A new framework for access to molecular-guided treatments in Belgium GeNeo and Ballett clinical trials under the Precision umbrella

15th BSMO-Bordet Symposium on the integration of molecular biology advances into oncology clinical practice

Kevin Punie, MD

Medical Oncologist
Department of General Medical Oncology and Multidisciplinary Breast Centre, Leuven Cancer Institute, University Hospitals Leuven, Belgium
Laboratory of Experimental Oncology, KU Leuven, Belgium
Committee member of ESMO Young Oncologists and ESMO Resilience Task Force
Board member of Belgian Society of Medical Oncology BSMO

Disclosure information

- **Personal financial interests**: /
- **Institutional financial interests**: Astra Zeneca (Consultancy), Eli Lilly (Advisory Board, Speaker Fee's), Gilead Sciences (Speakers Fee's, Advisory Board, Consultancy), Medscape (Speaker Fee's), MSD (Advisory Board, Speaker Fee's), Mundi Pharma (Speaker Fee's), Novartis (Consultancy, Advisory Board, Speaker Fee's), Pfizer (Consultancy, Speaker Fee's), Pierre Fabre (Advisory Board), Roche (Consultancy, Advisory Board, Speaker Fee's), Sanofi (Research Funding), Teva (Advisory Board), Vifor Pharma (Advisory Board)
- **Travel support**: Astra Zeneca, Novartis, Pfizer, PharmaMar, Roche
- **Non-financial interests**:

  Investigator in GeNeo and Ballett study, member of MTB

  Committee member of ESMO Young Oncologists Committee
  Board member of Belgian Society of Medical Oncology (BSMO)
  EORTC Breast Cancer Group co-PI in EORTC 1745-ETF-BCG trial
  Advisory role in commission personalized medicine of government in Belgium

Molecular guided treatment options in oncology

Requirements for succesful MGTO in oncology:

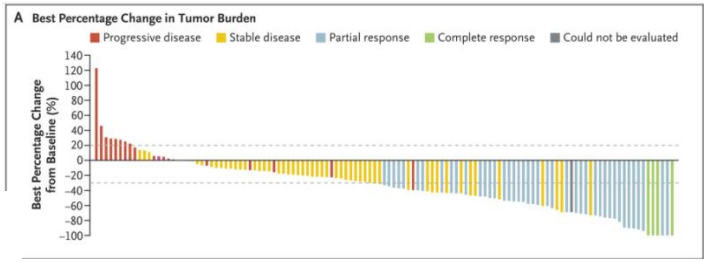
- Tissue to test
- Physician who recommends a genomic test
- Access to genomic profiling diagnostics
- Diagnostic test should not fail
- Presence of driver alteration
- Identification and interpretation of driver alteration
- Prioritization of the optimal (molecular guided) treatment option
- Access to molecular guided therapy through reimbursement, clinical trials, medical need programs or off-label MGTO
- Patient that qualifies the requirements to access the drug
- Activity of the MGTO in your patient
- Tolerability of the MGTO in your patient
- Someone who pays for all this

Rapid emergence of several new MGTO's

ORIGINAL ARTICLE

Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

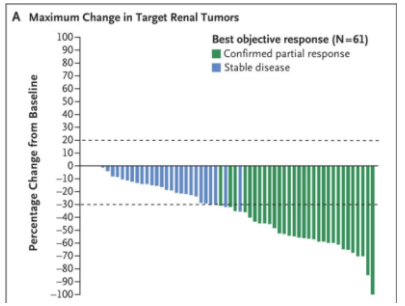
Ferdinandos Skoulidis, M.D., Ph.D., Bob T. Li, M.D., Ph.D., M.P.H., Grace K. Dy, M.D., Timothy J. Price, M.B., B.S., D.H.Sc., Gerald S. Falchook, M.D., Jürgen Wolf, M.D., Antoine Italiano, M.D., Martin Schuler, M.D., Hossein Borghaei, D.O., Fabrice Barlesi, M.D., Ph.D., Terufumi Kato, M.D., Alessandra Curioni-Fontecedro, M.D., et al.



ORIGINAL ARTICLE

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

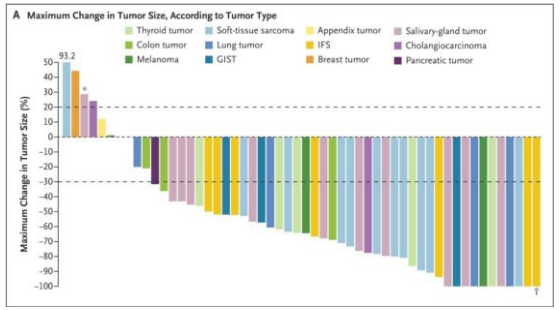
Eric Jonasch, M.D., Frede Donskov, M.D., Ph.D., Othon Iliopoulos, M.D., W. Kimryn Rathmell, M.D., Ph.D., Vivek K. Narayan, M.D., Benjamin L. Maughan, M.D., Stephane Oudard, M.D., Tobias Else, M.D., Jodi K. Maranchie, M.D., Sarah J. Welsh, M.D., Sanjay Thamake, Ph.D., Eric K. Park, M.D., et al., for the MK-6482-004 Investigators*



ORIGINAL ARTICLE

Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children

Alexander Drilon, M.D., Theodore W. Laetsch, M.D., Shivaani Kummar, M.D., Steven G. DuBois, M.D., Ulrik N. Lassen, M.D., Ph.D., George D. Demetri, M.D., Michael Nathenson, M.D., Robert C. Doebele, M.D., Ph.D., Anna F. Farago, M.D., Ph.D., Alberto S. Pappo, M.D., Brian Turpin, D.O., Afshin Dowlati, M.D., et al.



⇔ Often very slow reimbursement procedures

DRUGS FOR ADVANCED BREAST CANCER	FDA	EMA	FAGG MNP/CU/ETA/ samples	REIMBURSED IN BELGIUM
Atezolizumab + chemo	Mar 2019	Aug 2019		1-4-2021
Olaparib	Jan 2018	Apr 2019		
Talazoparib	Oct 2018	Jun 2019		1-7-2021

Molecular guided treatment options in oncology: Main challenges in clinical practice

Target Identification

- Tissue availability
- No access to comprehensive genomic profiling
- No targetable alterations

Treatment selection

- Variant interpretation and classification
- Drug access

Data collection

- Mutational landscape
- Clinical outcomes

Ongoing initiatives from BSMO that try to tackle these challenges

- Access to comprehensive genomic profiling
  - → GeNeo + Ballett clinical trials
- Improve genomic + clinical interpretation of diagnostic tests
  - → National Molecular Tumor Board
- Access to MGTO
  - → Clinical trials: Precision II and other trials
  - → New framework for patients that don't fit in trials
- Data collection
  - → Precision 1

GeNeo study (P.I. Dr. Philippe Aftimos)

- 1000 Belgian patients with metastatic solid tumors

GeNeo PRECISION ONCOLOGY

CGP report +/- Treatment recommendation

Informed consent
- GeNeo (13 sites)
- Precision 1

Comprehensive Genomic Profiling
Foundation One

Molecular Tumor Board
Navify Platform

MGTO options

Roche

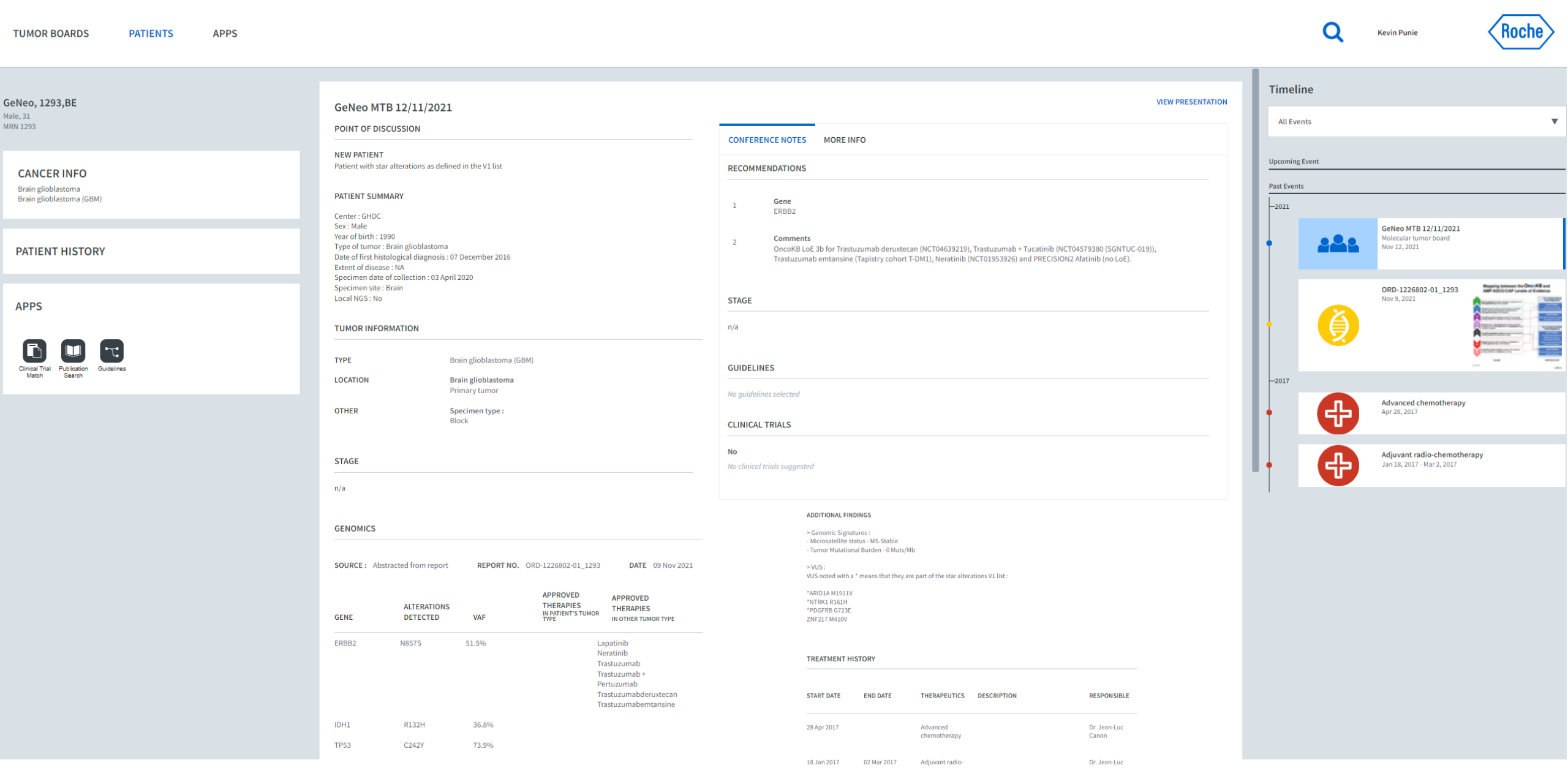
Data collection
Precision 1
- Redcap
- HealthData

BSMO

GeNeo study (P.I. Dr. Philippe Aftimos)

- Main objectives

- To determine the added value of tissue-agnostic CGP versus 'real-world' practice according to reimbursement in providing patients access to MGTO
- To describe the landscape of genomic alterations detected by reimbursed NGS
- To describe the landscape of genomic alterations detected by CGP
- To assess the technical success rate of CGP
- To describe the uptake of MGTO recommended by the MTB



GeNeo Navify Platform: ERBB2 mutation in glioblastoma

Ballett study (P.I. Dr. Brigitte Maes)

- Belgian Approach for Local Laboratory Extensive Tumor Testing
- 936 Belgian patients with metastatic solid tumors

CGP report +/- Treatment recommendation

Informed consent
- Ballett (13 sites)
- Precision 1

Data collection
Precision 1

CGP
TruSightOncology 500
9 Belgian laboratories

Molecular Tumor
Board
Dedicated Platform

MGTO options

illumina

OncoDNA
THE CANCER THERANOSTIC COMPANY

pieriandx

JESSA
ZIEKENHUIS

BSMO

Ballett study Objectives (P.I. Dr. Brigitte Maes)

To evaluate the clinical value of CGP in “real-world” practice for offering more therapeutic options to patients and a broader access to precision medicine => to support decision for reimbursement of CGP

To describe the landscape of genomic alterations and quantify the actionable alterations detected by CGP

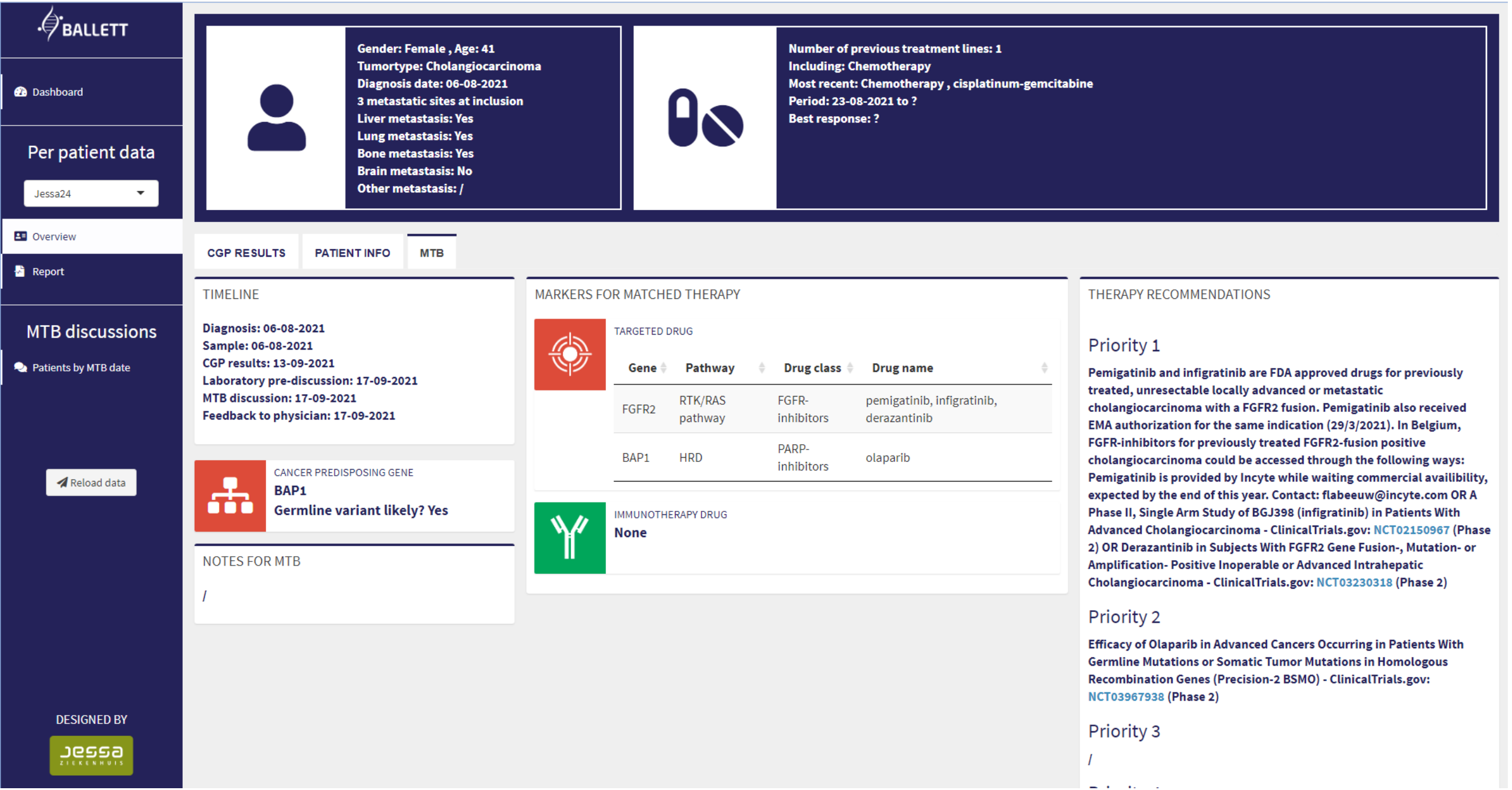
To evaluate the number of actionable alterations that would have been missed by the limited NGS testing that is reimbursed in Belgium - www.ComPerMed.be

To fully standardize CGP wet-lab performance, data analysis, clinical interpretation, therapy recommendation and reporting among 9 participating Belgian NGS laboratories

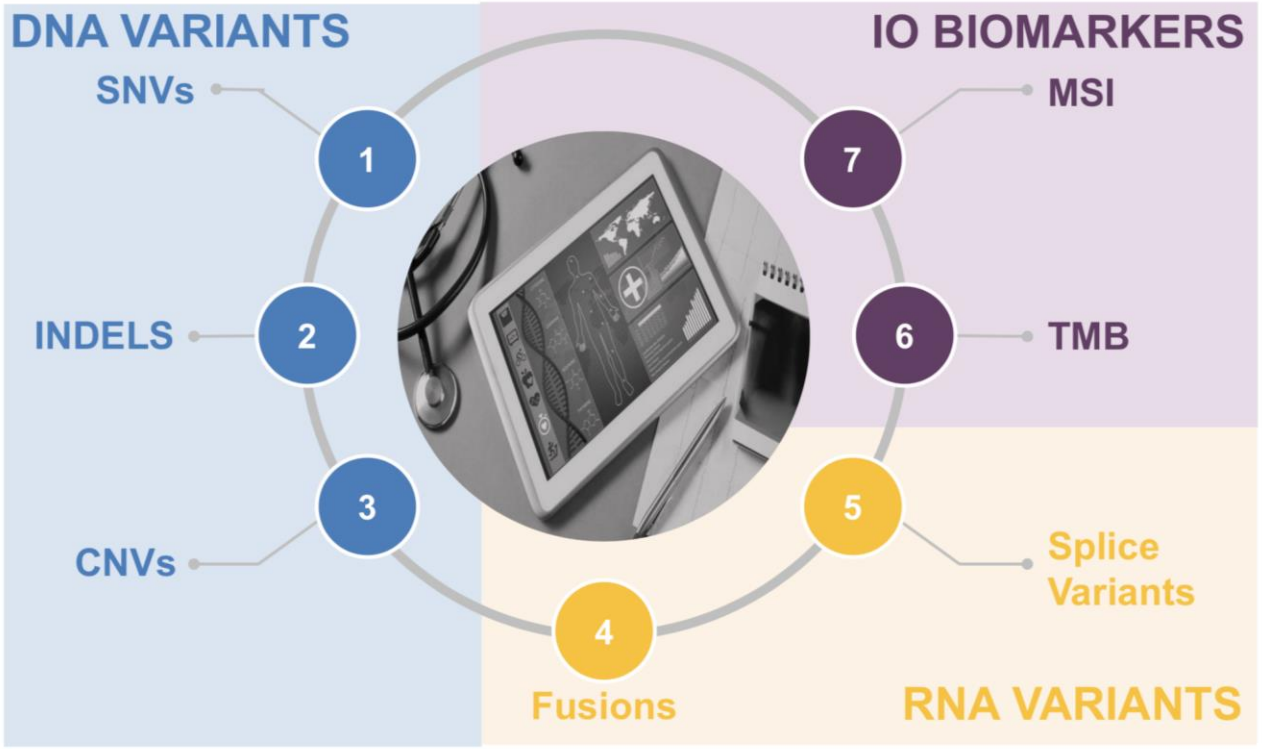
To describe and quantify the uptake of treatments and the inclusion in clinical trials recommended by the molecular tumor board guided by the CGP

To work in a multi-stakeholder approach to attract more innovative treatments and clinical trials in Belgium

To establish a Belgian genomic tumor database under the authority of the governmental ‘Sciensano’ thereby increasing public health knowledge in Belgium


BALLETT
Dashboard
Per patient data
Jessa24
Overview
Report
MTB discussions
Patients by MTB date
Reload data
DESIGNED BY
Jessa ZIEKENHUIS
Gender: Female , Age: 41
Tumortype: Cholangiocarcinoma
Diagnosis date: 06-08-2021
3 metastatic sites at inclusion
Liver metastasis: Yes
Lung metastasis: Yes
Bone metastasis: Yes
Brain metastasis: No
Other metastasis: /
Number of previous treatment lines: 1
Including: Chemotherapy
Most recent: Chemotherapy , cisplatinum-gemcitabine
Period: 23-08-2021 to ?
Best response: ?
CGP RESULTS
PATIENT INFO
MTB
TIMELINE
Diagnosis: 06-08-2021
Sample: 06-08-2021
CGP results: 13-09-2021
Laboratory pre-discussion: 17-09-2021
MTB discussion: 17-09-2021
Feedback to physician: 17-09-2021
CANCER PREDISPOSING GENE
BAP1
Germline variant likely? Yes
NOTES FOR MTB
/
MARKERS FOR MATCHED THERAPY
TARGETED DRUG
Gene
Pathway
Drug class
Drug name
FGFR2
RTK/RAS pathway
FGFR-inhibitors
pemigatinib, infigratinib, derazantinib
BAP1
HRD
PARP-inhibitors
olaparib
IMMUNOTHERAPY DRUG
None
THERAPY RECOMMENDATIONS
Priority 1
Pemigatinib and infigratinib are FDA approved drugs for previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion. Pemigatinib also received EMA authorization for the same indication (29/3/2021). In Belgium, FGFR-inhibitors for previously treated FGFR2-fusion positive cholangiocarcinoma could be accessed through the following ways: Pemigatinib is provided by Incyte while waiting commercial availibility, expected by the end of this year. Contact: flabeeuw@incyte.com OR A Phase II, Single Arm Study of BGJ398 (infigratinib) in Patients With Advanced Cholangiocarcinoma - ClinicalTrials.gov: NCT02150967 (Phase 2) OR Derazantinib in Subjects With FGFR2 Gene Fusion-, Mutation- or Amplification- Positive Inoperable or Advanced Intrahepatic Cholangiocarcinoma - ClinicalTrials.gov: NCT03230318 (Phase 2)
Priority 2
Efficacy of Olaparib in Advanced Cancers Occurring in Patients With Germline Mutations or Somatic Tumor Mutations in Homologous Recombination Genes (Precision-2 BSMO) - ClinicalTrials.gov: NCT03967938 (Phase 2)
Priority 3
/

Comprehensive Genomic Profiling: Identification

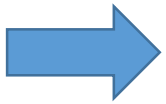


Up to 523 genes, including many HRD (BRCA-like) and other DNA Damage Repair genes

DNA content									
ABL1	BRD4	CUX1	FAM175A	GATA6	IGF1	MAP3K13	NOTCH4	POLE	RPTOR	TAF1
ABL2	BRIP1	CXCR4	FAM46C	GEN1	IGF1R	MAP3K14	NPM1	PPARG	RUNX1	TBX3
ACVR1	BTG1	CYLD	FANCA	GID4	IGF2	MAP3K4	NRAS	PPM1D	RUNX1T1	TCEB1
ACVR1B	BTK	DAXX	FANCC	GLI1	IKBKE	MAPK1	NRG1	PPP2R1A	RYBP	TCF3
AKT1	C11orf30	DCUN1D1	FANCD2	GNA11	IKZF1	MAPK3	NSD1	PPP2R2A	SDHA	TCF7L2
AKT2	CALR	DDR2	FANCE	GNA13	IL10	MAX	NTRK1	PPP6C	SDHAF2	TERC
AKT3	CARD11	DDX41	FANCF	GNAQ	IL7R	MCL1	NTRK2	PRDM1	SDHB	TERT
ALK	CASP8	DHX15	FANCG	GNAS	INHA	MDC1	NTRK3	PREX2	SDHC	TET1
ALOX12B	CBFB	DICER1	FANCI	GPR124	INHBA	MDM2	NUP93	PRKAR1A	SDHD	TET2
ANKRD11	CBL	DIS3	FANCL	GPS2	INPP4A	MDM4	NUTM1	PRKCI	SETBP1	TFE3
ANKRD26	CCND1	DNAJB1	FAS	GREM1	INPP4B	MED12	PAK1	PRKDC	SETD2	TFRC
APC	CCND2	DNMT1	FAT1	GRIN2A	INSR	MEF2B	PAK3	PRSS8	SF3B1	TGFBR1
AR	CCND3	DNMT3A	FBXW7	GRM3	IRF2	MEN1	PAK7	PTCH1	SH2B3	TGFBR2
ARAF	CCNE1	DNMT3B	FGF1	GSK3B	IRF4	MET	PALB2	PTEN	SH2D1A	TMEM127
ARFRP1	CD274	DOT1L	FGF10	H3F3A	IRS1	MGA	PARK2	PTPN11	SHQ1	TMPRSS2
ARID1A	CD276	E2F3	FGF14	H3F3B	IRS2	MITF	PARP1	PTPRD	SLIT2	TNFAIP3
ARID1B	CD74	EED	FGF19	H3F3C	JAK1	MLH1	PAX3	PTPRS	SLX4	TNFRSF14
ARID2	CD79A	EGFL7	FGF2	HGF	JAK2	MLL	PAX5	PTPRT	SMAD2	TOP1
ARID5B	CD79B	EGFR	FGF23	HIST1H1C	JAK3	MLLT3	PAX7	QKI	SMAD3	TOP2A
ASXL1	CDC73	EIF1AX	FGF3	HIST1H2BD	JUN	MPL	PAX8	RAB35	SMAD4	TP53
ASXL2	CDH1	EIF4A2	FGF4	HIST1H3A	KAT6A	MRE11A	PBRM1	RAC1	SMARCA4	TP63
ATM	CDK12	EIF4E	FGF5	HIST1H3B	KDM5A	MSH2	PDCD1	RAD21	SMARCB1	TRAF2
ATR	CDK4	EML4	FGF6	HIST1H3C	KDM5C	MSH3	PDCD1LG2	RAD50	SMARCD1	TRAF7
ATRX	CDK6	EP300	FGF7	HIST1H3D	KDM6A	MSH6	PDGFRA	RAD51	SMC1A	TSC1
AURKA	CDK8	EPCAM	FGF8	HIST1H3E	KDR	MST1	PDGFRB	RAD51B	SMC3	TSC2
AURKB	CDKN1A	EPHA3	FGF9	HIST1H3F	KEAP1	MST1R	PDK1	RAD51C	SMO	TSHR
AXIN1	CDKN1B	EPHA5	FGFR1	HIST1H3G	KEL	MTOR	PDPK1	RAD51D	SNCAIP	U2AF1
AXIN2	CDKN2A	EPHA7	FGFR2	HIST1H3H	KIF5B	MUTYH	PGR	RAD52	SOCS1	VEGFA
AXL	CDKN2B	EPHB1	FGFR3	HIST1H3I	KIT	MYB	PHF6	RAD54L	SOX10	VHL
B2M	CDKN2C	ERBB2	FGFR4	HIST1H3J	KLF4	MYC	PHOX2B	RAF1	SOX17	VTCN1
BAP1	CEBPA	ERBB3	FH	HIST2H3A	KLHL6	MYCL1	PIK3C2B	RANBP2	SOX2	WISP3
BARD1	CENPA	ERBB4	FLCN	HIST2H3C	KMT2B	MYCN	PIK3C2G	RARA	SOX9	WT1
BBC3	CHD2	ERCC1	FLI1	HIST2H3D	KMT2C	MYD88	PIK3C3	RASA1	SPEN	XIAP
BCL10	CHD4	ERCC2	FLT1	HIST3H3	KMT2D	MYOD1	PIK3CA	RB1	SPOP	XPO1
BCL2	CHEK1	ERCC3	FLT3	HLA-A	KRAS	NAB2	PIK3CB	RBM10	SPTA1	XRCC2
BCL2L1	CHEK2	ERCC4	FLT4	HLA-B	LAMP1	NBN	PIK3CD	RECQL4	SRC	YAP1
BCL2L11	CIC	ERCC5	FOXA1	HLA-C	LATS1	NCOA3	PIK3CG	REL	SRSF2	YES1
BCL2L2	CREBBP	ERG	FOXL2	HNF1A	LATS2	NCOR1	PIK3R1	RET	STAG1	ZBTB2
BCL6	CRKL	ERRFI1	FOXO1	HNRNPK	LMO1	NEGR1	PIK3R2	RFWD2	STAG2	ZBTB7A
BCOR	CRLF2	ESR1	FOXP1	HOXB13	LRP1B	NF1	PIK3R3	RHEB	STAT3	ZFHX3
BCORL1	CSF1R	ETS1	FRS2	HRAS	LYN	NF2	PIM1	RHOA	STAT4	ZNF217
BCR	CSF3R	ETV1	FUBP1	HSD3B1	LZTR1	NFE2L2	PLCG2	RICTOR	STAT5A	ZNF703
BIRC3	CSNK1A1	ETV4	FYN	HSP90AA1	MAGI2	NFKBIA	PLK2	RIT1	STAT5B	ZRSR2
BLM	CTCF	ETV5	GABRA6	ICOSLG	MALT1	NKX2-1	PMAIP1	RNF43	STK11	
BMPR1A	CTLA4	ETV6	GATA1	ID3	MAP2K1	NKX3-1	PMS1	ROS1	STK40	
BRAF	CTNNA1	EWSR1	GATA2	IDH1	MAP2K2	NOTCH1	PMS2	RPS6KA4	SUFU	
BRCA1	CTNNB1	EZH2	GATA3	IDH2	MAP2K4	NOTCH2	PNRC1	RPS6KB1	SUZ12	
BRCA2	CUL3	FAM123B	GATA4	IFNGR1	MAP3K1	NOTCH3	POLD1	RPS6KB2	SYK	
RNA‡ content									
ABL1	BCL2	CSF1R	ESR1	EWSR1	FLI1	KIF5B	MSH2	NRG1	PAX7	RAF1
AKT3	BRAF	EGFR	ETS1	FGFR1	FLT1	KIT	MYC	NTRK1	PDGFRA	RET
ALK	BRCA1	EML4	ETV1	FGFR2	FLT3	MET	NOTCH1	NTRK2	PDGFRB	ROS1
AR	BRCA2	ERBB2	ETV4	FGFR3	JAK2	MLL	NOTCH2	NTRK3	PIK3CA	RPS6KB1
AXL	CDK4	ERG	ETV5	FGFR4	KDR	MLLT3	NOTCH3	PAX3	PPARG	TMPRSS2

BALLETT

Comprehensive Genomic Profiling: Classification



BIOLOGICAL CLASSIFICATION

Belgian Consensus:

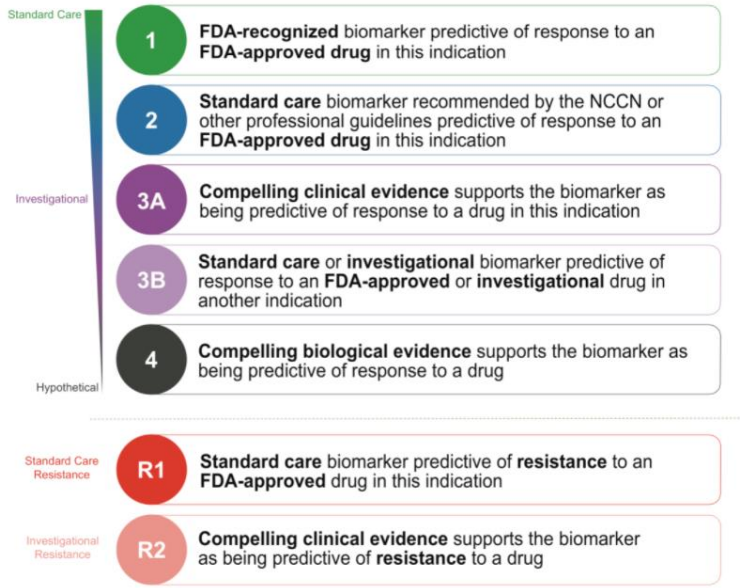
- **Benign or Likely Benign**
- **Variant of Unknown Significance (VUS)**
- **Likely Pathogenic**
- **Pathogenic**

CLINICAL CLASSIFICATION

AMP/ASCO/CAP

ESMO ESCAT

OncoKb



National Molecular Tumor Board

- **Aim:**

  To identify, interpret, discuss and/or recommend potential **therapeutic strategies based on molecular alterations**

- **Composition:**
  - Study coordinator
  - Medical oncologists
    - Interest in molecular oncology
    - Knowledge of interpretation genetic alterations, matched treatment options, clinical trial landscape
    - Knowledge of standard-of-care options : all subspecialities important !
  - Pathologist with interest in molecular oncology
  - Clinical Geneticist
  - Molecular biologist

  - Physicians and scientists with molecular expertise
  - Bioinformatician, Pharmacist, Ethicist
  - Students

National Molecular Tumor Board

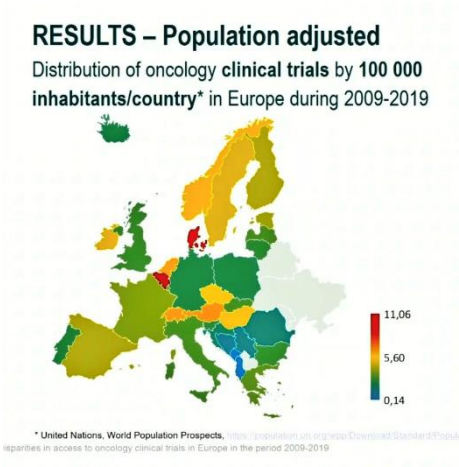
- **Identification** of alteration(s) of interest:
  - Pre-identification of level of pathogenicity by genomic test provider (e.g. Foundation Medicine in GeNeo) or by molecular biologists (e.g. in Ballett)
  - Identification of pathogenic variants with potential therapeutic relevance (MGTO or resistance) by MTB
- **Interpretation**:
  - Quality control metrics (e.g. coverage, DNA quantity, cellularity, variant allelic frequency VAF, …)
  - Test characteristics, sample type
  - Alteration type (e.g. SNVs, CNVs, rearrangements)
  - Potential alteration significance for diagnosis (e.g. specific rearrangements), treatment (e.g. treatment recommendation) or for patient (e.g. referral for germline testing)
  - Contextualize in specific molecular context/patient setting (importance of medical history + expert physician's)
- **Discussion**: Complementarity of the composition is key in the success of an MTB.
- **Recommendation**: Reimbursed treatment, clinical trial, MNP/CUP, off-label MGTO's, treatment resistance, referral for genetic counseling, reconsider pathology
  - Based on **level of evidence** (ESCAT, JCR, OncoKB)

Treatment recommendations

Reimbursed Treatments

Slow or no (agnostic) reimbursement

Clinical Trials



Patient and trial eligibility

MNP, CUP

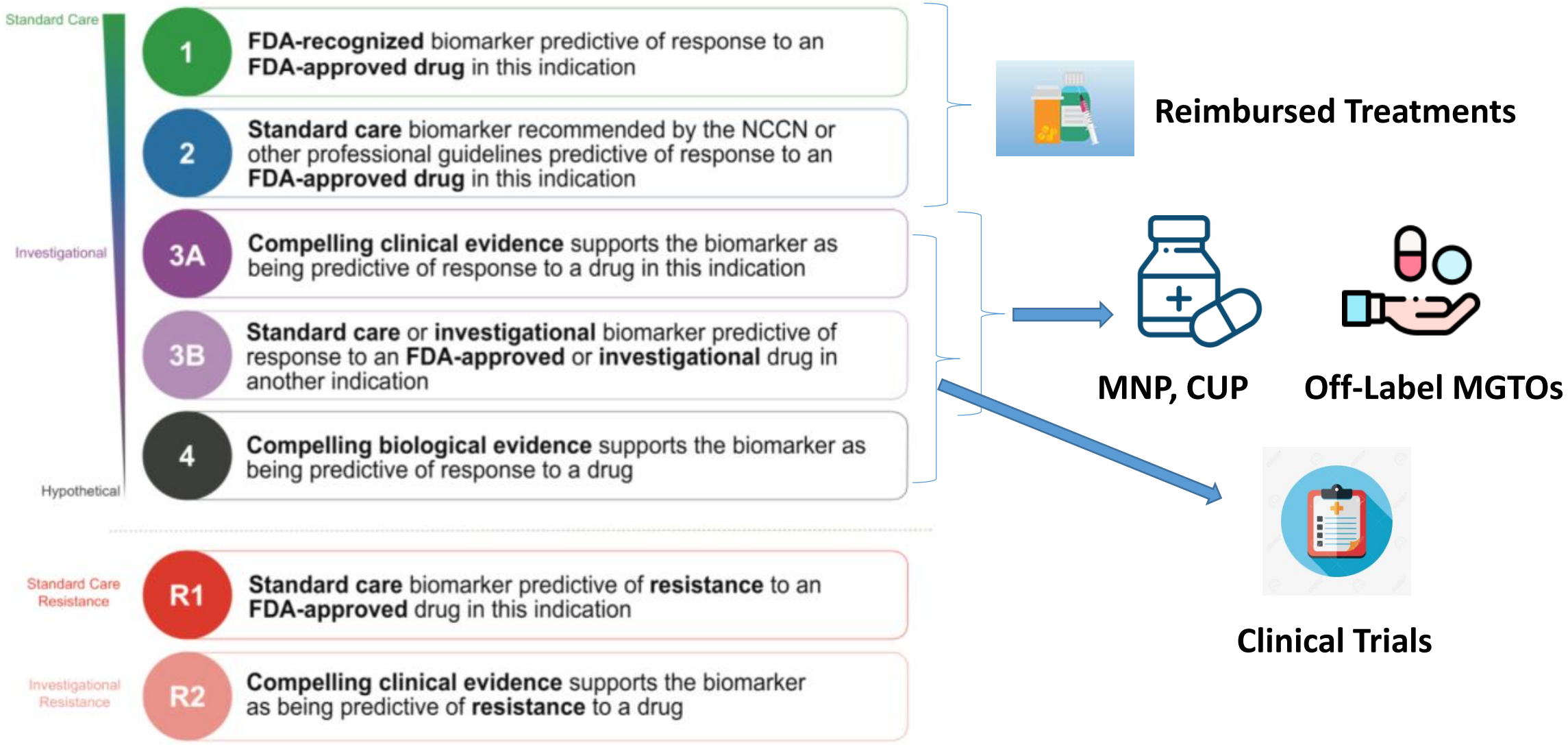
Company and product dependent
Long duration, high costs, no data generation

Off-Label MGTOs

Virtual reality for patients with Belgian insurance who aren't millionaires

BSMO

OncoKB Therapeutic Levels of Evidence: Optimal situation



OncoKB Therapeutic Levels of Evidence: Current Belgian Situation

Standard Care

1 **FDA-recognized** biomarker predictive of response to an **FDA-approved drug** in this indication

2 **Standard care** biomarker recommended by the NCCN or other professional guidelines predictive of response to an **FDA-approved drug** in this indication

Investigational

3A **Compelling clinical evidence** supports the biomarker as being predictive of response to a drug in this indication

3B **Standard care** or **investigational** biomarker predictive of response to an **FDA-approved** or **investigational** drug in another indication

4 **Compelling biological evidence** supports the biomarker as being predictive of response to a drug

Hypothetical

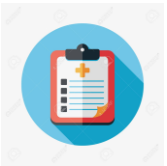
Standard Care Resistance

R1 **Standard care** biomarker predictive of **resistance** to an **FDA-approved** drug in this indication

Investigational Resistance

R2 **Compelling clinical evidence** supports the biomarker as being predictive of **resistance** to a drug

Reimbursed?...



Clinical Trials

MNP, CUP

Off-Label MGTOs?

Despite all efforts in target identification and clinical trial activity, drug access remains the bottleneck of Precision Medicine in Belgium

=>There is a need for sustainable access to MGTO

- Improve reimbursement procedures, decisions and timelines
- Increase clinical trial availability ?
- Increase access to medical need ?
- Framework for off-label MGTOs

Potential framework for off-label MGTOs

- Patients with advanced solid tumors
- Molecular-guided drug/regimen with at least 1 EMA approval in advanced solid tumor indication
- Evidence-based treatment recommendation by national MTB
- Systematic data collection

- Criteria for biomarker ?
  - OncoKb 1-2-3A?-(3B?)
  - ESCAT Tier I-II-IIIA?-(IIIB?)

Potential framework for off-label MGTOs

Patient

CGP

- Optimize target identification
- Avoid sequential testing and related tissue availability issues

National MTB

- MTB could be recognized as Governance Body in terms of recommending MGTO based on latest evidence and authorizing funding
- ≈Compermed for diagnostic tests

Off-label MGTO

- Sustainable access/funding of Off-label MGTO
- Increase equality in oncology drug access without social and medical selection

Data Collection

Thank YOU and acknowledgements




Kevin.punie@uzleuven.be

@kevinpunie

Prof. Dr. Jacques De Grève – Prof. Dr. Roberto Salgado

Precision Steering Committee

Current and previous BSMO Board members

Dr. Brigitte Maes

Dr. Philippe Aftimos

Members of the National Molecular Tumor Board

Sciensano – Cancer Centre : Marc Van den Bulcke – Gordana Raicevic

Toungouz – Julie Maetens – Maité De Hemptinne

Participating hospitals, investigators and teams

- Institut Bordet – UZ Gent – Jessa Hospital Hasselt – UZ Antwerpen – AZ Delta Roeselare – GHd Charleroi - AZ St-Jan Brugge – UZ Brussel – UZ Leuven – AZ Turnhout – ASZ Aalst – AZ Nikolaas – ZN Antwerpen – GZ Antwerpen

Consortium of Belgian NGS Labs

- UZ Gent – Jessa Hospital Hasselt – UZ Antwerpen – AZ Delta Roeselare – AZ St-Jan Brugge – IPG – UZ Leuven – UZ Brussel – CellCarta

Roche – Foundation Medicine

Illumina

OncoDNA

PierianDx