mass in the liver with no extrahepatic biliary or pancreatic mass. IHC staining was consistent with iCCA.

IGV view of homozygous *MLH1* N168fs*34 frameshift mutation predicted to be a germline mutation.

Clinically advanced iCCA involving the liver and periportal lymph nodes at presentation in a 73-year-old female. This tumor showed a Microsatellite status MSI-High status and a Tumor Mutational Burden of 29 Mut/Mb. Comprehensive genomic profiling revealed a homozygous *MLH1* frameshift N168fs*34 mutation predicted to be germline. These findings strongly suggest that this iCCA arose in a background of Lynch Syndrome. Addition short variant mutations were found in *ARID1A, BCOR, CREBBP, CTNNA1, CTNNB1, FAM123B, JAK3, NF1, NOTCH1, PIK3CA, PTCH1, SETD2, STK11* and *TP53*.

Conclusions

TMB-H is nearly mutually exclusive with previously identified iCCA drivers such as *IDH1*, *IDH2* and *FGFR2* fusions. Additionally, TMB-H cases have a nearly two-fold increase in mutations in *TP53* and *ARID1A*. Mutations in homologous recombination genes such as *BRCA2* and *ATM* are enriched, but their overall incidence is low. Finally, TMB-H cases are enriched in multiple independent biomarkers of response to immunotherapy such as MSI, PD-L1, evolving ones such as *PBRM1* and *STK11* and depleted in resistance biomarkers such as *MTAP*. These findings support the clinical development of immunotherapy approaches for the treatment of TMB-H iCCA.

Disclosures

All authors affiliated with Foundation Medicine, Cambridge have employment by Foundation Medicine Inc. and equity ownership in F. Hoffman-La Roche Ltd. The remaining authors have no disclosures.

Contact

TTang7@mdanderson.org