

Supplementary Materials to Molecular Tumor Board-Guided Targeted Treatments for Biliary Tract Cancers in a Publicly Funded Healthcare System

Table S1

Molecular Tumor Board documentation.

Category	Consideration
Drivers	Mutations, copy number variations, structural variations including fusions
Genome-wide biomarkers	Tumor Mutational Burden (TMB), Mismatch Repair Deficiency (MMRD), Homologous Recombination Deficiency (HRD)
Targets	Alterations indicating drug resistance or sensitivity, as well as potentially available clinical trials
Conclusions	Treatment recommendations based on targetable alterations and patient history

Table S2

Recommendations for targeted treatments based on OncoKB.

ID	Target	Variant type	Possible therapies
BTC0010	<i>FGFR2</i>	Fusion	Futibatinib; Pemigatinib; RLY-4008
BTC0011	<i>MET</i>	Amplification	Capmatinib; Crizotinib; Tepotinib; Telisotuzumab Vedotin
BTC0013	MSI	MSI-H	Pembrolizumab; Ipilimumab + Nivolumab; Nivolumab; Dostarlimab + Carboplatin + Paclitaxel
BTC0013	<i>PIK3CA</i>	H1047R	Alpelisib + Fulvestrant; Capivasertib + Fulvestrant
BTC0013	TMB	TMB-H	Pembrolizumab
BTC0014	<i>MDM2</i>	Amplification	Brigimadlin; Milademetan
BTC0014	TMB	TMB-H	Pembrolizumab
BTC0015	<i>BRAF</i>	V600E	Vemurafenib; Vemurafenib + Atezolizumab + Cobimetinib; Dabrafenib + Trametinib; Encorafenib + Cetuximab; Dabrafenib; Encorafenib + Binimetinib; Trametinib; Vemurafenib + Cobimetinib; Vemurafenib, Dabrafenib; Encorafenib + Panitumumab; Selumetinib
BTC0016	<i>PTEN</i>	Deletion	Capivasertib + Fulvestrant
BTC0018	<i>FGFR2</i>	Fusion	Futibatinib; Pemigatinib; RLY-4008
BTC0018	<i>IDH1</i>	R132H	Ivosidenib; Olutasidenib; Vorasidenib
BTC0019	<i>KRAS</i>	G12D	Cobimetinib, Trametinib; RMC-6236
BTC0020	<i>EGFR</i>	Amplification	Cetuximab, Cetuximab + Chemotherapy, Panitumumab, Panitumumab + Chemotherapy
BTC0024	<i>ERBB2</i>	Amplification	Ado-Trastuzumab Emtansine; Lapatinib + Capecitabine, Lapatinib + Letrozole; Margetuximab + Chemotherapy; Neratinib, Neratinib + Capecitabine; Trastuzumab + Pertuzumab + Chemotherapy; Trastuzumab + Tucatinib + Capecitabine; Trastuzumab

			Deruxtecan; Trastuzumab, Trastuzumab + Chemotherapy; Tucatinib + Trastuzumab; Pembrolizumab + Trastuzumab + Chemotherapy; Trastuzumab + Chemotherapy; Trastuzumab + Pertuzumab; Lapatinib + Trastuzumab; Trastuzumab + Carboplatin-Taxol
BTC0024	<i>MET</i>	Amplification	Capmatinib; Crizotinib; Tepotinib; Telisotuzumab Vedotin
BTC0025	TMB	TMB-H	Pembrolizumab
BTC0026	<i>FGFR2</i>	fusion	Futibatinib; Pemigatinib; RLY-4008
BTC0027	<i>PIK3CA</i>	E545K	Alpelisib + Fulvestrant; Capivasertib + Fulvestrant
BTC0028	<i>IDH1</i>	R132C	Ivosidenib; Olutasidenib; Vorasidenib
BTC0033	<i>ERBB2</i>	Amplification	Ado-Trastuzumab Emtansine; Lapatinib + Capecitabine, Lapatinib + Letrozole; Margetuximab + Chemotherapy; Neratinib, Neratinib + Capecitabine; Trastuzumab + Pertuzumab + Chemotherapy; Trastuzumab + Tucatinib + Capecitabine; Trastuzumab Deruxtecan; Trastuzumab, Trastuzumab + Chemotherapy; Tucatinib + Trastuzumab; Pembrolizumab + Trastuzumab + Chemotherapy; Trastuzumab + Chemotherapy; Trastuzumab + Pertuzumab; Lapatinib + Trastuzumab; Trastuzumab + Carboplatin-Taxol
BTC0034	<i>MDM2</i>	Amplification	Brigimadlin; Milademetan
BTC0038	<i>ERBB2</i>	FISH	Ado-Trastuzumab Emtansine; Lapatinib + Capecitabine, Lapatinib + Letrozole; Margetuximab + Chemotherapy; Neratinib, Neratinib + Capecitabine; Trastuzumab + Pertuzumab + Chemotherapy; Trastuzumab + Tucatinib + Capecitabine; Trastuzumab Deruxtecan; Trastuzumab, Trastuzumab + Chemotherapy; Tucatinib + Trastuzumab; Pembrolizumab + Trastuzumab +

			Chemotherapy; Trastuzumab + Chemotherapy; Trastuzumab + Pertuzumab; Lapatinib + Trastuzumab; Trastuzumab + Carboplatin-Taxol
BTC0039	<i>MDM2</i>	Amplification	Brigimadlin; Milademetan
BTC0042	<i>IDH1</i>	R132C	Ivosidenib; Olutasidenib; Vorasidenib
BTC0045	MSI	MSI-H	Pembrolizumab; Ipilimumab + Nivolumab; Nivolumab; Dostarlimab + Carboplatin + Paclitaxel
BTC0045	TMB	TMB-H	Pembrolizumab
BTC0052	<i>PTEN</i>	Deletion	Capivasertib + Fulvestrant
BTC0054	<i>IDH1</i>	R132C	Ivosidenib; Olutasidenib; Vorasidenib
BTC0057	<i>MDM2</i>	Amplification	Brigimadlin; Milademetan
BTC0064	<i>IDH1</i>	R132H	Ivosidenib; Olutasidenib; Vorasidenib
BTC0064	<i>PIK3CA</i>	E542K	Alpelisib + Fulvestrant; Capivasertib + Fulvestrant
BTC0070	<i>FGFR2</i>	Fusion	Futibatinib; Pemigatinib; RLY-4008
BTC0077	<i>KRAS</i>	G12R	Cobimetinib, Trametinib; RMC-6236
BTC0078	<i>MDM2</i>	Amplification	Brigimadlin; Milademetan

Table S3

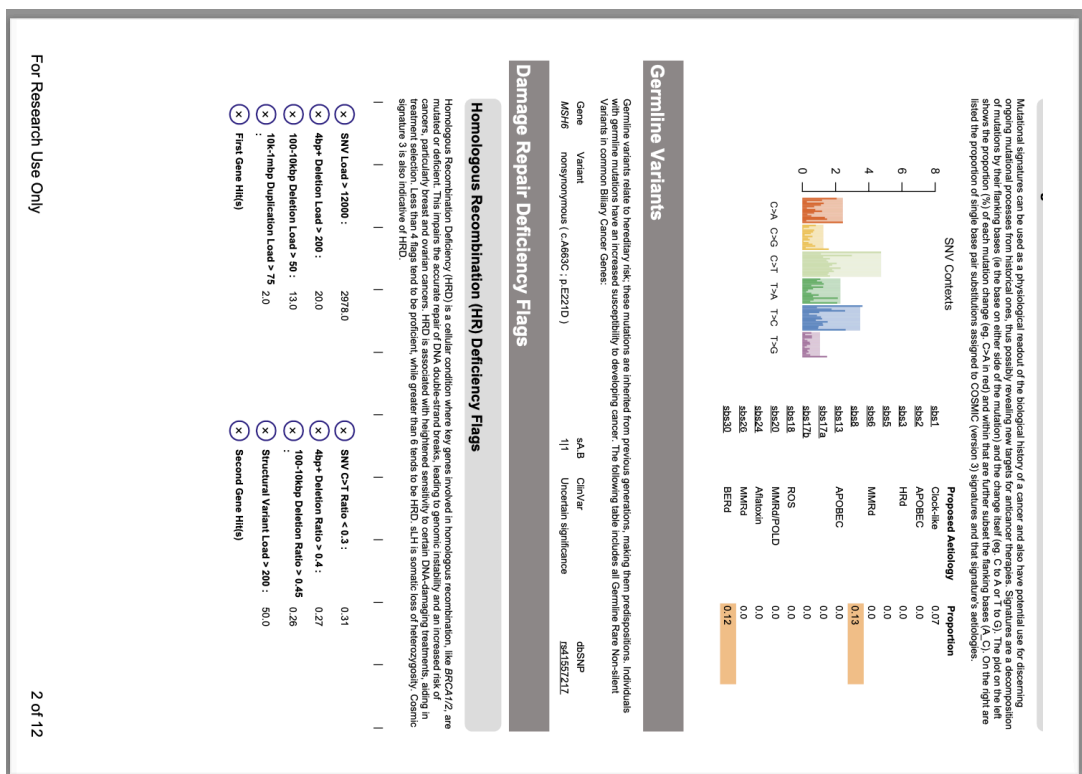
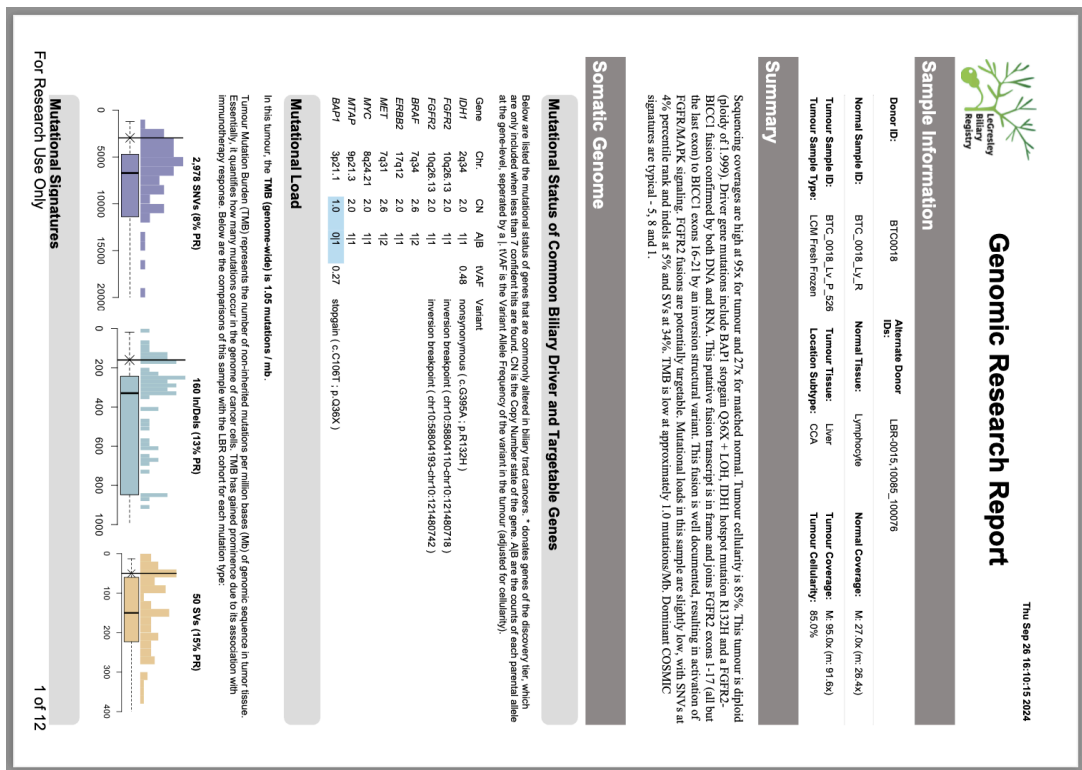
Recommendations for targeted treatments from the molecular tumor board for alterations not in OncoKB.

ID	Gene	Variant_type	Therapy	OncoKb
BTC0011	<i>CDK6</i>	Strong amplification	CDK4/6 inhibitor	New biomarker
BTC0017	<i>PBRM1</i>	Indel	PARPi	New biomarker

BTC0024	<i>CDK6</i>	Strong amplification	CDK4/6 inhibitor	New biomarker
BTC0014	<i>STK11</i>	Indel	mTOR inhibitor	New biomarker
BTC0014	<i>STK11</i>	Indel	DDR repair	New biomarker
BTC0034	<i>MTAP</i>	Deletion	PRMT5 inhibitor	New biomarker
BTC0037	<i>HAS2</i>	Strong amplification	HAS2 inhibitor	New biomarker
BTC0036	<i>MTAP</i>	Deletion	PRMT5 inhibitor	New biomarker
BTC0038	<i>MTAP</i>	Deletion	PRMT5 inhibitor	New biomarker
BTC0044	<i>MTAP</i>	Strong amplification	PRMT5 inhibitor	New biomarker
BTC0042	<i>MTAP</i>	Strong amplification	PRMT5 inhibitor	New biomarker
BTC0056	HRD	HRD	PARPi	New biomarker
BTC0059	<i>MTAP</i>	CNV	PRMT5 inhibitor	New biomarker
BTC0058	<i>MTAP</i>	CNV	PRMT5 inhibitor	New biomarker
BTC0061	<i>HRD</i>	HRD	PARPi	New biomarker
BTC0067	<i>MTAP</i>	Deletion	PRMT5 inhibitor	New biomarker
BTC0062	<i>RASGRF2</i>	Fusion	MEK inhibitor	New biomarker
BTC0063	<i>MTAP</i>	Deletion	PRMT5 inhibitor	New biomarker
BTC0049	<i>BAP1</i>	SNV	PARPi	New biomarker
BTC0069	<i>MTAP</i>	Deletion	PRMT5 inhibitor	New biomarker
BTC0069	<i>MTAP</i>	Deletion	MAT2A inhibitor	New biomarker
BTC0072	HRD	HRD	PARPi	New biomarker
BTC0078	<i>CCNE1</i>	Strong amplification	CCNE1 targeting trial	New biomarker
BTC0080	HRD	HRD	PARPi	New biomarker
BTC0077	<i>MTAP</i>	Deletion	PRMT5 inhibitor	New biomarker
BTC0013	<i>MLH1</i>	Deletion	immune checkpoint inhibition	Unknown variant effect

BTC0017	<i>RAD51B</i>	Deletion	DDR repair	Unknown variant effect
BTC0016	<i>MTOR</i>	Indel	mTOR inhibitor	Unknown variant effect
BTC0027	<i>IDH2</i>	Indel	IDH inhibitor	Unknown variant effect
BTC0028	<i>ERBB2</i>	Weak amplification	HER2 inhibitor	Unknown variant effect
BTC0035	<i>MDM2</i>	Overexpression	MDM2-inhibitor	Unknown variant effect
BTC0043	<i>FGFR3</i>	SNV	FGFR inhibitor	Unknown variant effect
BTC0053	<i>RET</i>	Overexpression	RET inhibitor	Unknown variant effect
BTC0057	<i>MTOR</i>	CNV	MTOR inhibitor	Unknown variant effect
BTC0061	<i>NF1</i>	SNV	MEK inhibitor	Unknown variant effect
BTC0064	<i>FGFR2</i>	SNV	FGFR inhibitor	Unknown variant effect
BTC0067	<i>NF1</i>	Complex knock-out	MEK inhibitor	Unknown variant effect

Legresley Biliary Registry Genomics Research Report for an example case (BTC0010).



Mismatch Repair (MMR) Deficiency Flags

Mismatch Repair Deficiency (MMRD) is a cellular condition marked by impaired DNA mismatch repair mechanisms. This deficiency prevents the correction of errors that occur during DNA replication, leading to the accumulation of mutations and microsatellite instability. MMRD is often associated with Lynch syndrome, a hereditary cancer syndrome, and is associated with microsatellite instability (MSI) or polymerase deficiencies (POLD1). Cosmic signature 20 and 25 are also indicative of MMRD.



Tandem Duplicate Phenotype (TDP) Flags

Some (non-BRCA1) tumours are associated with a tandem duplicate phenotypes (TDP) that may be associated with perturbations in CDK12, FBXW7, and CCNE1 and predicts platinum and PARP inhibitor sensitivity. Both flags - including a positive Mwangi score from Mwangi et al., 2018 - are required for a positive TDP call.



Gene Expression (WTS)

Transcriptome Quality Control

The RNA from this sample is of good quality. We observe:

- 39,341,954 uniquely mapping reads (>3,000,000)
- 36.4 % unmapped reads (<50%)

Expression Status of Common Biliary Driver and Targetable Genes

Gene	Chr.	CN	TPM	Exp. %ile	Variant
FGFR2	10q26.13	2.0	1779.6	98.7	BICC1::FGFR2 (gene inversion)
PICHT1	8q22.32	2.0	71.0	97.4	upregulated

Additional Information

Figure S2

CONSORT diagram.

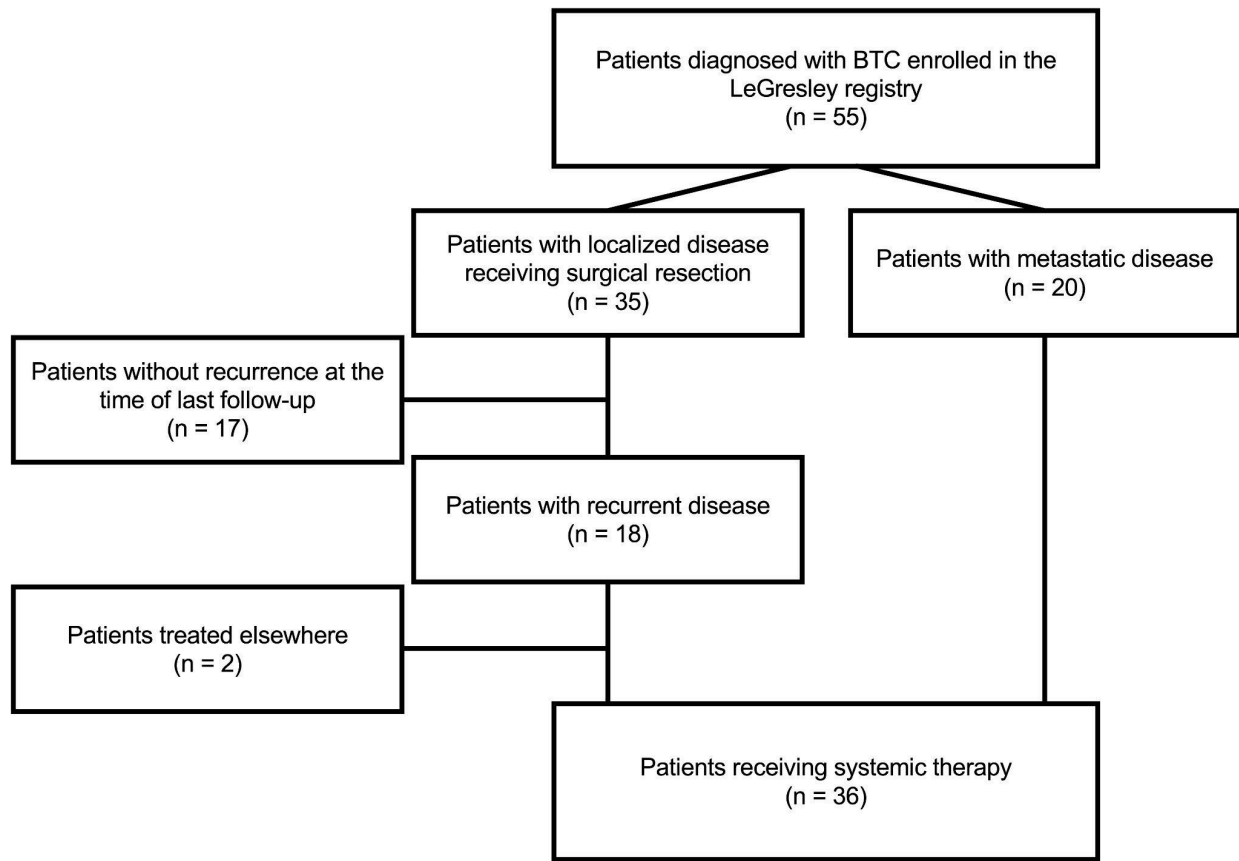


Figure S3

Molecular alterations recommended by the molecular tumor board.

a) Counts and b) identities of molecular alterations recommended by the molecular tumor board compared to OncoKB. MTB: molecular tumor board. TMB: High tumor mutational burden. CNV: copy number variant. HRD: homologous recombination deficiency. SNV: single-nucleotide variant. INDEL: small insertion or deletion. SV: structural variant.

