OncoSHARE™ by OncoDNA

Результат OncoDEEP

Дані пацієнта
Дата народження:

Стать:

Клінічні дані:
Клінічний діагноз:

Гістологічний діагноз:

Зразок:
Локалізація первинної пухлини:

КЛЮЧОВІ ГЕНЕТИЧНІ ЗМІНИ*

ARID1A p.(E38*) VF: 38.07%, ймовірно патогенний
FANCL p.(E222*) VF: 10.11%, ймовірно патогенний
RAD52 p.(D387Efs* 6) VF: 38.97%, ймовірно патогенний
MUTYH p.(R19*) VF:72.47%, ймовірно патогенний

ГЕНОМНІ ПОКАЗНИКИ

TMB: високий (10.73 Mut/Mb)
MSI: стабільний (4.75%)
HRD: позитивний_BRCAwt_GS+ (44.2)

ДОДАТКОВІ МАРКЕРИ

CD8: позитивний (10.0%)
Fusion Panel: не виявлено
PD-L1 (шкала SP142 IC) : високий (30.0%)

ГЕНИ БЕЗ ЗМІН-МІШЕНЕЙ ДЛЯ ТЕРАПІЇ*

N/A

*Наведені тільки патогенні і ймовірно патогенні варіанти. Повний список виявлених варіантів наведено в оригіналі репорту.
**Специфічні для даного діагнозу

ПОТЕНЦІЙНО ЕФЕКТИВНА ТЕРАПІЯ

Назва препаратів	*Клас препаратів*	*Статус*	*Показання*
Асоційований біомаркер: PD-L1 (шкала SP142 IC): Висока експресія / Tumor Mutational Burden: високий			
Атезолізумаб	Інгібітори PD-L1	Схвалено FDA / NCCN / ESMO / EMA	Діагноз пацієнта
Асоційований біомаркер: ARID1A: p.(E38*) / Tumor Mutational Burden: високий			
Ніволумаб	Інгібітори PD-L1	Схвалено FDA / NCCN / ESMO / EMA	Діагноз пацієнта
Асоційований біомаркер: MSI: стабільний / Tumor Mutational Burden: високий			
Пембролізумаб	Інгібітори PD-L1	Схвалено FDA / NCCN / ESMO / EMA	Діагноз пацієнта
Асоційований біомаркер: RAD52: INS / MUTYH: p.(R19*) / FANCL: p.(E222*) / HRD: позитивний_BRCAwt_GS+			
Олапариб	Інгібітори PARP	Схвалено для інших діагнозів	Інші типи пухлин
Асоційований біомаркер: ARID1A: p.(E38*)			
Таземетостат	Інгібітори EZH2	Схвалено для інших діагнозів	Інші типи пухлин

КЛІНІЧНІ ДОСЛІДЖЕННЯ

Назва	*Фаза*	*Країни*	*NCT ID*
Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158)	2	FR IL MX NL AU BR CL CO DE DK ES US IT KR NO PE PL PT RU TW ZA	NCT02628067
Testing Olaparib in Patients With Advanced or Metastatic (Cancer That Has Spread) Bladder Cancer and Other Genitourinary Tumors With DNA-Repair Genetic Changes	2	US	NCT03375307
A Study of CPI-0209 in Patients With Advanced Solid Tumors and Lymphomas	2	FR GB ES US IT KR PL	NCT04104776
Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study		FR GB HK IL NL SG AU BE BR CA CH CN DE DK ES US IT JP KR NZ PL PR PT RU TW ZA	NCT04589845
A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer, Extra-Pulmonary Small Cell Neuroendocrine Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors	2	US	NCT04826341
Phase 1/2 Clinical Trial of CP-506 (HAP) in Monotherapy or With Carboplatin or ICI	2	NL BE	NCT04954599
Nivolumab for the Treatment of Metastatic or Unresectable Solid Tumors With ARID1A Mutation and CXCL13 Expression	2	US	NCT04957615
Niraparib and Dostarlimab in HRD Solid Tumors	2	US	NCT04983745
A Trial of Pamiparib With Tislelizumab in Patients With Advanced Tumours With Homologous Recombination Repair Defects	2	AU	NCT04985721
Phase II Study of Tazemetostat in Solid Tumors Harboring an ARID1A Mutation Phase 2 US NCT05023655	2	US	NCT05023655
Spartalizumab and Low-dose PAzopanib in Refractory or Relapsed Solid TumOrs of Pediatric and Adults	2	FR	NCT05210413
JAB-2485 Activity in Adult Patients With Advanced Solid Tumors	2	CN US	NCT05490472
A Study of a Selective T Cell Receptor (TCR) Targeting, Bifunctional Antibody-fusion Molecule STAR0602 in Participants with Advanced Solid Tumors	2	FR CA ES US	NCT05592626

Назва	*Фаза*	*Країни*	*NCT ID*
Phase II Trial of the PARP Inhibitor Niraparib and PD-1 Inhibitor Dostarlimab in Patients With Advanced Cancers With Active Progressing Brain Metastases (STARLET)	2	US	NCT05700721
DETERMINE (Determining Extended Therapeutic Indications for Existing Drugs in Rare Molecularly Defined Indications Using a National Evaluation Platform Trial) - Master Screening Protocol	3	GB	NCT05722886
Tiragolumab and Atezolizumab in Advanced Pan-cancer Patients	2	AU	NCT06003621
A Study of Adjuvant Atezolizumab or Atezolizumab Plus Tiragolumab in Solid Tumors With Resectable Disease With Intermediate-High Risk of Recurrence and High Tumor Mutational Burden (TMB-H) or Microsatellite Instability (MSI-H)	2	ES	NCT06331598

РЕЗЮМЕ ДОСЛІДЖЕННЯ

Ми виявили варіант у гені **ARID1A**, що ймовірно викликає втрату функції білка. Хоча на даний момент не існує терапій, спрямованих на відновлення цієї функції, відомо, що інактивація ARID1A може збільшити чутливість до інгібіторів PARP (таких як олапариб, велипариб і BMN673, які блокують шляхи репарації пошкоджень ДНК), а також потенційно до інгібіторів шляху PI3K/AKT ((PMID:26069190; PMID:24036443).

Варто зазначити, що втрата функції ARID1A асоціюється з підвищеним мутаційним навантаженням, що може забезпечити клінічну користь від імунотерапії при різних типах раку, проте цей терапевтичний ефект потребує подальшого підтвердження (http://ascopubs.org/doi/abs/10.1200/PO.17.00146; PMID:31277418; PMID:31911080). Наразі проводяться клінічні дослідження, що вивчають можливості лікування, пов'язаного з втратою функції цього гена при різних типах раку.

Ми виявили стоп-кодон у гені **MUTYH**, що призводить до втрати функції білка. Терапевтичний ефект цього варіанту не був визначений, однак клінічне випробування олапарибу відкрите для набору пацієнтів.

Також ми виявили стоп-кодон, ймовірно, що спричиняє втрату функції білка **FANCL**. Оскільки цей білок бере участь у репарації ДНК шляхом гомологічної рекомбінації, втрата функції генів, які залучені до цього процесу, може бути пов'язана з дефектами в репарації пошкоджень ДНК. Терапевтичний ефект цього варіанту не був встановлений, але клінічне випробування олапарибу також відкрите для набору пацієнтів.

Ми виявили стоп-кодон у гені **RAD52**, що призводить до утворення укороченого білка, ймовірно, внаслідок втрати його функції. Роль Rad52 у реплікації, індукованій розривами (BIR), може пояснити, чому його виснаження у клітинах, що зазнають онкоген-індукованого стресу реплікації ДНК (DRS), призводить до підвищеного рівня пошкоджень ДНК (PMID: 27984746). Оскільки Rad52 бере участь у відновленні дволанцюгових розривів ДНК через механізм гомологічної рекомбінації, втрата функції RAD52 може бути пов'язана з клінічною користю від інгібіторів PARP. Наразі проводяться кілька клінічних випробувань.

Ми не виявили наявності шкідливого або потенційно шкідливого варіанту в генах BRCA1/2. До цієї категорії належать варіанти, для яких опубліковані дані свідчать про втрату функції відповідних білків, а також великі генетичні перебудови.

Ми зафіксували позитивний геномний шрам у цього пацієнта.

Отже, **результати тесту показують дефіцит гомологічної рекомбінації (HRD), який базується на геномному шрамі для цього пацієнта. Лікування інгібіторами PARP може бути корисним для цього пацієнта.**

Примітка:

Дані випробування ATLAS (NCT03397394) не змогли знайти кореляцію між статусом HRD і відповіддю на лікування рукапарибом. Медіана часу до прогресування хвороби (PFS) становила 1,8 місяця (95% CI, 1,6–1,9) у загальній популяції, і була подібною між підгрупами HRD, з медіаною PFS відповідно 1,8 та 1,4 місяця для пацієнтів із негативним та позитивним статусом HRD (PMID: 34030643). Однак чисельність досліджуваної популяції цього клінічного випробування була занадто малою (HRD–позитивні *n=20*; HRD–негативні *n=30*), щоб зробити висновки про вплив статусу HRD на відповідь на інгібітори PARP. Наразі інші клінічні випробування відкриті для набору.

На основі аналізу пакетних даних цей пацієнт **має бути чутливим чутливим до інгібіторів PD–1/PD–L1.**

З іншого боку, цей пацієнт **не має бути чутливим чутливим до інгібіторів NTRKx, FGFRx та RET.**

Примітка:

Імунограма показує високий потенціал для відповіді на імунотерапію. Ми продемонстрували позитивну інфільтрацію CD8+ Т-клітин у пухлину, а також високу експресію PD–L1 (30% імунних клітин). Крім того, ми виявили високий рівень мутаційного навантаження пухлини (TMB). У пацієнтів із високим TMB інгібітори контрольних точок (блокада PD–1/PD–L1) асоціюються з клінічною користю для різних видів пухлин (PMID:28835386).

Разом з тим ми не виявили мікросателітної нестабільності (MSI) або мутацій, що відповідають за чутливість/резистентність. Отже, на основі високого мутаційного навантаження (TMB), рівня CD8+ лімфоцитів та експресії PD–L1, лікування на основі інгібіторів PD–1/PD–L1 **може бути пов'язане з потенційною клінічною користю** для цього пацієнта.

Аналізи були виконані на зразку з маркуванням 12345.

СПИСОК ПРЕПАРАТІВ

Назва препаратів	*Клас препаратів*	*Статус*	*Показання*	*Клінічна користь*
Асоційований біомаркер: PD-L1 (шкала SP142 IC): Висока експресія / Tumor Mutational Burden: високий				
Атезолізумаб	Інгібітори PD-L1	Схвалено FDA / NCCN / ESMO / EMA	Діагноз пацієнта	Потенційно ефективно
Асоційований біомаркер: ARID1A: p.(E38*) / Tumor Mutational Burden: високий				
Ніволумаб	Інгібітори PD-L1	Схвалено FDA / NCCN / ESMO / EMA	Діагноз пацієнта	Потенційно ефективно
Асоційований біомаркер: MSI: стабільний / Tumor Mutational Burden: високий				
Пембролізумаб	Інгібітори PD-L1	Схвалено FDA / NCCN / ESMO / EMA	Діагноз пацієнта	Потенційно ефективно
Асоційований біомаркер:				
Дабрафеніб і Траметиніб	Інгібітори BRAF і MEK	Схвалено FDA	Діагноз пацієнта	Потенційно неефективно
Асоційований біомаркер: Fusion Panel: не виявлено				
Ентретиніб	Інгібітори рецепторних тирозинкіназ	Схвалено FDA	Діагноз пацієнта	Потенційно неефективно
Ердафініб	Інгібітори FGFR	Схвалено FDA / NCCN / ESMO / EMA	Діагноз пацієнта	Потенційно неефективно
Ларотректиніб	Інгібітори NTRK	Схвалено FDA	Діагноз пацієнта	Потенційно неефективно
Репотректиніб	Інгібітори рецепторних тирозинкіназ	Схвалено FDA	Діагноз пацієнта	Потенційно неефективно
Селперкатиніб	Інгібітори RET	Схвалено FDA	Діагноз пацієнта	Потенційно неефективно
Асоційований біомаркер: RAD52: INS / MUTYH: p.(R19*) / FANCL: p.(E222*) / HRD: позитивний_BRCAwt_GS+				
Олапариб	Інгібітори PARP	Схвалено для інших діагнозів	Інші типи пухлин	Потенційно ефективно
Асоційований біомаркер: ARID1A: p.(E38*)				
Таземетостат	Інгібітори EZH2	Схвалено для інших діагнозів	Інші типи пухлин	Потенційно ефективно

СПИСОК ВИЯВЛЕНИХ ВАРІАНТІВ

Ген	Категор.	Частота/ № копій	Зміна ДНК	Зміна білку	Біол. Категор.	Терап. Категор.	Потенц. Спадк.	Глибина прочит.
TERT	SNV	37.50%	NM_198253.2:c.-58-66C>T	-	пат	Tier III	Hi	632
TP53	SNV	40.72%	NM_000546.5:c.738G>T	p.(M246I)	пат	Tier III	Hi	528
ARID1A	SNV	38.07%	NM_006015.4:c.112G>T	p.(E38*)		Tier IIC	Hi	197
FANCL	SNV	10.11%	NM_001114636.1:c.664G>T	p.(E222*)		Tier IIC	Hi	742
RAD52	INS	38.97%	NM_134424.3:c.1160dup	p.(D387Efs*6)		Tier IIC	Hi	970
MUTYH	SNV	72.47%	NM_012222.2:c.55C>T	p.(R19*)		Tier IID	Так	603
BLM	LOH	1.00	-	-		Tier III	Hi	-
KDM6A	INS	38.18%	NM_021140.3:c.347delins TT	p.(Y116Ffs*10)		Tier III	Hi	385
KEAP1	LOH	1.00	-	-		Tier III	Hi	-

Ген	Категор.	Частота/ № копій	Зміна ДНК	Зміна білку	Біол. Категор.	Терап. Категор.	Потенц. Спадк.	Глибина прочит.
RAD51	LOH	1.00	-	-		Tier III	Hi	-
STK11	LOH	1.00	-	-		Tier III	Так	-
TP53	SNV	45.48%	NM_000546.5:c.587G>A	p.(R196Q)		Tier III	Hi	686
AR	INS	29.17%	NM_000044.3:c.1418_1420dup	p.(G473dup)	VUS	Tier III	Hi	192
ARID1A	SNV	42.25%	NM_006015.4:c.577G>A	p.(E193K)	VUS	Tier III	Hi	471
CHD4	SNV	19.18%	NM_001273.3:c.4234G>A	p.(E1412K)	VUS	Tier III	Hi	610
CHD4	SNV	43.46%	NM_001273.3:c.181C>T	p.(R61W)	VUS	Tier III	Hi	1123
CREBBP	SNV	54.67%	NM_004380.2:c.4303G>T	p.(D1435Y)	VUS	Tier III	Hi	364
CSDE1	SNV	38.81%	NM_0010075 53.2:c.118A>C	p.(I40L)	VUS	Tier III	Hi	737

Ген	Категор.	Частота/ № копій	Зміна ДНК	Зміна білку	Біол. Категор.	Терап. Категор.	Потенц. Спадк.	Глибина прочит.
CUX1	SNV	14.89%	NM_0012025 43.1:c.1904G >A	p.(R635H)	VUS	Tier III	Hi	618
CYP19A1	SNV	5.60%	NM_000103. 3:c.222C>A	p.(C74*)	VUS	Tier III	Так	678
DDR2	SNV	13.68%	NM_0010147	p.(V327I)	VUS	Tier III	Hi	943
DNMT1	SNV	12.66%	NM_0011308 23.2:c.4769G >A	p.(R1590Q)	VUS	Tier III	Hi	537
EPHB4	SNV	65.33%	NM_004444. 4:c.703C>T	p.(P235S)	VUS	Tier III	Hi	851
ERBB4	SNV	35.70%	NM_005235. 2:c.3195_3200delinsGTAC CA	p.(R1067Q)	VUS	Tier III	Hi	451
HGF	SNV	12.09%	NM_000601. 5:c.294G>T	p.(W98C)	VUS	Tier III	Hi	612
IRS1	SNV	16.77%	NM_005544. 2:c.1546G>C	p.(D516H)	VUS	Tier III	Hi	620
JAK1	SNV	32.30%	NM_002227. 3:c.1516C>T	p.(R506C)	VUS	Tier III	Hi	808

Ген	Категор.	Частота/ № копій	Зміна ДНК	Зміна білку	Біол. Категор.	Терап. Категор.	Потенц. Спадк.	Глибина прочит.
KMT2C	SNV	8.98%	NM_170606.2:c.2573_2578delinsTGTC CT	p.(W858_P860delinsLSS)	VUS	Tier III	Hi	657
LRP1B	SNV	16.43%	NM_018557.2:c.10580G>T	p.(C3527F)	VUS	Tier III	Hi	560
MAP3K13	SNV	13.51%	NM_004721.4:c.2470G>A	p.(D824N)	VUS	Tier III	Hi	659
MAP3K4	SNV	31.31%	NM_005922.3:c.974A>G	p.(Q325R)	VUS	Tier III	Hi	559
NCOR1	SNV	25.59%	NM_006311.3:c.568_571delinsTGAA	p.(R190*)	VUS	Tier III	Hi	551
PAK3	DEL	8.94%	NM_001128168.2:c.337del	p.(M113Cfs* 31)	VUS	Tier III	Hi	425
PARP2	SNV	26.38%	NM_005484.3:c.704A>G	p.(D235G)	VUS	Tier III	Hi	633
PBRM1	SNV	29.25%	NM_018313.4:c.1727G>A	p.(R576H)	VUS	Tier III	Hi	588
PIK3C2B	SNV	13.13%	NM_002646.3:c.680A>G	p.(D227G)	VUS	Tier III	Hi	830

Ген	Категор.	Частота/ № копій	Зміна ДНК	Зміна білку	Біол. Категор.	Терап. Категор.	Потенц. Спадк.	Глибина прочит.
PTPRD	SNV	76.42%	NM_002839.3:c.3914C>T	p.(P1305L)	VUS	Tier III	Hi	865
RHOA	SNV	27.01%	NM_001664.3:c.137T>C	p.(I46T)	VUS	Tier III	Hi	485
RTEL1	SNV	23.74%	NM_016434.3:c.2155G>A	p.(D719N)	VUS	Tier III	Hi	577
SDHA	SNV	11.86%	NM_004168.3:c.1335_1346delinsTGCA CATGGTGT	p.(V446_A449delinsAHGV)	VUS	Tier III	Hi	1020
SDHA	SNV	15.33%	NM_004168.3:c.1367_1371delinsTGCT A	p.(S456_L457 delinsLL)	VUS	Tier III	Hi	1070
SDHA	SNV	45.27%	NM_004168.3:c.1804G>C	p.(D602H)	VUS	Tier III	Hi	455
SETD8	DEL	9.25%	NM_020382.4:c.31_47delinsTGCGCGG TGGA	p.(R11_A16delinsCAVE)	VUS	Tier III	Hi	227
SETD8	SNV	12.72%	NM_020382.4:c.719A>C	p.(D240A)	VUS	Tier III	Hi	920
STAG2	SNV	44.63%	NM_001042749.2:c.13C>G	p.(P5A)	VUS	Tier III	Hi	410

Ген	Категор.	Частота/ № копій	Зміна ДНК	Зміна білку	Біол. Категор.	Терап. Категор.	Потенц. Спадк.	Глибина прочит.
TERT	SNV	100.00%	NM_198253. 2:c.-58-1597G>A	-	VUS	Tier III	Hi	600
TERT	SNV	99.62%	NM_198253. 2:c.-58-2096A>G	-	VUS	Tier III	Hi	525
TERT	SNV	73.68%	NM_198253. 2:c.-58-2326G>A	-	VUS	Tier III	Hi	718
TERT	SNV	100.00%	NM_198253. 2:c.-58-910T>C	-	VUS	Tier III	Hi	890
TERT	INS	68.56%	NM_198253. 2:c.-58-1094 _-58-1093ins C	-	VUS	Tier III	Hi	738
TERT	SNV	26.24%	NM_198253. 2:c.-58-1324T>C	-	VUS	Tier III	Hi	644
TSHR	SNV	28.78%	NM_000369. 2:c.203C>T	p.(P68L)	VUS	Tier III	Hi	410
USP8	SNV	10.92%	NM_005154. 4:c.2353A>G	p.(T785A)	VUS	Tier III	Hi	467

OncoSHARE™ by OncoDNA

OncoDEEP Analysis Report

Patient

Date of Birth:
Sex:
Cancer Type:

Clinical

Medical Doctor:

Clinical Diagnosis:
Histological Diagnosis:

Sample

Primary Tumor Site:
Tumor Percentage:
Collection Date:

KEY GENOMIC ALTERATIONS*

Gene	AA / Cat.	Var. Freq. / Copy Nb	cDNA	Biological Impact	Therapeutical Impact
ARID1A	p.(E38*)	38.07%	NM_006015.4:c.112G>T	Likely Pathogenic	Tier IIC
FANCL	p.(E222*)	10.11%	NM_001114636.1:c.664G>T	Likely Pathogenic	Tier IIC
RAD52	p.(D387Efs*6)	38.97%	NM_134424.3:c.1160dup	Likely Pathogenic	Tier IIC
MUTYH	p.(R19*)	72.47%	NM_012222.2:c.55C>T	Likely Pathogenic	Tier IID

● Pathogenic variants of interest

GENOMIC SIGNATURES

TMB: High (10.73 Mut/Mb) **MSI:** Stable (4.75%) **HRD:** Positive_BRCAwt_GS+ (44.2)

ADDITIONAL BIOMARKERS

CD8: Positive (10.0%) **Fusion Panel:** NO **PD-L1 (SP142 IC scoring) :** High (30.0%)

RELEVANT GENES WITH NO ACTIONABLE ALTERATIONS**

None

* Only variants classified as pathogenic and likely pathogenic are reported here. The full list of identified variants is available in the report.

** Cancer type specific

THERAPIES ASSOCIATED WITH CLINICAL BENEFIT

Drug Name	Class	Status	Indicated for
Associated Biomarker: PD-L1 (SP142 IC scoring) : High expression / Tumor Mutational Burden: High			
Atezolizumab	PD-L1 inhibitor	FDA / NCCN / ESMO / EMA approved	patient's tumor type
Associated Biomarker: ARID1A: p.(E38*) / Tumor Mutational Burden: High			
Nivolumab	PD-1 inhibitor	FDA / NCCN / ESMO / EMA approved	patient's tumor type
Associated Biomarker: MSI: Stable / Tumor Mutational Burden: High			
Pembrolizumab	PD-1 inhibitor	FDA / NCCN / ESMO / EMA approved	patient's tumor type
Associated Biomarker: RAD52: INS / MUTYH: p.(R19*) / FANCL: p.(E222*) / HRD: Positive_BRCAwt_GS+			
Olaparib	PARP inhibitors	Approved for other	other tumor types
Associated Biomarker: ARID1A: p.(E38*)			
Tazemetostat	EZH2 inhibitors	Approved for other	other tumor types

CLINICAL TRIALS

Name	Phase	Countries	NCT ID
Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158)	Phase 2	FR IL MX NL AU BR CL CO DE DK ES US IT KR NO PE PL PT RU TW ZA	NCT02628067
Testing Olaparib in Patients With Advanced or Metastatic (Cancer That Has Spread) Bladder Cancer and Other Genitourinary Tumors With DNA-Repair Genetic Changes	Phase 2	US	NCT03375307
A Study of CPI-0209 in Patients With Advanced Solid Tumors and Lymphomas	Phase 2	FR GB ES US IT KR PL	NCT04104776
Tumor-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You (TAPISTRY) Platform Study	Phase 2	FR GB HK IL NL SG AU BE BR CA CH CN DE DK ES US IT JP KR NZ PL PR PT RU TW ZA	NCT04589845
A Phase I/II Study of Sacituzumab Govitecan Plus Berzosertib in Small Cell Lung Cancer, Extra-Pulmonary Small Cell Neuroendocrine Cancer and Homologous Recombination-Deficient Cancers Resistant to PARP Inhibitors	Phase 2	US	NCT04826341
Phase 1/2 Clinical Trial of CP-506 (HAP) in Monotherapy or With Carboplatin or ICI	Phase 2	NL BE	NCT04954599
Nivolumab for the Treatment of Metastatic or Unresectable Solid Tumors With ARID1A Mutation and CXCL13 Expression	Phase 2	US	NCT04957615
Niraparib and Dostarlimab in HRD Solid Tumors	Phase 2	US	NCT04983745
A Trial of Pamiparib With Tislelizumab in Patients With Advanced Tumours With Homologous Recombination Repair Defects	Phase 2	AU	NCT04985721
Phase II Study of Tazemetostat in Solid Tumors Harboring an ARID1A Mutation	Phase 2	US	NCT05023655
Spartalizumab and Low-dose PAzopanib in Refractory or Relapsed Solid TumOrs of Pediatric and Adults	Phase 2	FR	NCT05210413
JAB-2485 Activity in Adult Patients With Advanced Solid Tumors	Phase 2	CN US	NCT05490472
A Study of a Selective T Cell Receptor (TCR) Targeting, Bifunctional Antibody-fusion Molecule STAR0602 in Participants with Advanced Solid Tumors	Phase 2	FR CA ES US	NCT05592626
Phase II Trial of the PARP Inhibitor Niraparib and PD-1 Inhibitor Dostarlimab in Patients With Advanced Cancers With Active Progressing Brain Metastases (STARLET)	Phase 2	US	NCT05700721
DETERMINE (Determining Extended Therapeutic Indications for Existing Drugs in Rare Molecularly Defined Indications Using a National Evaluation Platform Trial) - Master Screening Protocol	Phase 3	GB	NCT05722886
Tiragolumab and Atezolizumab in Advanced Pan-cancer Patients	Phase 2	AU	NCT06003621
A Study of Adjuvant Atezolizumab or Atezolizumab Plus Tiragolumab in Solid Tumors With Resectable Disease With Intermediate-High Risk of Recurrence and High Tumor Mutational Burden (TMB-H) or Microsatellite Instability (MSI-H)	Phase 2	ES	NCT06331598

COMPREHENSIVE SUMMARY

We found a variant in the **ARID1A** gene inducing a probable loss of function of the protein. Although there are no therapies targeting such loss of function, inactivation of ARID1A has been reported to lead to an increased sensitivity to inhibitors of PARP (such as olaparib, veliparib and BMN673, which block DNA damage repair pathways) and potentially to PI3K/AKT pathway inhibitors (PMID:26069190; PMID:24036443).

Note that loss of function of ARID1A has been associated with a higher mutational burden which could lead to the clinical benefit of the immunotherapies in several cancers but the corresponding therapeutical impact needs to be confirmed. (http://ascopubs.org/doi/abs/10.1200/PO.17.00146; PMID:31277418; PMID:31911080). Some clinical trials are recruiting associated with a loss of function of this gene in different cancer types.

We found a stop codon in **MUTYH** leading to a loss of function of the protein. No therapeutical impact has been associated with this variant but a clinical trial is recruiting for olaparib.

We found a stop codon leading to a probable loss of function of the protein **FANCL**. Since it is involved in homology–directed DNA repair. It has been reported that loss of function of gene involved in this pathway should be associated with defective DNA damage repair phenotype. No therapeutical impact has been associated with this variant but a clinical trial is recruiting for olaparib.

We found a stop codon in the **RAD52** gene inducing a truncated protein. It could be therefore associated with a loss of function of the protein. A role for Rad52 in break–induced replication (BIR) can explain why its depletion in cells with oncogene–induced DNA replication stress (DRS) leads to increased DNA damage (PMID:27984746). Because of its role in the repair DNA double–strand breaks by homologous recombination mechanism, loss of function of RAD52 could be associated with a clinical benefit to PARP inhibitors. Several clinical trials are ongoing.

We did not demonstrate the presence of a deleterious (or suspected deleterious) BRCA1/2 variant. This category includes variants for which published data demonstrate a lost of function of the corresponding proteins as well as the large rearrangements.

We observed a positive genomic scar for this patient.

Therefore, **the test results demonstrate a homologous recombination deficiency based on the genomic scar alone for this patien**t. Treatment based on PARP inhibitors could be beneficial for this patient.

Rmk: Data of the ATLAS trial (NCT03397394) were not able to find a correlation between HRD status and response to rucaparib treatment. The median PFS was 1.8 months (95% CI, 1.6–1.9) in the ITT population, and was similar across HRD subgroup, with a median PFS of respectively 1.8 and 1.4 for the HRD–negative and HRD–positive population (PMID: 34030643). However, the studied population of this clinical trial is too small (HRD–positve n=20; HRD–negative n=30) to conlcude on the impact of HRD status on the response to PARP inhibitors. Other clinical trials are currently recruiting.

Based on package plus analysis, this patient ***should be sensitive*** to PD–1/PD–L1 inhibitors.

On the other hand this patient ***should not be sensitive*** to NTRKx, FGFRx and RET inhibitors.

Rmk:

The immunogram shows a high potential response to immunotherapy. We showed a positive infiltration of CD8 + T cells in the tumor and also a high expression of PD–L1 (30% of immune cells). We also observed a high tumor mutational burden (TMB). In patients with high TMB, checkpoint inhibitors (PD–1/PD–L1 blockade) have been associated with clinical benefits across diverse tumors (PMID:28835386). Moreover, we didn't observe microsatellite instability (MSI) or sensibility/resistance mutation. Therefore, based on high mutational burden (TMB) and the level of CD8+ lymphocytes and PD–L1 expression, treatment based on PD–1/PD–L1 inhibitors ***could be associated with potential clinical benefit*** for this patient.

The analyses were performed on the block labelled 12345

THERAPIES (FULL LIST)

Drug Name	*Class*	*Status*	*Indicated for*	*Clinical Benefit*
Associated Biomarker: PD-L1 (SP142 IC scoring) : High expression / Tumor Mutational Burden: High				
Atezolizumab	PD-L1 inhibitor	FDA / NCCN / ESMO / EMA approved	patient's tumor type	Potential
Associated Biomarker: ARID1A: p.(E38*) / Tumor Mutational Burden: High				

(Continues on next page)

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Drug Name	Class	Status	Indicated for	Clinical Benefit
Nivolumab	PD-1 inhibitor	FDA / NCCN / ESMO / EMA approved	patient's tumor type	Potential
Associated Biomarker: MSI: Stable / Tumor Mutational Burden: High				
Pembrolizumab	PD-1 inhibitor	FDA / NCCN / ESMO / EMA approved	patient's tumor type	Potential
Associated Biomarker:				
dabrafenib and trametinib	BRAF and MEK inhibitors	FDA Approved	patient's tumor type	Potential Lack
Associated Biomarker: Fusion Panel: NO				
Entrectinib	Receptor tyrosine kinase inhibitors	FDA Approved	patient's tumor type	Potential Lack
Erdafitinib	FGFR inhibitors	FDA / NCCN / ESMO / EMA approved	patient's tumor type	Potential Lack
Larotrectinib	NTRK inhibitors	FDA Approved	patient's tumor type	Potential Lack
Repotrectinib	Receptor tyrosine kinase inhibitors	FDA Approved	patient's tumor type	Potential Lack
Selpercatinib	RET inhibitors	FDA Approved	patient's tumor type	Potential Lack
Associated Biomarker: RAD52: INS / MUTYH: p.(R19*) / FANCL: p.(E222*) / HRD: Positive_BRCAwt_GS+				
Olaparib	PARP inhibitors	Approved for other	other tumor types	Potential
Associated Biomarker: ARID1A: p.(E38*)				
Tazemetostat	EZH2 inhibitors	Approved for other	other tumor types	Potential

GENOMIC SIGNATURES

TMB: High (10.73 Mut/Mb)

We observed a high tumor mutational burden (TMB). In patients with high TMB, checkpoint inhibitors (PD–1/PD–L1 blockade) have been associated with clinical benefits across diverse tumors (PMID:28835386). Moreover, pembrolizumab has been FDA approved for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden–high. Therefore, treatments based on pembrolizumab or associated clinical trials would be associated with potential clinical benefit for this patient.

The TMB calculation is performed by the biologists as stated below:
TMB is defined as the number of mutations per megabase (Mb).

First, the number of covered bases during the sequencing of the patient's DNA is calculated. On average, 2Mb is sequenced but, this number may slightly vary in each run. Hence, this calculation is done for every patient.

Then, the number of mutations is assessed considering only the SNVs and insertions/deletions that are either damaging/potentially damaging or VUS (VAF <80%) and excluding specific germline mutations (50% +–10). Synonymous mutations, polymorphisms (MAF ≥ 1%), low coverage, and low–frequency variants (<5%) are excluded.

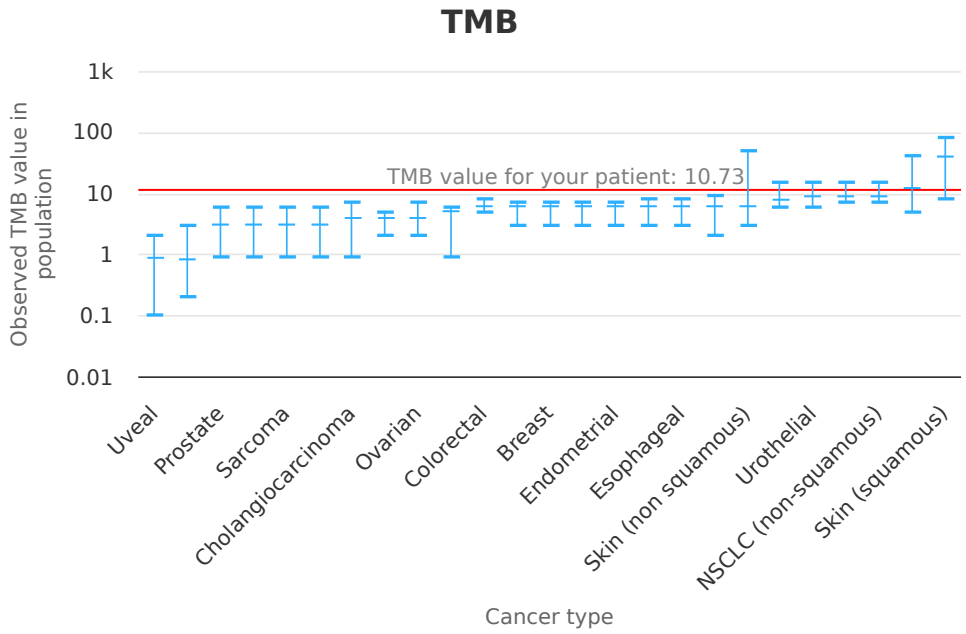
The TMB obtained is classified as the following (PMID:28835386):

High: ≥ 10 mut/Mb
Low: <10 mut/Mb

Remark 1: Our TMB calculation has been benchmarked against the Sample Seracare Tumor Mutation Load Assay, obtaining similar result:

Remark 2: For the moment, the cut–offs used are the same independently of the cancer type; however, we are working on a cancer type–specific TMB determination, as the number of mutations varies greatly across tumor types, and different

cut–offs may be needed.



MSI: Stable (4.75%)

We did not observe a high level of microsatellite instability (MSI). MSI–High has been linked to increased sensitivity to immune checkpoint inhibitor drugs (PD–1/PD–L1 inhibitors) (PMID:28877075). Therefore, PD–1/PD–L1 inhibitors would be associated with a lack of clinical benefit for this patient. Nonetheless, this information may need to be combined with other biomarkers like the ones present in the personalized immunogram.

Microsatellite instability (MSI) is a hypermutable phenotype caused by the loss of DNA mismatch repair (MMR) activity (PMID:20420947), which is associated with inactivation, loss or epigenetic silencing of MMR genes (MSH2, MLH1, MSH6 and PMS2).

METHOD

We rely on an automated process for MSI testing and prediction of MSI state via a machine learning process driven from microsatellite region mappings for specific loci in the genome.

DATA PREPROCESSING

After an initial read mapping against the human reference genome, an alignment processing using BWA and a duplicate reads removing using Picard, a fully local indel realignment was then performed using ABRA (Assembly Based ReAligner) [https://doi.org/10.1093/bioinformatics/btu376]. Indel calling was performed through a home made process to find complex alterations using pysam library. Indel detection is performed only for markers with a minimum coverage of 80. Therefore, microsatellite loci covered by a read depth below 80 were not considered and instead were reported as failed markers.

MSI–Detecting

For each marker passing the coverage QC check, read counts for each indel of a unique length were quantified. Thus the number of alleles observed and their size is calculated for each marker and compared to a population of normal controls. Loci were considered unstable if the observed number of repeats was statistically diffrent from that observed in the control population. MSI status was determined by the fraction of unstable microsatellite loci. Microsatellite instability for at least 40% of the analyzed markers is interpreted as MSI–High.

Baseline construction

We first calculated descriptive statistics about the number and size of unique alleles observed at each locus across an independent population of MSI–negative control samples to establish

baseline reference values. Assuming that the distribution and variance of alleles within the population is unknown. We perform an estimatimation by a confidence interval. The unique alleles observed in the population are thus framed by a two–sided confidence interval with an error rate of 5% (i.e. 2.5% on each side). Thus for an analyzed sample, if the number of unique alleles is outside the calculated confidence intervals, it is considered statistically different from what is normally expected in a population and the loci is considered as unstable.

USUAL MARKERS FOR MSI

Here follows a list of the usual markers used for detecting MSI in the cancer and their status. These markers are located in specific regions of the genome and are known to be prone to MSI.

Marker	*Status*
BAT-25	Stable
BAT-26	Stable
D2S123	Stable
NR-21	Stable
NR-27	Stable

HRD: Positive_BRCAwt_GS+ (44.2)

We **did not demonstrate** the presence of a deleterious (or suspected deleterious) BRCA1/2 variant. This category includes variants for which published data demonstrate a lost of function of the corresponding proteins as well as the large rearrangements.

We observed a **positive genomic scar** for this patient.

Therefore, the test results demonstrate a **homologous recombination deficiency** based on the genomic scar alone for this patient. Treatment based on PARP inhibitors could be beneficial for this patient.

Rmk: Data of the ATLAS trial (NCT03397394) were not able to find a correlation between HRD status and response to rucaparib treatment. The median PFS was 1.8\! months (95% CI, 1.6–1.9) in the ITT population, and was similar across HRD subgroup, with a median PFS of respectively 1.8 and 1.4 for the HRD–negative and HRD–positive population (PMID:34030643). However, the studied population of this clinical trial is too small (HRD–positve n=20; HRD–negative n=30) to conlcude on the impact of HRD status on the response to PARP inhibitors. Other clinical trials are currently recruiting.

Module to detect Loss of Heterozygosity events (LOH) and to predict homologous recombination deficiency (HRD).

The **HRD test** is a combination of the analysis of the BRCA1/2 status and the genomic scar (GS).

The module is based on the analysis of highly polymorphic SNPs from dbSNP with MAF>0.3. These selected SNPs are distributed along the genome and on telomeric regions . LOH is computed on targeted genes and HRD score is computed on 3 ways:

a global score called genomic scar (GS) on all the targets:

- a score only on the Allelic Disparity on Telomere (ADT)
- a score on all the regions except the telomeric ones (LOH)
- a score of large–scale Rearrangements (LR)

GS is considered as positive if >37

Rmk: The genomic HRD test should be interpreted with caution and take into consideration with other information and data available. The HRD test is relevant for tumor types for which defective DNA repair is well documented (e.g. breast, ovarian, pancreatic and prostate cancer) since its significance with other cancer remains unknown and under investigation trough clinical trials. Caution should also be used when interpreting score associated with poor quality or low tumoral content (<20%) sample since this may cause bias.

ADDITIONAL BIOMARKERS

CD8: Positive (10.0%)

We showed by IHC analysis a positive expression of CD8, indicating the presence of CD8+ T cells around the tumor. Since the formation of the complex between PD–1 (on the surface of T cells) and PD–L1 (on the surface of tumor cells) transmits an inhibitory signal to CD8+ T cells, treatments based on PD–1/PD–L1 inhibitors would be associated with potential clinical benefit for this patient. Nonetheless, this marker may not be enough by its own and it may need to be combined with other biomarkers like the ones present in the immunogram.

The CD8 co–receptor is expressed on the surface of cytotoxic T cells (also called CD8+ T cells or CTLs). CD8 has been shown to be involved in CTL co–activation by increasing antigen sensitivity and stabilising the interaction between TCR (on T cells) and peptide–MHC class I (pMHCI; on target cell). In order to carry out these functions, the CD8 co–receptor binds to a largely invariant region of MHCI that is spatially distinct from the TCR binding platform, allowing the potential for tripartite (TCR–pMHC1–CD8) complex formation.

Scoring criteria

CD8+ infiltration is scored semi–quantitatively. Ideally, 8–10 representative tumor fields are assessed when possible. We avoid counting areas with necrosis to minimize false or non–specific reactions. The 0–1–2–3 score represents average infiltration into the pathologist selection.
To provide a more quantitative assessment of these four levels of infiltration, we determine the approximate numbers of CD8+ cells per mm2, which correspond to the 0–3 scores.
(Although they vary between microscopes, a typical high–powered field (10x ocular and 40x objective) is 0.15 mm2, meaning that there are ∼7 high power fields (HPF) per mm2)
Lymphocyte CD8+ infiltration is considered as positive for score of 2 or greater.

Scoring:

0 (absent/negative) = 0–14 Lymphocytes CD8+/HPF
1 (low/negative) = 15–39 Lymphocytes CD8+/HPF
2 (moderate/positive) = 40–69 Lymphocytes CD8+/HPF
3 (high/positive) ≥ 70 Lymphocytes CD8+/HPF

Fusion Panel: NO

We didn't observe any translocation nor splicing variants in this RNAseq panel. Therefore treatment targeting any of these protein associated with a positive fusion/splicing variant will be associated with a potential lack of clinical benefit for this patient.

This analysis applies to the identification of somatic mutations with the OncoDEEP V7 RNA panel. The panel is composed of probes targeting 22 genes for fusion analysis and unusual splicing events (ALK, ROS1, RET, FGFR1, FGFR2, FGFR3, NTRK1, NTRK2, NTRK3, BRAF, NRG1, BRCA1, BRCA2, PTEN, AR, EGFR, ERBB2, MET, PALB2, RB1, TMPRSS2 and EWSR1).

PD-L1 (SP142 IC scoring) : High (30.0%)

We showed by IHC analysis a high expression of PD–L1. Since the formation of the complex between PD–1 (on the surface of T cells) and PD–L1 (on the surface of tumor cells) transmits an inhibitory signal to T cells, treatments based on PD–1/PD–L1 inhibitors would be associated with potential clinical benefit for this patient.

Atezolizumab has been recommended by NCCN (2023) for the treatment of patients with advanced or metastatic (Stage 4) utothelial carcinoma who are not eligible for cisplatin–containing chemotherapy and whose tumors express high PD–L1. High PD–L1 expression is defined as having PD–L1 expression on:

- ≥ 5% of tumor–infiltrating immune cells [IC ≥ 5%] covering the tumor area

Programmed death–ligand 1 (PD–L1) is a 40kDa type 1 transmembrane protein that has been speculated to play a major role in suppressing the immune system during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis. Normally the immune system reacts to foreign antigens where there is some accumulation in the lymph nodes or spleen which triggers a proliferation of antigen–specific CD8+ T cell. The formation of

PD–1 receptor / PD–L1 or B7.1 receptor /PD–L1 ligand complex transmits an inhibitory signal which reduces the proliferation of these CD8+ T cells at the lymph nodes and supplementary to that PD–1 is also able to control the accumulation of foreign antigen specific T cells in the lymph nodes through apoptosis which is further mediated by a lower regulation of the gene Bcl–2.

- Programmed Death Ligand (PD–L1) Clone SP142 VENTANA Assay for TECENTRIQ (Atezolizumab) : VENTANA PD–L1 (SP142) Assay is a qualitative immunohistochemical assay using rabbit monoclonal anti–PD–L1 clone SP142 intended for use in the assessment of the programmed death–ligand 1 (PD–L1) protein in tumor cells and tumor–infiltrating immune cells in the formalin–fixed, paraffin–embedded (FFPE) tissues indicated below stained with OptiView DAB IHC Detection Kit and OptiView Amplification Kit on a BenchMark ULTRA instrument. Determination of PD–L1 status is indication–specific, and evaluation is based on either the proportion of tumor area occupied by PD–L1 expressing tumor–infiltrating immune cells (% IC) of any intensity or the percentage of PD–L1 expressing tumor cells (% TC) of any intensity. VENTANA PD–L1 (SP142) Assay is approved by the FDA as an aid in identifying patients with NSCLC for treatment with atezolizumab, and recommended by NCCN (2023) as an aid in identifying patients with bladder cancer for the treatment with atezolizumab.

Scoring Criteria

IC: The proportion of tumor area occupied by PD–L1 expressing tumor–infiltrating immune cells (% IC) of any intensity.

IC <5% = No Expression (Negative, low expression).

IC ≥ 5% = High Expression

ACTIONABLE VARIANTS DESCRIPTION

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
TERT	SNV	-	37.50%	NM_198253.2:c.-58-66C>T	-		

BIOLOGICAL IMPACT: PATHOGENIC
Also known as C228T, this variant occurs in up to 83% of primary glioblastomas, 71% of melanomas, 66% of urothelial carcinomas of the bladder, 47% of hepatocellular carcinomas, 21% of medulloblastomas and up to 40% of thyroid cancers. Its represents an E26 transformation–specific family transcription factor (ETS) binding site recognized by GABPA transcription factor required for the e TERT expression (PMID:24803525; https://oncologypro.esmo.org/education-library/factsheets-on-biomarkers/tert-mutations-in-glioma).

THERAPEUTICAL IMPACT: TIER III
pTERT mutation has been reported in several cancers and associated with a poor prognosis. There is no pan–cancer trial recruiting for this variant.

INCIDENTAL FINDING
This variant has not been associated with any inherited disease.

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
TP53	SNV	7	40.72%	NM_000546.5:c.738G>T	p.(M246I)		

BIOLOGICAL IMPACT: PATHOGENIC
This variant is located in the DNA–binding domain of the protein. *In vitro* studies showed this variant has an inactivating impact as measured by the loss of transactivational activity (PMID:10777217, PMID:9524109). A reduction of tumor cell growth was also observed when the levels of mutated P53 were reduced by lentivirus infection expressing shp53 as compared to shGFP controls (PMID:22198284). It is classified as non–functional on IARC TP53 Database.

THERAPEUTICAL IMPACT: TIER III
No therapeutical impact has been associated with this variant.

INCIDENTAL FINDING

This variant has not been associated with any inherited disease.

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
ARID1A	SNV	1	38.07%	NM_006015.4:c.112G>T	p.(E38*)		5

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
This variant induces a truncated protein leading to a probable loss of function of the protein. ARID1A has been reported to act as tumor suppressor in gynecological cancers (PMID:21900401). Molecular studies using over–expression and RNAi silencing models have demonstrated that ARID1A negatively regulates cellular proliferation and tumorigenicity. This negative regulation is achieved through a molecular collaboration between ARID1A/BRG1 and p53, regulating tumor–inhibiting p53–downstream target genes such as CDKN1A and SMAD3. Using mutational studies, Guan et al. (PMID:23097632) have further confirmed the role of ARID1A as tumor suppressor, and they have demonstrated that all in–frame indel mutants analyzed lost their ability to inhibit cellular proliferation or activate transcription of CDKN1A.

THERAPEUTICAL IMPACT: TIER IIC
ARID1A is located at chromosome 1p, frequently deleted in tumours. ARID1A sequence mutations, deletions, and rearrangements were identified in ovarian, kidney, breast, lung, pancreatic and stomach cancer. This variant induces a probable loss of function of the protein, and there are no therapies targeting such loss of function. However, inactivation of ARID1A has been reported to lead to an increased sensitivity to inhibitors of PARP (such as olaparib, veliparib and BMN673, which block DNA damage repair pathways) and PI3K/AKT pathways (PMID:26069190; PMID:24036443).

Note that loss of function of ARID1A has been associated with a higher mutational burden which could lead to the clinical benefit of the immunotherapies in several cancers but the corresponding therapeutical impact needs to be confirmed. (http://ascopubs.org/doi/abs/10.1200/PO.17.00146; PMID:31277418; PMID:31911080).

INCIDENTAL FINDING
This variant has not been associated with any inherited disease.

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
FANCL	SNV	8	10.11%	NM_001114636.1:c.664G>T	p.(E222*)		3

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
This variant induces a stop codon leading to a probable loss of function of the protein.

THERAPEUTICAL IMPACT: TIER IIC
No therapeutical impact has been associated with this variant but a clinical trial is recruiting for olaparib.

INCIDENTAL FINDING
This variant has not been associated with any inherited disease.

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
RAD52	INS	11	38.97%	NM_134424.3:c.1160dup	p.(D387Efs*6)		2

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
This variant leads to a stop codon inducing a truncated protein. It could be therefore associated with a loss of function of the protein. A role for Rad52 in break–induced replication (BIR) can explain why its depletion in cells with oncogene–induced DNA replication stress (DRS) leads to increased DNA damage (PMID:27984746).

THERAPEUTICAL IMPACT: TIER IIC
Because of its role in the repair DNA double–strand breaks by homologous recombination mechanism, loss of function of RAD52 could be associated with a clinical benefit to PARP inhibitors. Several clinical trials are ongoing.

INCIDENTAL FINDING
This variant has not been associated with any inherited disease.

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Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
MUTYH	SNV	2	72.47%	NM_012222.2:c.55C>T	p.(R19*)		1

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
This variant produces a truncated protein leading to a loss of function of the protein.

THERAPEUTICAL IMPACT: TIER IID
No therapeutical impact has been associated with this variant but a clinical trial is recruiting for olaparib.

INCIDENTAL FINDING
This variant might be associated with a predisposition to colorectal cancer (PMID:11818965), but the evidences are not strong.

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
BLM	LOH	-	1.00	-	-		

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
This variant induces the loss of one copy of the protein. BLM gene encodes for a RecQ helicase protein, involved in the maintenance of the genome integrity during DNA replication. Loss–of–function mutations of BLM cause Bloom's syndrome, autosomal recessive disorder characterized by a greatly increased risk of early onset of cancer and the development of multiple cancers (PMID:28232778).

THERAPEUTICAL IMPACT: TIER III
No therapeutical impact has been associated with this variant. However, loss of function of BLM has been associated with microsatellite intsability (PMID:9731483). The FDA has approved several ICIs for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability–high (MSI–H) or mismatch repair deficient (dMMR) solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options. But we don't have enough clinical evidence to make a final conclusion.

INCIDENTAL FINDING
This variant has not been associated with any inherited disease.

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
KDM6A	INS	4	38.18%	NM_021140.3:c.347delinsTT	p.(Y116Ffs*10)		

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
This variant leads to a stop codon inducing a truncated protein. It could be therefore associated with a loss of function of the protein. Because of its role as chromatin modifier, mutations in KDM6A have been associated with several cancer as tumor suppressor gene (PMID:24622842). This gene is located on the X chromosome and is the corresponding locus to a Y–linked gene which encodes an histone demethylase that specifically demethylates 'Lys–27' of histone H3, thereby playing a central role in histone code. It plays a central role in regulation of posterior development, by regulating HOX gene expression. It has been involved in the Kabuki syndrome (PMID:24664873).

THERAPEUTICAL IMPACT: TIER III
Loss of function of KDM6A has been linked to a more malignant phenotype of multiple myeloma. Moreover, in–vitro study showed a sensitization of cells with loss of KDM6A to EZH2 inhibitors or HDCA inhibitors (PMID:29045832; PMID:30556125). We don't have enough strong clinical evidences to make a conclusion about the potential benefit of EZH2 inhibitors.

INCIDENTAL FINDING
This variant has not been associated with any inherited disease.

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
KEAP1	LOH	-	1.00	-	-		

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
This variant is associated with the loss of one copy of KEAP1, while the remaining copy could be non–functional.

An abnormality in the Nrf2–Keap1 system may facilitate the growth of cancer cells because oxidative and electrophilic stresses cause many diseases, including cancer. The activation of Nrf2 through reduced Keap1 activity, either through a nonsense variant leading to a loss–of–function, provides growth advantages to lung cancer cells under homeostatic conditions. Indeed, there is a high incidence/frequent occurrence of loss of Keap1 function in patient with lung cancer and this loss of function enhanced the nuclear accumulation of Nrf2 and elevated the expression of antioxidative and antixenobiotic stress enzymes and drug efflux pumps, suggesting cancer cells with weakened. Keap1 acquire multiple advantages for proliferation (PMID:18316592).

THERAPEUTICAL IMPACT: TIER III
The loss of function of the other allele should be confirmed by the NGS results.

Activation of the Nrf2 pathway is critical for resistance to chemotherapeutic agents (PMID:25014534; PMID:25337579). At this moment there is no NRF2 inhibitors FDA approved or available through clinical trials. By screening natural products, data identified an antineoplastic compound brusatol as an Nrf2 inhibitor that enhances the chemotherapeutic efficacy of cisplatin (PMID:21205897). No therapeutical impact has been associated with this variant.

INCIDENTAL FINDING
This variant has not been associated with any inherited disease.

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
RAD51	LOH	-	1.00	-	-		

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
This variant is associated with the loss of one copy of RAD51, while the remaining copy could be non–functional. This could lead to a probable loss of function of the protein. RAD51 is one of the protein critical for genome stability and cancer prevention (PMID:30551670).

THERAPEUTICAL IMPACT: TIER III
No therapeutical impact has been associated with this variant. However, the loss of function of the other allele should be confirmed by the NGS results.

INCIDENTAL FINDING
This variant has not been associated with any inherited disease.

Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
STK11	LOH	-	1.00	-	-		

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
This variant is associated with the loss of one copy of STK11, while the remaining copy could be non–functional. Hence, it could lead to a probable loss of function of the protein.

STK11 loss or inactivating mutations have been shown to result in activation of the mTOR pathway and the kinases Src and FAK. In addition, since STK11 is involved in regulating multiple cellular functions (such as metabolism, cell cycle, DNA damage response and apoptosis), loss of STK11 function was found to promote the development of aggressive tumors, metastatic spread and survival of cancer cells (PMID:15261145; PMID:23637231; PMID:20541700; PMID:23178462).

THERAPEUTICAL IMPACT: TIER III
No therapeutical impact has been associated with this variant. However, the loss of function of the other allele should be confirmed by the NGS results.

INCIDENTAL FINDING
This variant has been associated with individuals affected by Peutz–Jeghers syndrome (PMID:24037887).

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Gene	Cat.	Exon	Var. Freq. / Copy Nb	cDNA	AA	Drugs related	
						to gene	to patient
TP53	SNV	6	45.48%	NM_000546.5:c.587G>A	p.(R196Q)		

BIOLOGICAL IMPACT: LIKELY PATHOGENIC
Although the functional impact of this variant has not been reported. It is located in a key amino acid and reported as likely pathogenic in several databases (IARC TP53 Database).

THERAPEUTICAL IMPACT: TIER III
No therapeutical impact has been associated with this variant.

INCIDENTAL FINDING
This variant has not been associated with any inherited disease.

DETECTED VARIANTS LIST

Gene	Cat.	Var. Freq. / Copy Nb	cDNA	AA	Biological Impact	Therapeutical Impact	Incidental Findings	Depth
TERT	SNV	37.50%	NM_198253.2:c.-58-66C>T	-	Pathogenic	Tier III	NO	632
TP53	SNV	40.72%	NM_000546.5:c.738G>T	p.(M246I)	Pathogenic	Tier III	NO	528
ARID1A	SNV	38.07%	NM_006015.4:c.112G>T	p.(E38*)	Likely Pathogenic	Tier IIC	NO	197
FANCL	SNV	10.11%	NM_001114636.1:c.664G>T	p.(E222*)	Likely Pathogenic	Tier IIC	NO	742
RAD52	INS	38.97%	NM_134424.3:c.1160dup	p.(D387Efs*6)	Likely Pathogenic	Tier IIC	NO	970
MUTYH	SNV	72.47%	NM_012222.2:c.55C>T	p.(R19*)	Likely Pathogenic	Tier IID	YES	603
BLM	LOH	1.00	-	-	Likely Pathogenic	Tier III	NO	-
KDM6A	INS	38.18%	NM_021140.3:c.347delinsTT	p.(Y116Ffs*10)	Likely Pathogenic	Tier III	NO	385
KEAP1	LOH	1.00	-	-	Likely Pathogenic	Tier III	NO	-
RAD51	LOH	1.00	-	-	Likely Pathogenic	Tier III	NO	-
STK11	LOH	1.00	-	-	Likely Pathogenic	Tier III	YES	-
TP53	SNV	45.48%	NM_000546.5:c.587G>A	p.(R196Q)	Likely Pathogenic	Tier III	NO	686
AR	INS	29.17%	NM_000044.3:c.1418_1420dup	p.(G473dup)	VUS	Tier III	NO	192

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Gene	Cat.	Var. Freq. / Copy Nb	cDNA	AA	Biological Impact	Therapeutical Impact	Incidental Findings	Depth
ARID1A	SNV	42.25%	NM_006015.4:c.577G>A	p.(E193K)	VUS	Tier III	NO	471
CHD4	SNV	19.18%	NM_001273.3:c.4234G>A	p.(E1412K)	VUS	Tier III	NO	610
CHD4	SNV	43.46%	NM_001273.3:c.181C>T	p.(R61W)	VUS	Tier III	NO	1123
CREBBP	SNV	54.67%	NM_004380.2:c.4303G>T	p.(D1435Y)	VUS	Tier III	NO	364
CSDE1	SNV	38.81%	NM_001007553.2:c.118A>C	p.(I40L)	VUS	Tier III	NO	737
CUX1	SNV	14.89%	NM_001202543.1:c.1904G>A	p.(R635H)	VUS	Tier III	NO	618
CYP19A1	SNV	5.60%	NM_000103.3:c.222C>A	p.(C74*)	VUS	Tier III	YES	678
DDR2	SNV	13.68%	NM_001014796.1:c.979G>A	p.(V327I)	VUS	Tier III	NO	943
DNMT1	SNV	12.66%	NM_001130823.2:c.4769G>A	p.(R1590Q)	VUS	Tier III	NO	537
EPHB4	SNV	65.33%	NM_004444.4:c.703C>T	p.(P235S)	VUS	Tier III	NO	851
ERBB4	SNV	35.70%	NM_005235.2:c.3195_3200delinsGTACCA	p.(R1067Q)	VUS	Tier III	NO	451
HGF	SNV	12.09%	NM_000601.5:c.294G>T	p.(W98C)	VUS	Tier III	NO	612
IRS1	SNV	16.77%	NM_005544.2:c.1546G>C	p.(D516H)	VUS	Tier III	NO	620
JAK1	SNV	32.30%	NM_002227.3:c.1516C>T	p.(R506C)	VUS	Tier III	NO	808
KMT2C	SNV	8.98%	NM_170606.2:c.2573_2578delinsTGTCCT	p.(W858_P860delinsLSS)	VUS	Tier III	NO	657
LRP1B	SNV	16.43%	NM_018557.2:c.10580G>T	p.(C3527F)	VUS	Tier III	NO	560
MAP3K13	SNV	13.51%	NM_004721.4:c.2470G>A	p.(D824N)	VUS	Tier III	NO	659
MAP3K4	SNV	31.31%	NM_005922.3:c.974A>G	p.(Q325R)	VUS	Tier III	NO	559
NCOR1	SNV	25.59%	NM_006311.3:c.568_571delinsTGAA	p.(R190*)	VUS	Tier III	NO	551

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Gene	Cat.	Var. Freq. / Copy Nb	cDNA	AA	Biological Impact	Therapeutical Impact	Incidental Findings	Depth
PAK3	DEL	8.94%	NM_001128168.2:c.337del	p.(M113Cfs*31)	VUS	Tier III	NO	425
PARP2	SNV	26.38%	NM_005484.3:c.704A>G	p.(D235G)	VUS	Tier III	NO	633
PBRM1	SNV	29.25%	NM_018313.4:c.1727G>A	p.(R576H)	VUS	Tier III	NO	588
PIK3C2B	SNV	13.13%	NM_002646.3:c.680A>G	p.(D227G)	VUS	Tier III	NO	830
PTPRD	SNV	76.42%	NM_002839.3:c.3914C>T	p.(P1305L)	VUS	Tier III	NO	865
RHOA	SNV	27.01%	NM_001664.3:c.137T>C	p.(I46T)	VUS	Tier III	NO	485
RTEL1	SNV	23.74%	NM_016434.3:c.2155G>A	p.(D719N)	VUS	Tier III	NO	577
SDHA	SNV	11.86%	NM_004168.3:c.1335_1346delinsTGCACATGGTGT	p.(V446_A449delinsAHGV)	VUS	Tier III	NO	1020
SDHA	SNV	15.33%	NM_004168.3:c.1367_1371delinsTGCTA	p.(S456_L457delinsLL)	VUS	Tier III	NO	1070
SDHA	SNV	45.27%	NM_004168.3:c.1804G>C	p.(D602H)	VUS	Tier III	NO	455
SETD8	DEL	9.25%	NM_020382.4:c.31_47delinsTGCGCGGTGGA	p.(R11_A16delinsCAVE)	VUS	Tier III	NO	227
SETD8	SNV	12.72%	NM_020382.4:c.719A>C	p.(D240A)	VUS	Tier III	NO	920
STAG2	SNV	44.63%	NM_001042749.2:c.13C>G	p.(P5A)	VUS	Tier III	NO	410
TERT	SNV	100.00%	NM_198253.2:c.-58-1597G>A	-	VUS	Tier III	NO	600
TERT	SNV	99.62%	NM_198253.2:c.-58-2096A>G	-	VUS	Tier III	NO	525
TERT	SNV	73.68%	NM_198253.2:c.-58-2326G>A	-	VUS	Tier III	NO	718
TERT	SNV	100.00%	NM_198253.2:c.-58-910T>C	-	VUS	Tier III	NO	890
TERT	INS	68.56%	NM_198253.2:c.-58-1094_-58-1093insC	-	VUS	Tier III	NO	738

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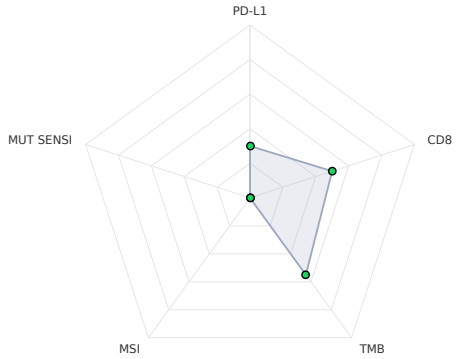
Gene	Cat.	Var. Freq. / Copy Nb	cDNA	AA	Biological Impact	Therapeutical Impact	Incidental Findings	Depth
TERT	SNV	26.24%	NM_198253.2:c.-58-1324T>C	-	VUS	Tier III	NO	644
TSHR	SNV	28.78%	NM_000369.2:c.203C>T	p.(P68L)	VUS	Tier III	NO	410
USP8	SNV	10.92%	NM_005154.4:c.2353A>G	p.(T785A)	VUS	Tier III	NO	467

IMMUNOGRAM



The immunogram shows a high potential response to immunotherapy. We showed a positive infiltration of CD8 + T cells in the tumor and also a high expression of PD–L1 (30% of immune cells). We also observed a high tumor mutational burden (TMB). In patients with high TMB, checkpoint inhibitors (PD–1/PD–L1 blockade) have been associated with clinical benefits across diverse tumors (PMID:28835386). Moreover, we didn't observe microsatellite instability (MSI) or sensibility/resistance mutation. Therefore, based on high mutational burden (TMB) and the level of CD8+ lymphocytes and PD–L1 expression, treatment based on PD–1/PD–L1 inhibitors ***could be associated with potential clinical benefit*** for this patient.

CLINICAL FORM

Date informed consent given/signed	Nov, 27 2024
Initial diagnosis date	Oct, 09 2024
Clinical diagnosis	Urinary bladder cancer
Primary tumour site	bladder
Known metastatic sites	Yes
Date of biopsy/surgery or blood withdrawal	Oct, 16 2024
Sample type(s)	Solid Tumor
Histological diagnosis	Urinary bladder cancer
TNM known ?	Yes
Biomarkers tested	No
Is the tissue sample sent for molecular diagnostics the one used for the diagnosis (detailed above) ?	Unmentioned
Sample site	Primary tumour
Does patient have comorbidities ?	-
Has the patient previously undergone organ cancer surgery?	-
Is patient currently receiving a cancer therapy ?	-
Known previous cancer therapies	No
Does the patient have a previous history of cancer?	-
ECOG	-

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Smoking status	Unknown
Alcohol consumption	Unknown
Comments	OncoDEEP I+

PROCESS

IPG is the biggest Belgian anatomopathology laboratory and is among the biggest laboratories of its kind in Europe with headquarters in Gosselies and a large section in Brussels. It has a total workspace of 285 people, among whom medical specialists including 20 pathologists and 8 geneticists, 10 clinical biologists and highly skilled technicians. It was one of the first companies to implement a high degree of integration of anatomic pathology data and molecular genetics. The ability to integrate pathological data and molecular biology is not common and is an asset for the products provided by OncoDNA.

All the technical processes including the pathology QC check are performed by the Institute of Pathology and Genetics (IPG) which is ISO15189 accredited (ISO15189:2012 Medical Laboratories – Requirements for Quality and Competence) since the 6th October 2009 by BELAC, an ILAC MRA signatory. The quality of raw data is validated by OncoDNA before any further interpretation.

OncoDNA is compliant with the Guideline for Good Practices of the International Conference on Harmonization (ICH GCP E6 R2) and certified ISO/IEC 27001:2013 (Requirement for Information Security Management Systems) since the 23rd November 2018 by the European Certification Accredity Body ICTS – International Certifcation Trust Services.

REPORT

Please keep in mind that this summary is not the complete report and is to be printed only for archiving purposes.
For more information, please see the dynamic version of the report displayed on oncoshare.oncokdm.com.
This report has been generated and validated on **December, 23 2024**

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