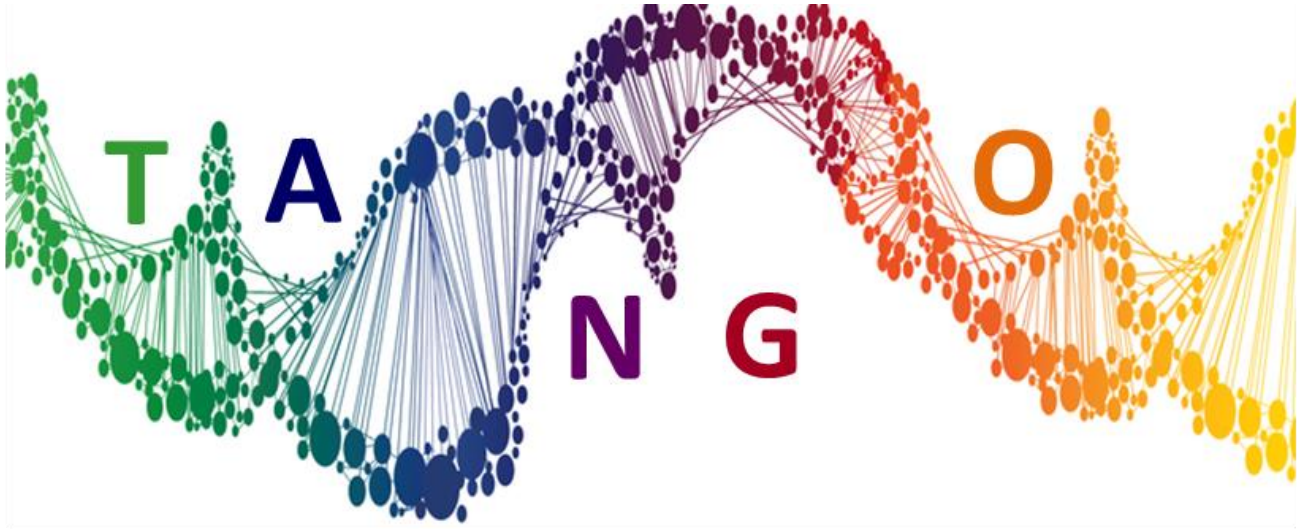


Technology Assessment of Next Generation Sequencing in Personalized Oncology

4rd TANGO symposium

October 28, 2020

Valesca Retèl

Edwin Cuppen

ZonMw

KWF KANKER BESTRIJDING

Zilveren Kruis

achmea

Welcome!

	TOPIC PRESENTATION	SPEAKERS
13:00 - 13:15	Welcome & Update	Edwin/Valesca
13:15 - 13:45	Genetics in oncology: a focus group study on recontact	Noor/Annelien/Wim
13:45 - 14:15	Development and validation of patient-level micro-simulation model for Cost effectiveness analysis of Immunotherapy in the Netherlands	Zakile/Veerle
14.15 - 14.25	Break	
14:25 - 14:55	The validation and implementation of WGS in the clinical practice	Rogier/Marc
14:55 - 15:40	Results for advanced lung cancer obtained in the framework of the TANGO	Joanne/Joachim/ Joris/Emile
15:40 - 15:50	Break	
15:50 - 16:20	Clinical response to systemic therapy in metastatic melanoma; towards a WGS-based biomarker	Jessica/Fons
16:20 - 16.50	Early cost-effectiveness modelling of WGS compared to standard diagnostics in NSCLC	Martijn/Manuela
16:50 - 17:00	Break	
17:00 - 17:30	Modelling the organization of care for WGS	Michiel/Erik
17:30 - 18:00	Summary & Closing	Edwin/Valesca

Online “rules”

Rationale

1. Large variability of sequencing/NGS tests in the Netherlands
2. Increased use of immunotherapy, while this is effective for only a small part of the patients

→*How can we optimize the use of NGS in the Netherlands?*

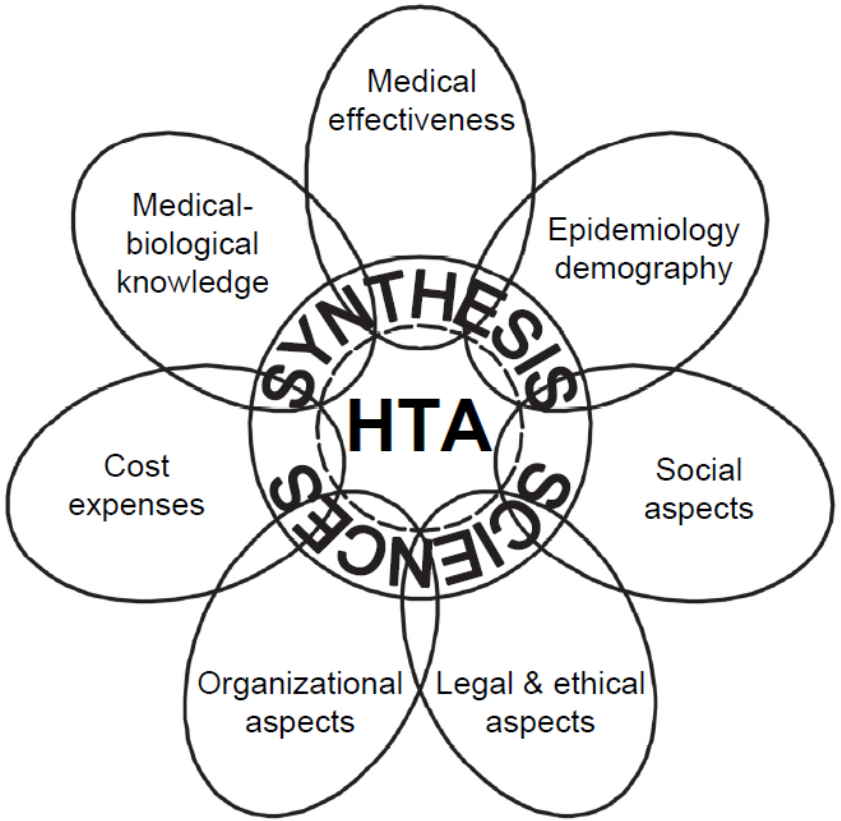
Technology Assessment of Next Generation Sequencing in Personalized Oncology

TANGO

Technology Assessment

HTA: broad evaluation of new or existing health technologies
-Clinical effectiveness
-Financial (cost-effectiveness)
-Patient related
-Ethical/legal
-Organizational

→ Information for policy making
→ Decision making for groups of patients



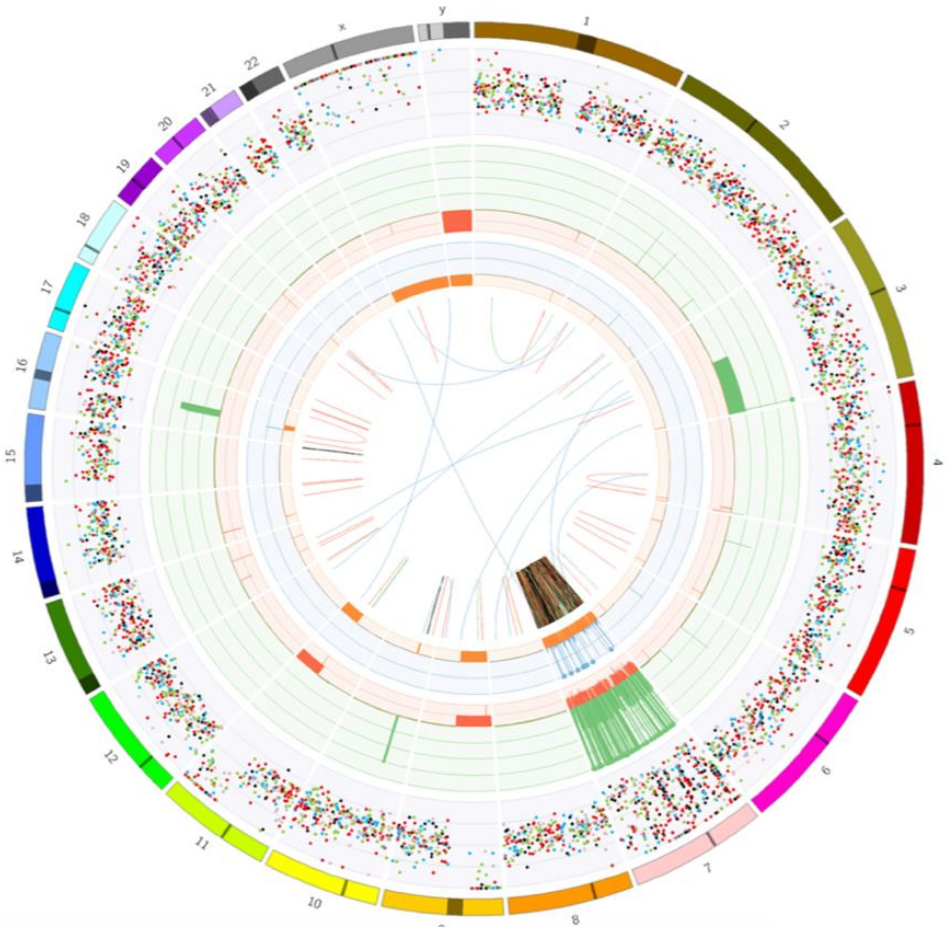
TA**NGO**

Next Generation sequencing in Oncology

-> focus = Whole Genome Sequencing: complete tumor DNA

- Tests for all relevant mutations in 1 experiment
- To prescribe the most optimal therapy
- This could improve survival with less toxicity
- Assist in controlling healthcare costs :

→ Offering (often expensive) treatment to only those likely to benefit.



Hartwig MEDICAL FOUNDATION

Purpose TANGO

A) to expand molecular profiling of tumors in order to improve immune- and targeted treatment selection and outcomes in patients with advanced NSCLC (and melanoma) **WP**: 1,2

B) to project long-term outcomes like cost-effectiveness, budget impact, and relevant patient & organizational issues related to the introduction of WGS compared to standard diagnostics. **WP**: 3,4,5,6

Timeline TANGO

2015
Start writing proposal

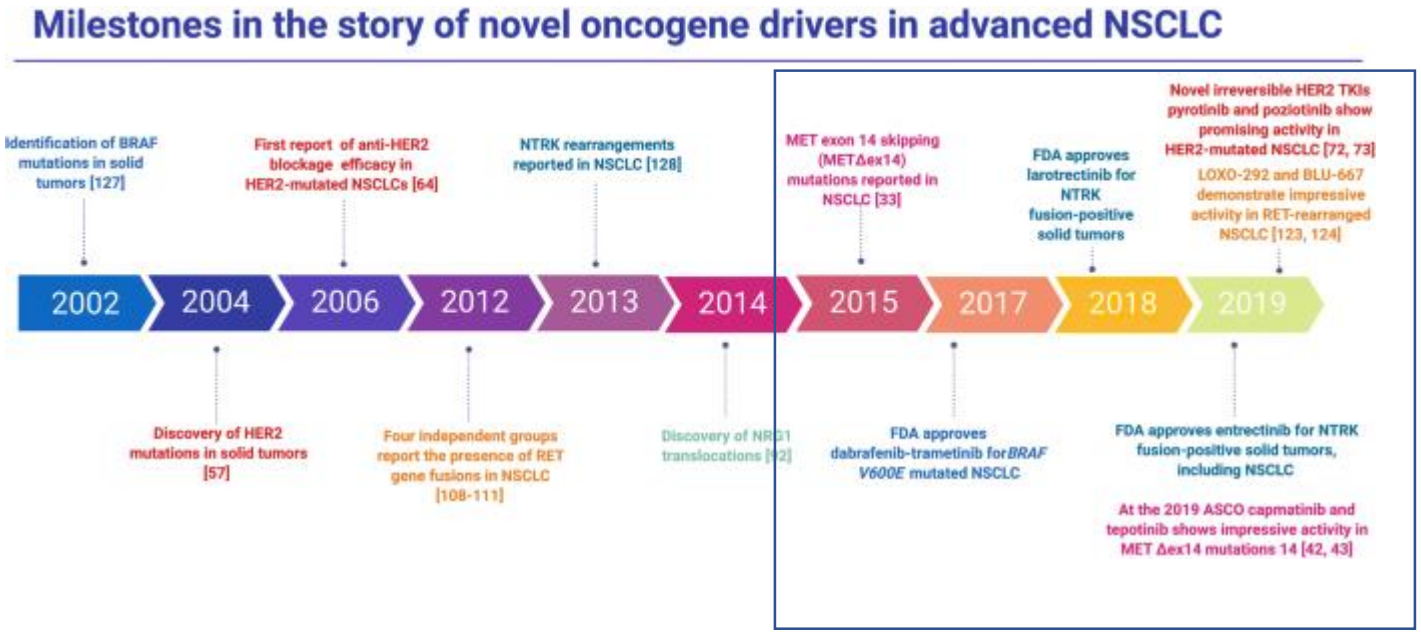
2017
Start TANGO
Jan 1st

2018
Implementation
GDPR

2019
Start melanoma

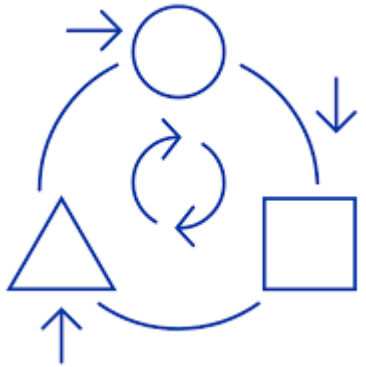
2020
COVID-19

2021
Stop TANGO
June 1st

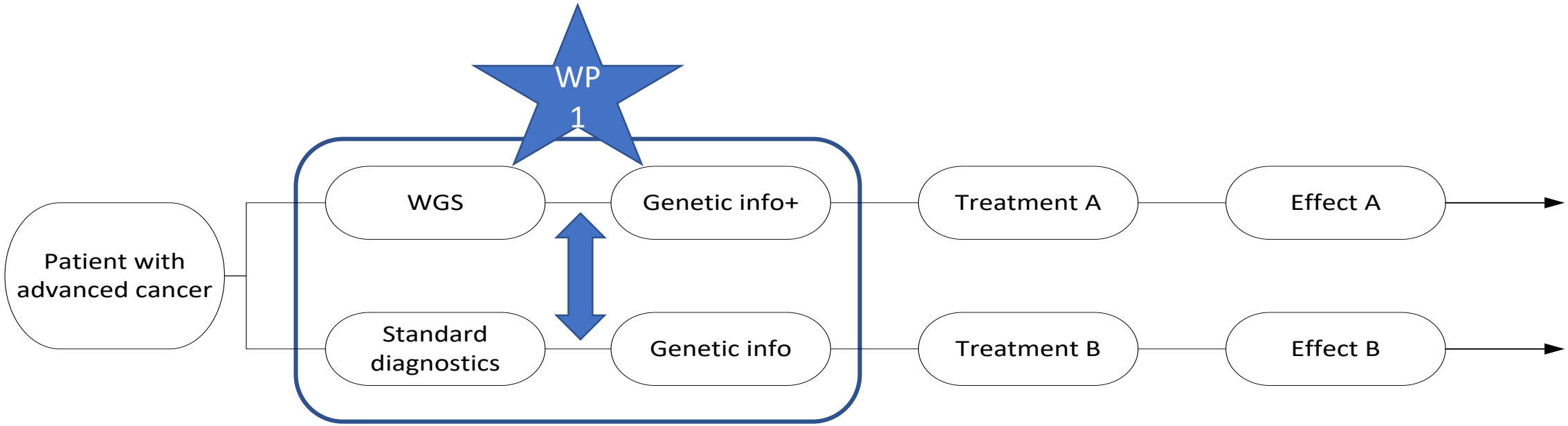


Russo, Lung Cancer, 2020

Continuous anticipation!



Diagnostic/patient pathway – micro level



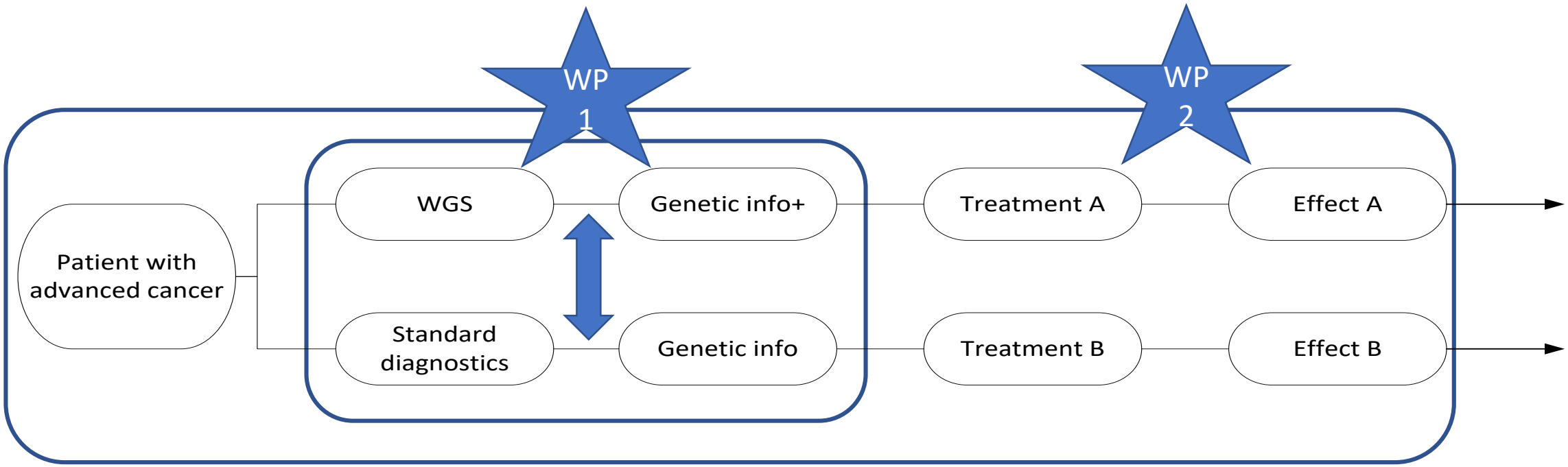
WP1	diagnostic pathway	-> based on CPCT-02
WP2	diagnostics + treatment + survival	-> based on CPCT-02
WP3	diagnostics + treatment longer FU	-> based on registry data

WP1: Molecular tumor diagnostics by WGS versus current diagnostics

Edwin Cuppen

Aims:	NSCLC	melanoma
-To identify the added value of WGS compared to SoC		
-To compare the total costs of WGS compared to SoC		
-To address the logistical and data challenges related to implementation of WGS		

Diagnostic/patient pathway – micro level



WP1	diagnostic pathway	-> based on CPCT-02
WP2	diagnostics + treatment + survival	-> based on CPCT-02
WP3	diagnostics + treatment longer FU	-> based on registry data

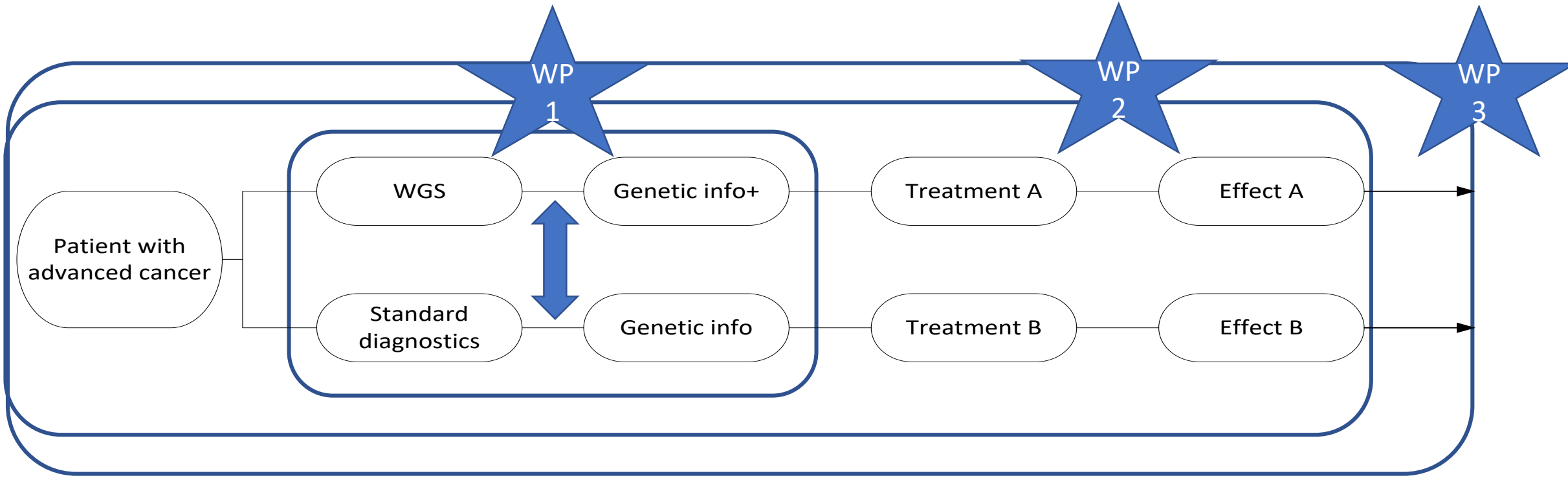
WP2: Treatment selection based on WGS vs current diagnostics

Joachim Aerts

Aim: to demonstrate value of immune- and targeted treatment selection and outcomes using WGS versus SoC in patients diagnosed with advanced NSCLC and melanoma

	NSCLC	melanoma
- 400 Biopsies		
- Primary endpoint: PFS		
- Secondary endpoints: RR		
- Biomarker for non-response IT		

Diagnostic/patient pathway – micro level



WP1	diagnostic pathway	-> based on CPCT-02
WP2	diagnostics + treatment + survival	-> based on CPCT-02
WP3	diagnostics + treatment longer FU	-> based on registry data

WP3: Prediction of population-based long-term health benefits and harms

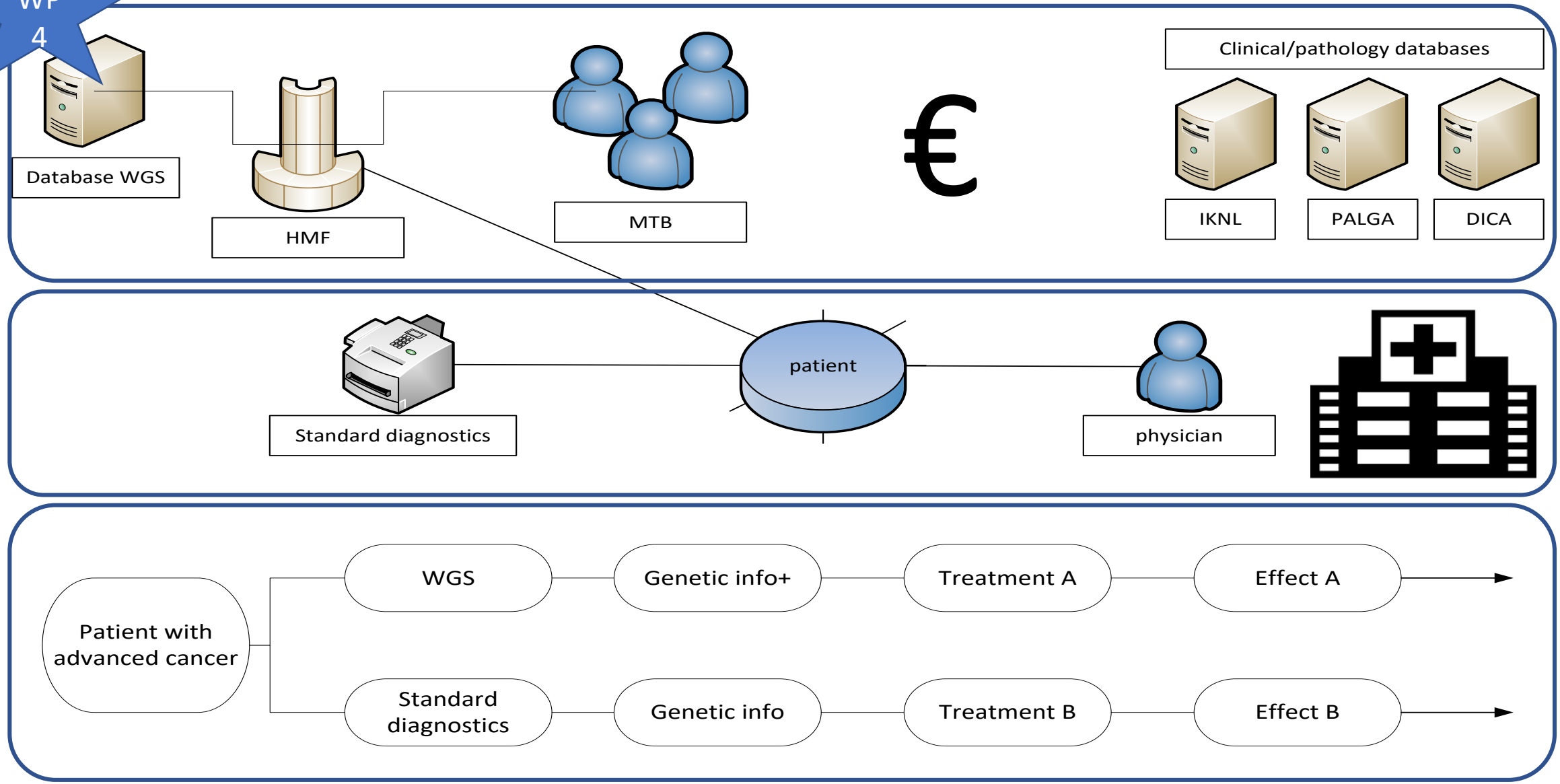
Veerle Coupé

Aim: to predict long-term health outcomes of WGS-based immunotherapy versus SoC for the Dutch advanced NSCLC and melanoma patient population

Strategies:	NSCLC	melanoma
- Current diagnostics, treatment & survival		
- Model incl WGS-based immunotherapy		
- Cost-effectiveness including WGS BM		
- (PET/CT-based tumor growth model)		

Diagnostic/patient pathway – system level

WP 4



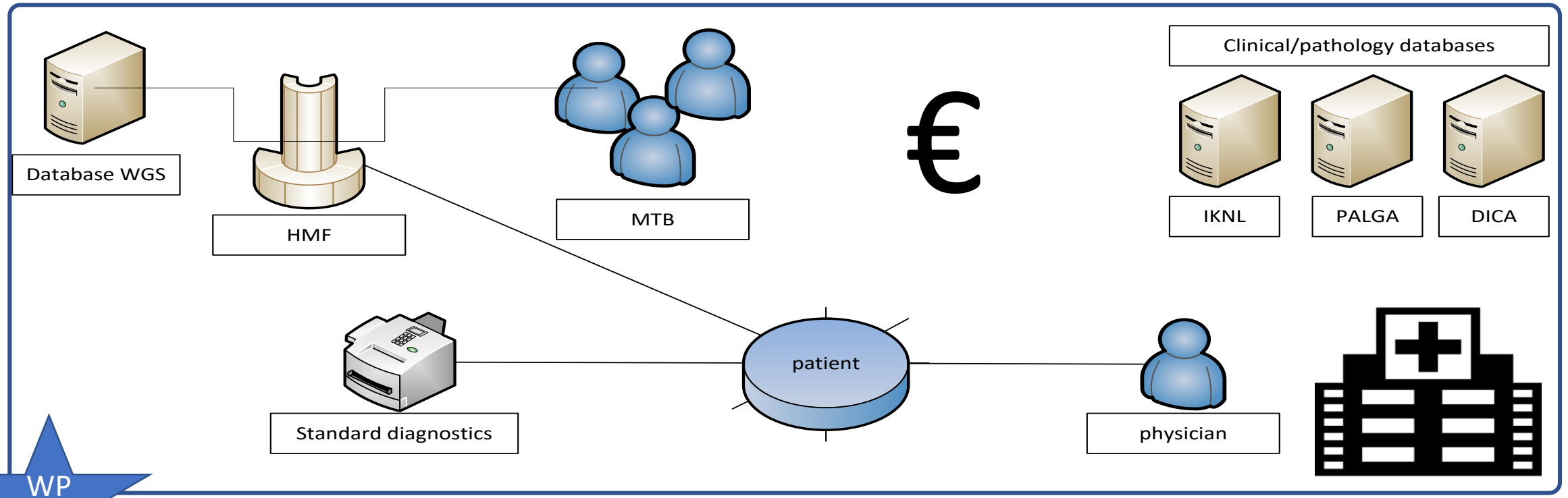
WP4: Tumor-overarching cost-effectiveness modeling

Manuela Joore

Aim: to provide information on the cost-effectiveness, budget impact and wider public benefits of WGS versus SoC for advanced NSCLC and melanoma patients.

	NSCLC	melanoma
- cost-effectiveness		
- Budget impact		
- Wider public benefits		
- Scenario’s (with WP5)		
- Quality of life		

Diagnostic/patient pathway – system level



WP 5

WP5: Nation-wide organization of WGS

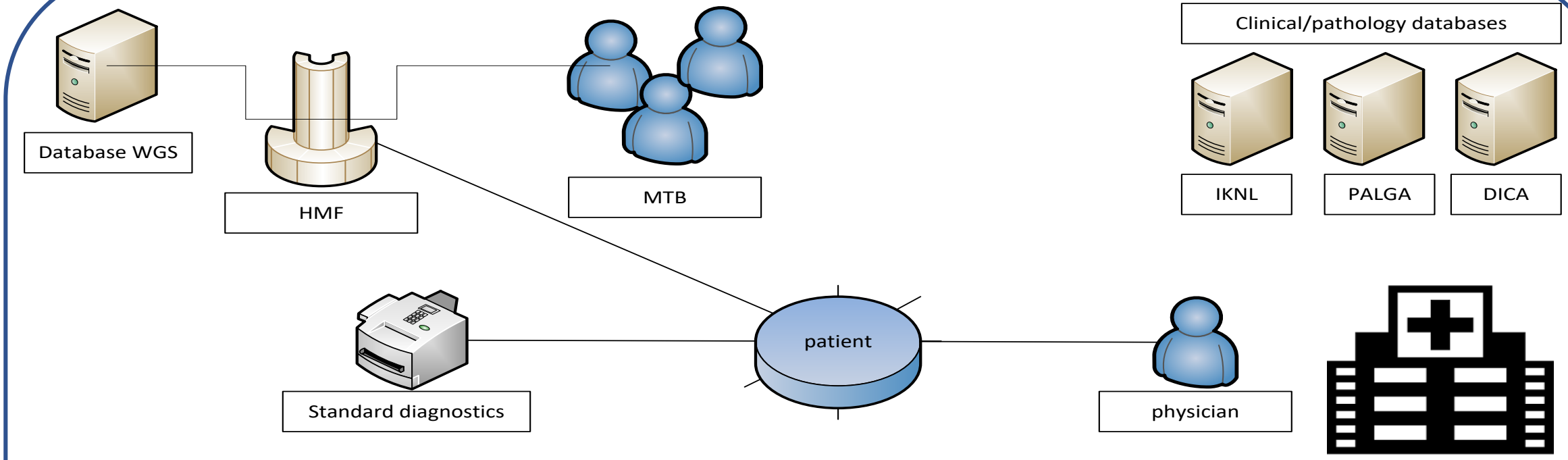

Maarten IJzerman

Aim: to provide insight in the consequences of implementation of WGS

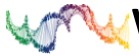
- Identify requirements for developing the simulation model
- Select the most appropriate modeling approach
- Map the current process of care
- Identify dynamic interactions and decisions of stakeholders
- Explore implementation of WGS in terms of access and treatment

Responsible implementation – ELSI

WP 6



WP6: Ethical, Legal and Societal Implications (ELSI) of WGS


Wim van Harten

Aim: to investigate whether medical professionals carry a responsibility to ‘re-contact’ their patients

-ethical:

- -systematic ‘review of reasons’
- -2 semi-structured focus groups (patients & stakeholders)

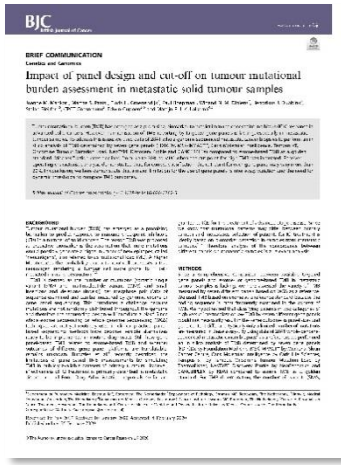
-legal:

- -systematic review of legal documents
- -in-depth study on the duty to re-contact

-ELSI:

- -Synthesis of findings in concluding paper with practical recommendations

Publications TANGO



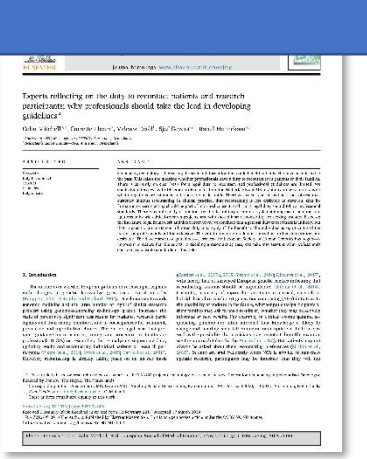
Mankor ea

Van de Ven ea

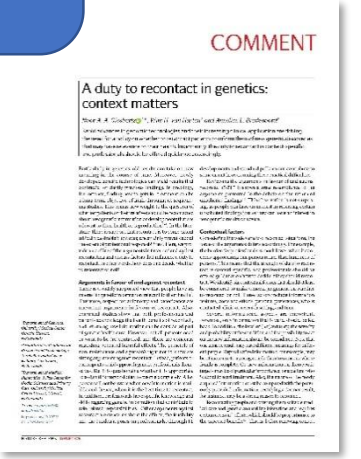
Many more in the pipeline
Including TANGO "design" paper: deadline in 2 weeks

Ploem ea

Butter ea



Mitchell ea



Giesbertz ea

Let’s start!

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Online “rules”

raise hand

Employees

TANGO

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Participating Centers

Dit project (846001002) wordt mogelijk gemaakt door

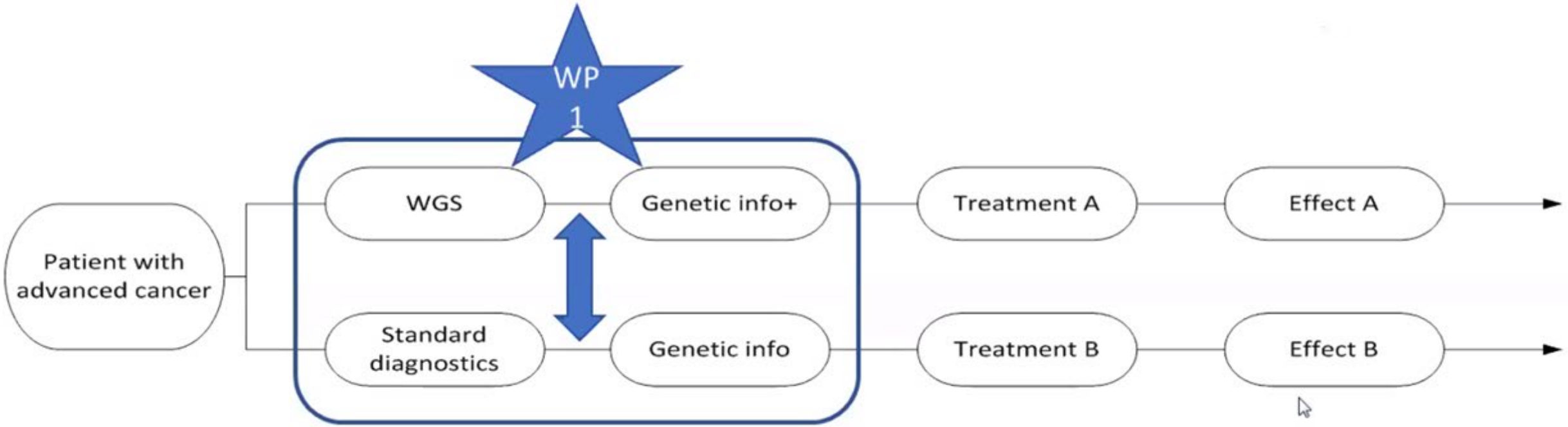
WP1: Molecular tumor diagnostics by WGS versus current diagnostics

PIs: Marc van de Vijver and Edwin Cuppen

PhD: Rogier Butter

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Work package 1: Three aims as previously described



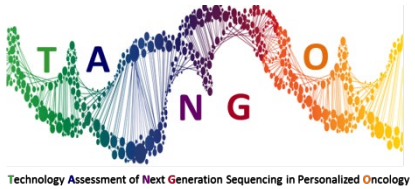
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Work package 1: Three aims as previously described

- To address the logistical and data challenges related to implementation of WGS
- To identify the potential added therapeutic value of WGS
- To compare the total costs of WGS compared to Standard of Care

Work package 1: Three aims previously described

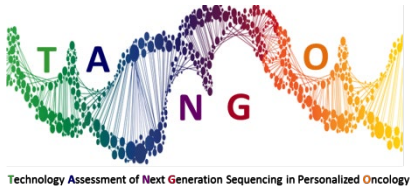
Logistical and data challenges	**How should WGS test results be presented to clinicians: Molecular Tumor Boards**
Potential added therapeutic value of WGS	**Compare test results WGS to standard of care**
Compare the total costs of WGS compared standard of care	**Previously investigated by Clémence Pasmans as part of this WP**



Potential added value of WGS: Paired comparison with standard tests

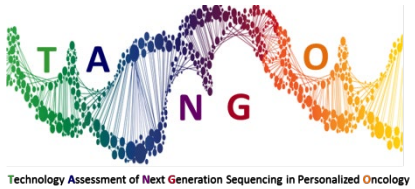
Inclusion criteria

- Patients were included in the CPCT-02
- Patients were diagnosed with NSCLC or Melanoma (independent of therapy)
- WGS was performed successfully → Available from HMF
- Routine molecular test results available → Retrospectively collected from patient records



Routine molecular test results retrospectively collected from centers with high volume inclusions

	NSCLC	Melanoma
Amsterdam UMC	5	50
Erasmus MC	20	72
NKI-AvL	97	30
Meander MC	23	2
UMC Utrecht	0	17
	138	171



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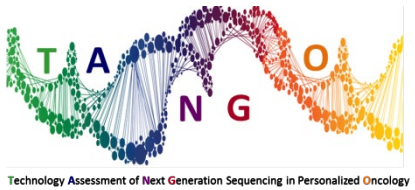


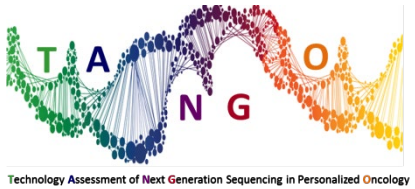
Preliminary results of NSCLC; awaiting large cohort of melanoma patients from one center

Breakdown Molecular diagnostics in included patients (n=138)	
1x WGS 1x Routine Molecular Test	88
1x WGS 2x Routine Molecular Test	26
1x WGS 3x Routine Molecular Test	14
1x WGS 4x Routine Molecular Test	3
2x WGS 1x Routine Molecular Test	3
2x WGS 2x Routine Molecular Test	4

Patients divided in four subgroups dependent on time and location of biopsy

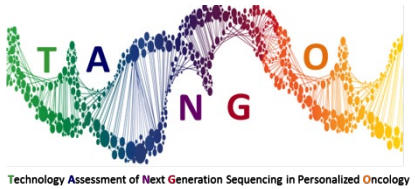
- Subgroup A – Biopsy for WGS and Routine test at same time and site
- Subgroup B – Biopsy for WGS and Routine test at different time but same site
- Subgroup C – Biopsy for WGS and Routine test at different time and site

Patients with repeated tests in multiple subgroups



Breakdown subgroup A (same site+time) and subgroup B (same site, different time)

		Subgroup A (n=104)	Subgroup B (n=54)
Site biopsy	Lung	39	16
	Lymph node	23	16
	Liver	17	13
	Pleural	9	2
	Bone	4	1
	Soft tissue	4	4
	Adrenal	3	0
	Other	5	2
Routine molecular test	NGS – Illumina	31	26
	NGS – Iontorrent	63	17
	MassArray	7	7
	smMIP – (PATH)	3	4
Mean interval Routine test – WGS		0 days	313 days (8-1264)



Breakdown Subgroup C (different site and different time)

Breakdown subgroup C (n=55)			
		WGS (n)	Routine test (n)
Site biopsy	Lung	16	11
	Bronchus	7	3
	Lymph node	7	14
	Liver	6	3
	Pleural	2	3
	Pleural effusion	1	6
	Bone	6	2
	Soft tissue	4	4
	Adrenal	2	4
	Other	3	5
Routine molecular test	NGS – Illumina		34
	NGS – Iontorrent		6
	MassArray		13
	smMIP – (PATH)		0
Median interval Routine test – WGS		240 days (15-995)	

Analysis ongoing: Discordance between WGS and Routine Molecular Tests

Is mutation X present in both WGS and the routine test within the same patient?

Analysis ongoing: Discordance between WGS and Routine Molecular Tests

- Gene mutation not reported in medical record
- Specific area of gene not covered by panel
- Allele frequency too low
- True discordance

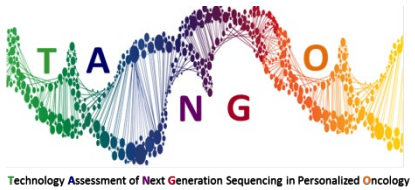
EGFR/KRAS in subgroup A as an example: Unlikely to be not reported or uncovered by panel + no bias of time and site

EGFR	Reference Test		
WGS	Positive	Negative	
Positive	60	14	74
Negative	4	x	
	64		

Agreement: 0.81

KRAS	Reference Test		
WGS	Positive	Negative	
Positive	19	0	19
Negative	0		
	19		

Agreement: 1.0



In some centers EGFR not entirely covered: Good agreement in hotspots

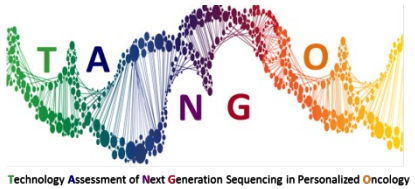
55242464 - Exon 19 deletion → TKI

55249071 - p.Thr790Met → TKI

55259515 - Exon 21 p.Leu858Arg → TKI

Genomic Location	WGS (n)	Routine (n)
55242464	17	18
55249071	17	18
55259515	11	12

Agreement: 0.97



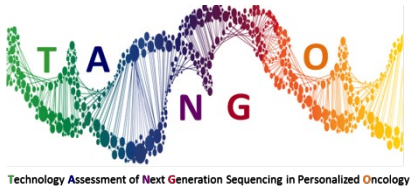
Conclusion and plan WGS vs. Routine Tests

NSLSC

- Contact centers: protocol for reporting mutations and coverage specific genes
- Sequencing depth, allele frequency in discordant cases

Melanoma

- Awaiting data from one center
- Large part of cohort BRAF-only routine testing

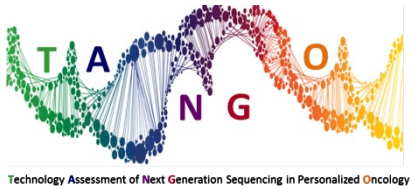


Technology Assessment of Next Generation Sequencing in Personalized Oncology

Implementation of WGS results in de clinical practice: Molecular Tumor Boards

Objective: To assess the minimum demands of a Molecular Tumor Boards (MTBs)

to discuss complex molecular diagnostic results (such as WGS)



Implementation of WGS results in de clinical practice: Molecular Tumor Boards

Objective: To assess the minimum demands of a Molecular Tumor Boards (MTBs) to discuss complex molecular diagnostic results (such as WGS)

- Questionnaire to pathologists, pulmonologists, oncologists and KMBP-ers
- Academic and peripheral centers
- Formulate an advise on MTBs

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Implementation of WGS results in de clinical practice: Molecular Tumor Boards

Five topics

- Participants
- Knowledge of participants
- Content of MTB
- Organization MTB
- Added value MTB

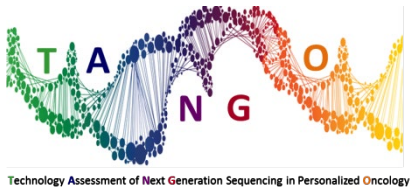
Five answers possible per statements

- Fully disagree
- Disagree
- Neutral
- Agree
- Fully agree

Technology Assessment of Next Generation Sequencing in Personalized Oncology

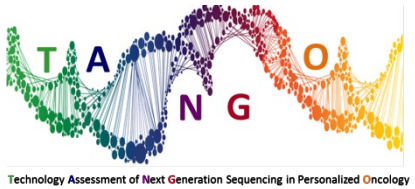
Implementation of WGS results in de clinical practice: Molecular Tumor Boards

Topic	Example statement
Participants	'The patients' specialist should always be part of the MTB'
Knowledge of participants	'I have sufficient knowledge for the interpretation of complex molecular diagnostics such as whole exome- genome sequencing'
Content of MTB	'The MTB should only discuss results which can be treated accoring to the guidelines'
Organization MTB	'A MTB in peripheral center should always be joined by an academic partner'
Added value MTB	'MTBs result in better cancer care'



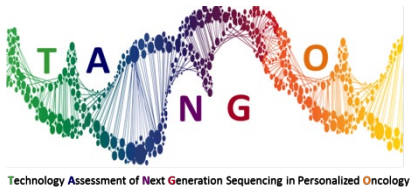
Plan WP1: Molecular Tumor Boards

Month	Progress
November	Distribution questionnaires
December	Collection of questionnaires
January	Data Analysis
February – March	Constructing advise/paper



Plan WP1: WGS vs. Routine tests

Month	Progress
November	**NSCLC:** Finish Analysis **Melanoma:** Receive final data
December	**NSCLC:** Discuss/ improve results **Melanoma:** Analysis
January	**NSCLC:** Final Analysis / Draft paper **Melanoma:** Final Analysis/ Draft paper
February – March	**NSCLC:** Draft paper **Melanoma:** Draft paper



Acknowledgements

Everyone from TANGO

Judith Herder (Meander)

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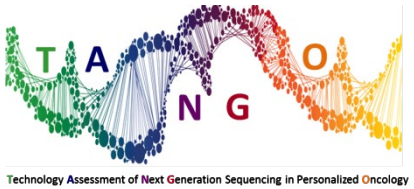
Jan von der Thusen (EMC)

Astrid van der Veldt (EMC)

Paul Roepman (HMF)

Teodora Radonic (Amsterdam UMC)



Whole-genome correlates of response to PD-1 blockade in non-small cell lung cancer

TANGO symposium

October 2020

Joanne Mankor & Joris van de Haar

Hartwig MEDICAL FOUNDATION

CPCT Center for Personalized Cancer Treatment

TANGO Technology Assessment of Next Generation Sequencing in Personalized Oncology

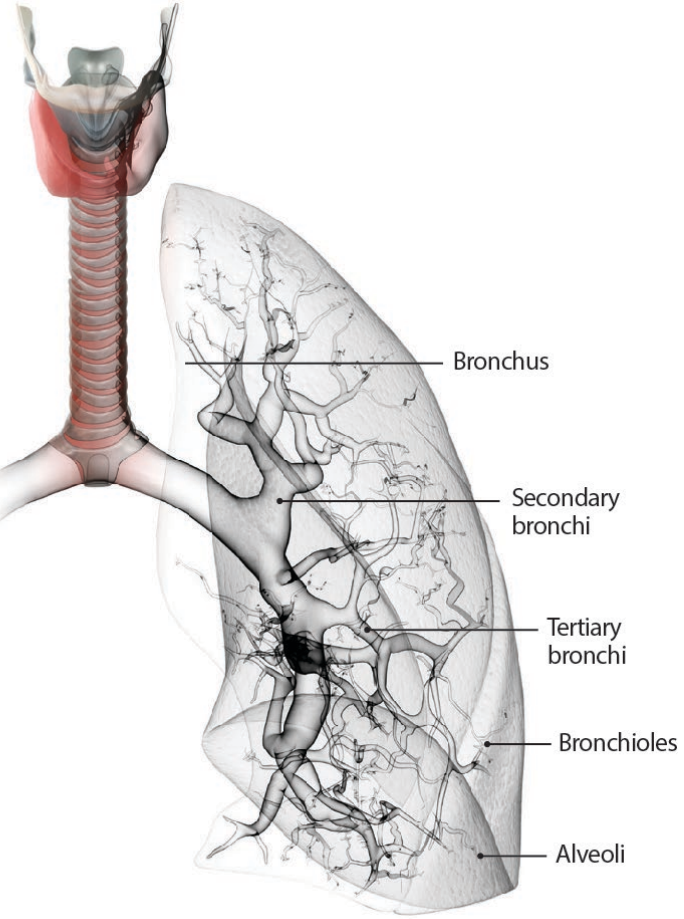
Outline presentation

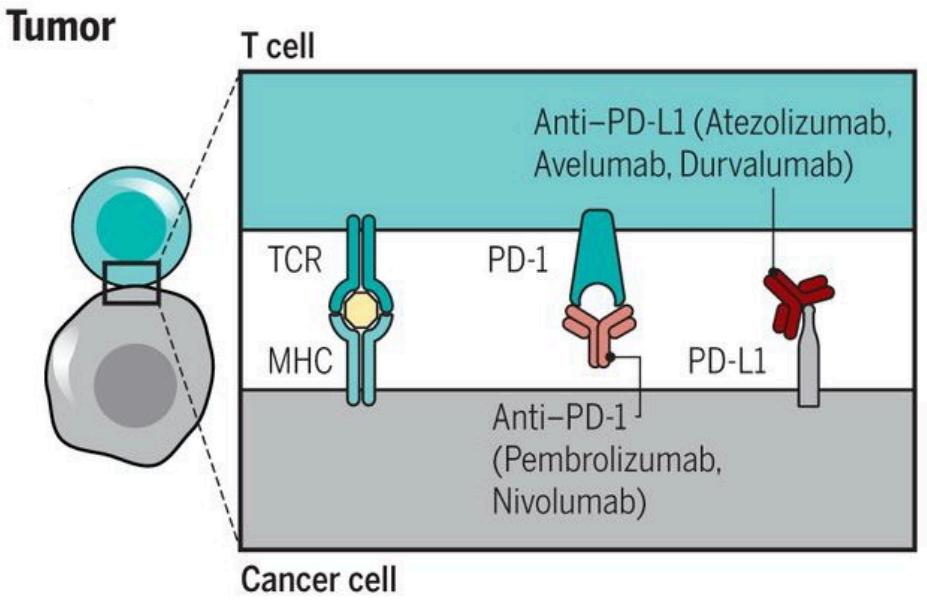
1) Clinical data of the TANGO NSCLC cohort, biomarker analysis in a discovery and a validation cohort (Joanne)

2) Validation of previously published biomarkers and discovery of novel biomarkers in the full cohort (Joris)

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Blocking the PD-1/PD-L1 axis has been shown to yield remarkable responses in NSCLC





Ribas et al. Science 2018

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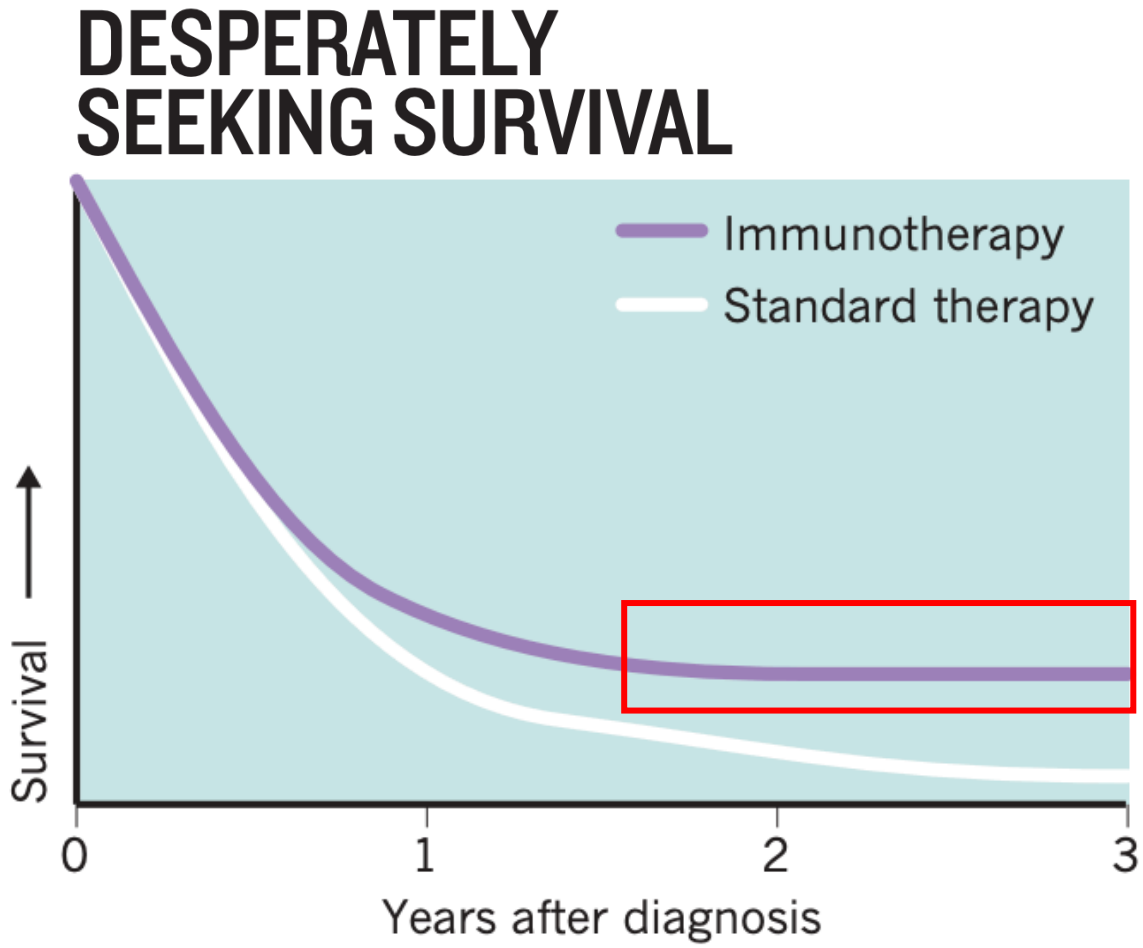
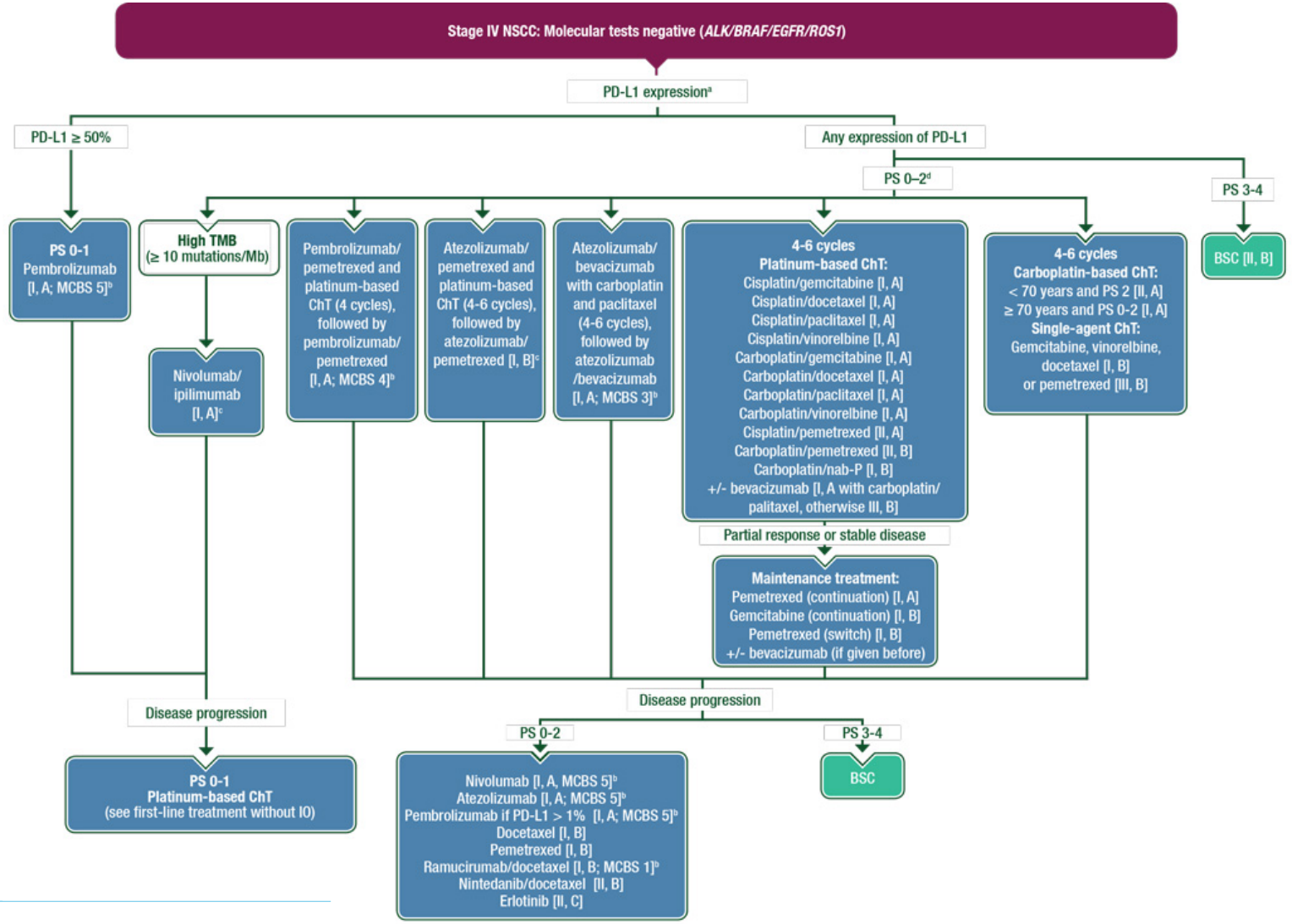
But immune checkpoint inhibitor treatment has its limitations: only the minority of patients benefit



Adapted from: Ledford, Nature New Feature, 2016

Current treatment regimen: overview



ESMO guidelines on NSCLC treatment 2019

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How to select for patients that will benefit from aPD-1 treatment, prior to treatment?

1) Who will benefit from aPD-1 monotherapy?
2) Who will not benefit from (the addition) of aPD-1 at all?

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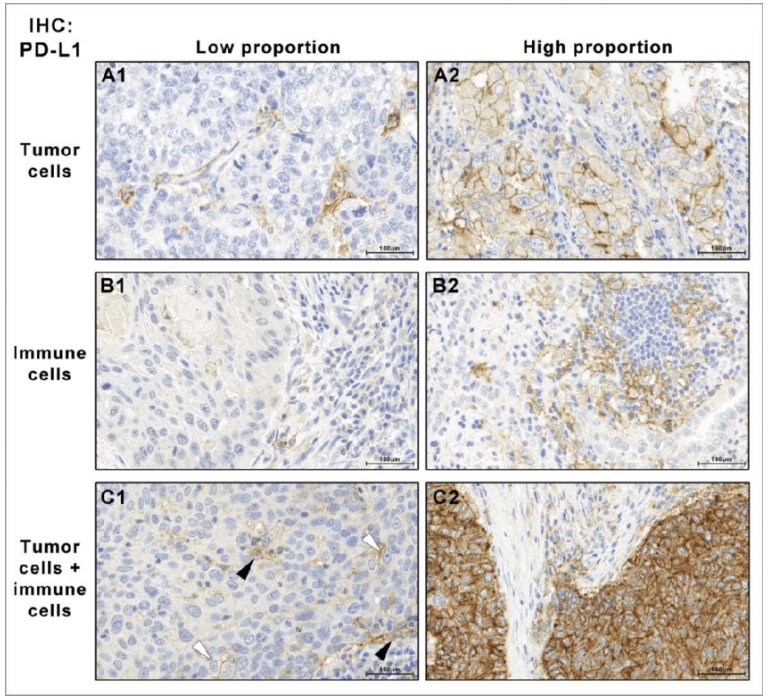
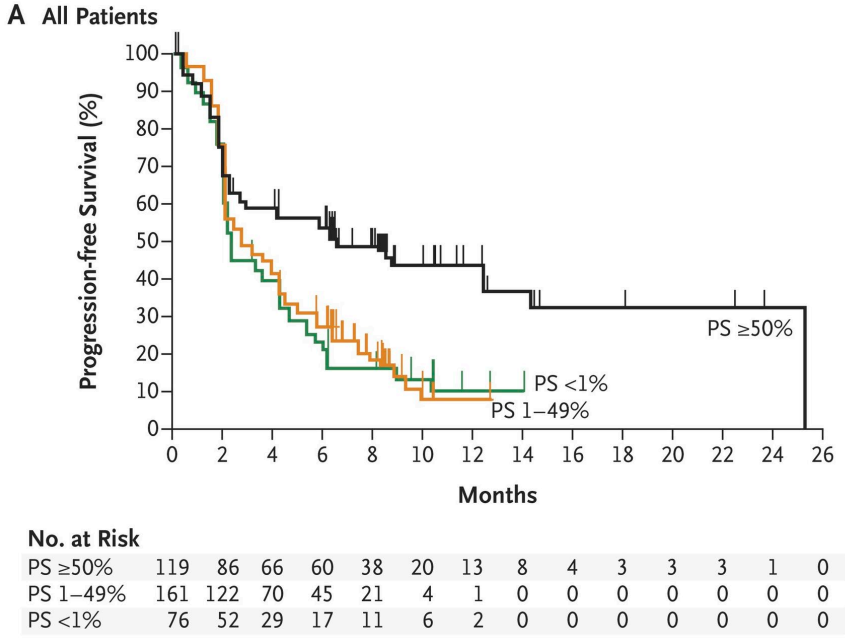
PD-L1 protein expression on tumor and immune cells is the only FDA approved biomarker for ICI treatment selection





Garon et al. NEJM 2015

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Milestones WP2: Demonstrate the value of WGS for immunotherapy treatment selection for NSCLC *and melanoma*

- Discovery of genomic correlates of ICI response
  - *Can the tumor genome help us understand mechanisms responsible for ICI response?*

- Identify potential biomarkers for patient stratification
  - *Can the tumor genome be a source of predictive biomarkers for ICI response?*

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Patient selection for TANGO (from CPCT-02)

CPCT inclusion 2016-2019	HMF database	HMF data request for TANGO (DR008)	TANGO database	Full cohort WGS analysis
N = **528 patients** NSCLC included in CPCT-02	N = 381 patients N = 397 biopsies In HMF DB Passed QC: N = **297 patients** N= 311 biopsies	N = 83 aPD-1 treatment monotherapy	N = 81 Immunotherapy	N = 70 Immunotherapy monotherapy
		N= 29 Combination Tx	N= 10 Chemo/IO	
		N = 35 Targeted Therapy		
		N = 2 Chemotherapy		
		N = 4 Unknown		

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Baseline characteristics

Characteristic	Value
N	70
Median age (year)	63
Male sex - no (%)	32
ECOG performance score - no (%)	
0	18 (26)
1	40 (57)
2	7 (10)
>2	1 (1.4)
Unknown	4 (5.7)
Smoking status - no (%)	
Never	14 (20)
Current	15 (21)
Former	41 (59)
Pack Years - mean (SD)	29 (19)
Treatment - no (%)	
Nivolumab	47 (67)
Pembrolizumab	23 (33)
Line of treatment	
1	11 (16)
2	51 (73)
3	5 (7.1)
4	2 (2.9)
Unknown	1 (1.4)
Best Overall Response - no (%)	
PR	15 (21)
SD	16 (23)
PD	39 (56)
PD-L1 expression - no (%)	
<1%	27 (39)
1-50%	14 (20)
>50%	13 (19)
Unknown	16 (23)

Challenges in biomarker research for ICI treatment

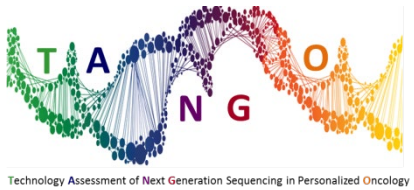
- Availability of (tumor) material
- Risks vs benefit for patients involved
- Costs of (molecular) testing

- Ideally, predictive biomarkers should be validated in prospective cohorts

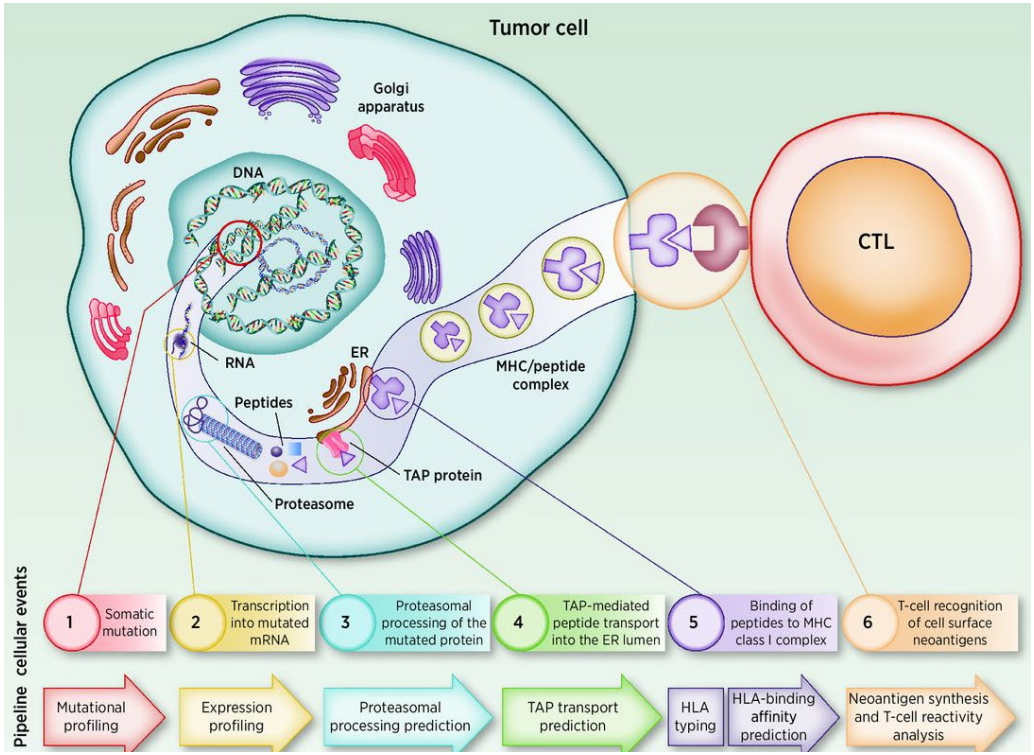
Several genomic biomarkers for ICI responses in NSCLC have been studied

Biomarker	Description	Reference
(Non-synomous) mutations (SNVs, MNVs, short INDELS): Tumor mutational burden (TMB)	(non-synonymous) mutations per Mb tumor genome/ exome sequenced	*Rizvi et al. Science 2015, Samstein et al. Nat Gen 2019, Chan et al. Ann Onc 2019*
Structural variants (SVs)	Frameshifts, translocations Copy number alterations/ aneuploidy, gene fusions	*Davoli et al. Science 2017, Yang Nat Med 2019*
Antigen presentation machinery defects	HLA diversity HLA LOH, B2M mutations, JAK1-JAK2 loss of function mutations	*McGranahan et al. Cell 2017, Sade-Delman et al. Nat Comm 2017*
Mutational signatures	Smoking signature: C>A transversions	*Alexandrov et al. Sience 2015, Anagnostou et al. Nat Can 2020*
Receptor tyrosine kinase (RTK) mutations	Enrichment activating RTK mutations in non-responders	*Anagnostou et al. Nat Can 2020*

Can a combined biomarker of mutational burden and tumor aneuploidy be a predictor of aPD-1 response?



Tumor mutational burden: Number of (non-synonymous mutations) per megabase sequenced



Chabanon et al. CCR 2016

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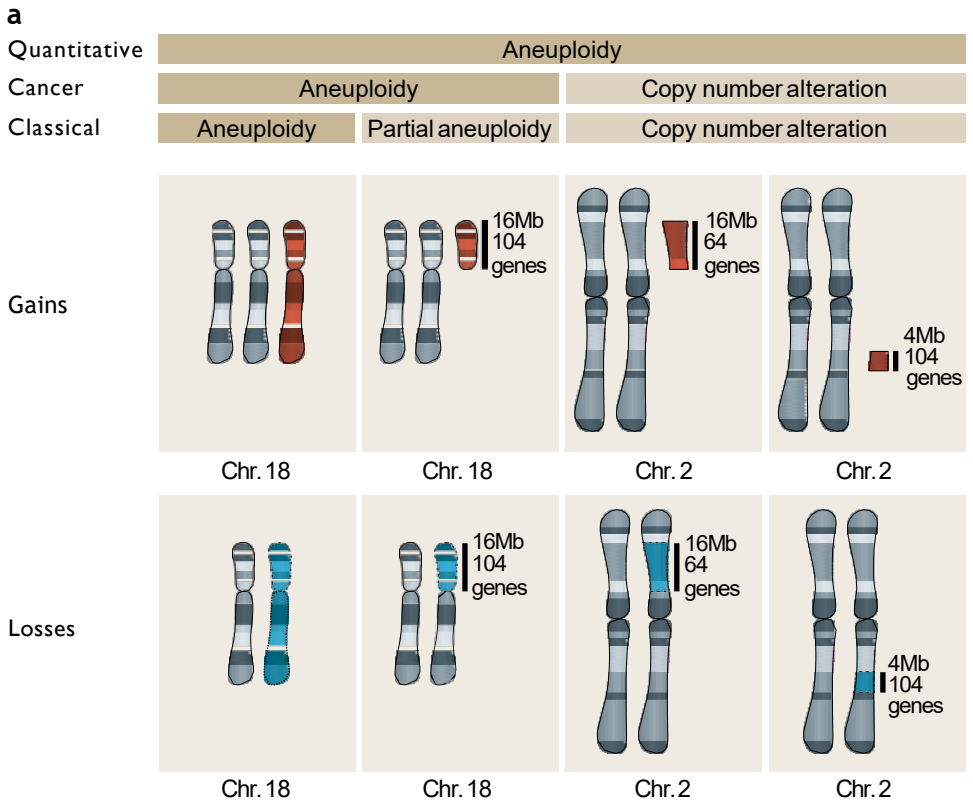
Tumor aneuploidy: chromosomal instability can lead to an uneven number of chromosome(s)(arms)



Ben-David et al. Nat Gen 2019

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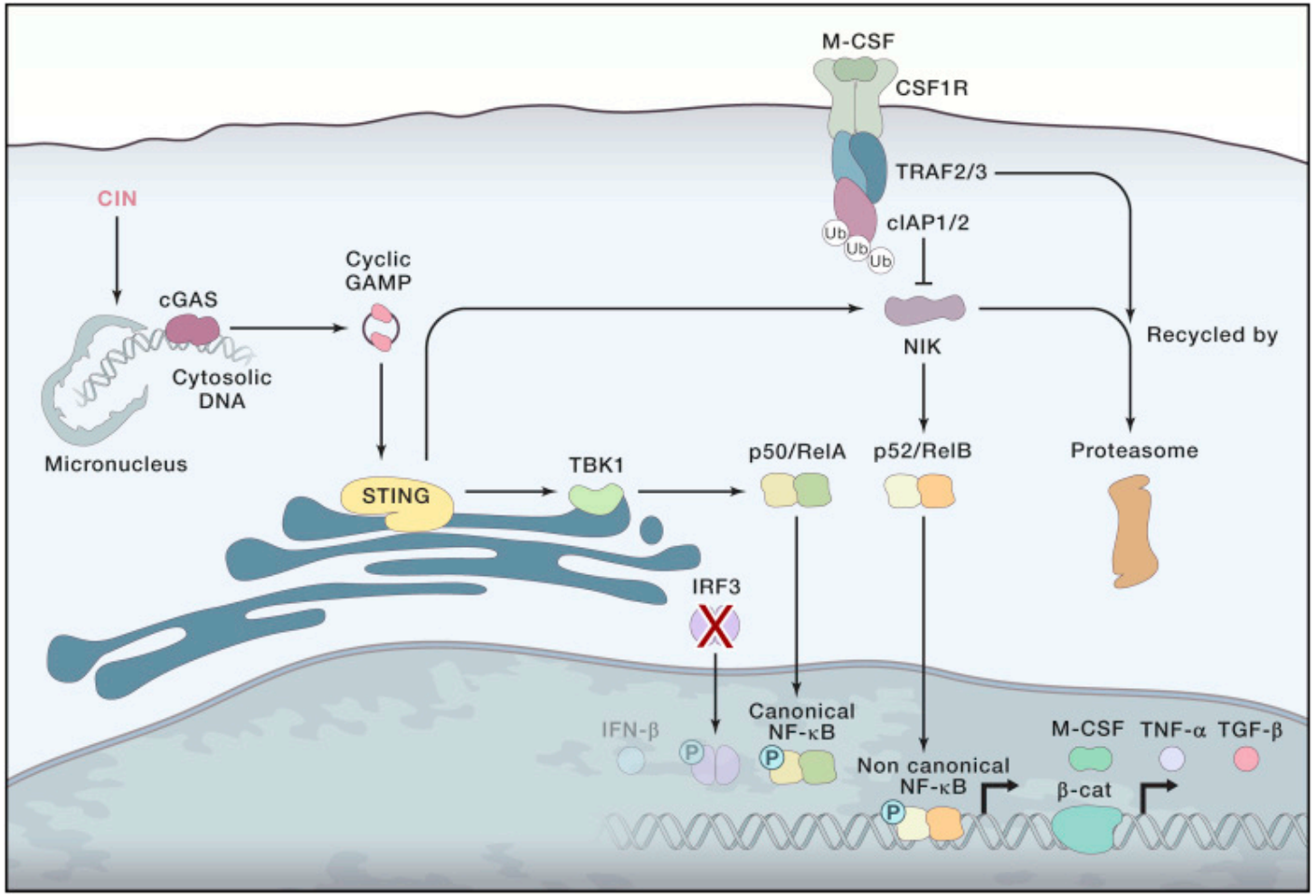
Chromosomal instability can induce anti-tumor immune responses through the cGAS/STING pathway



Bakhoum et al. Cell. 2018

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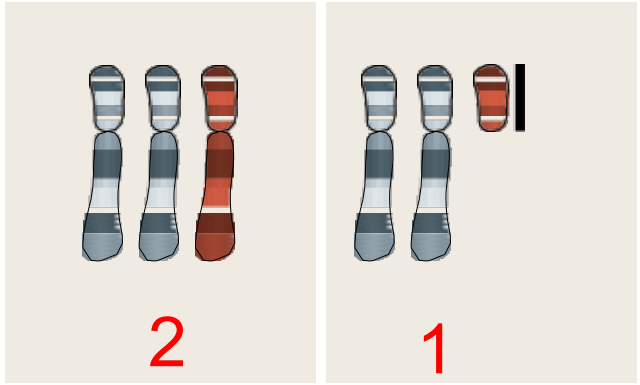
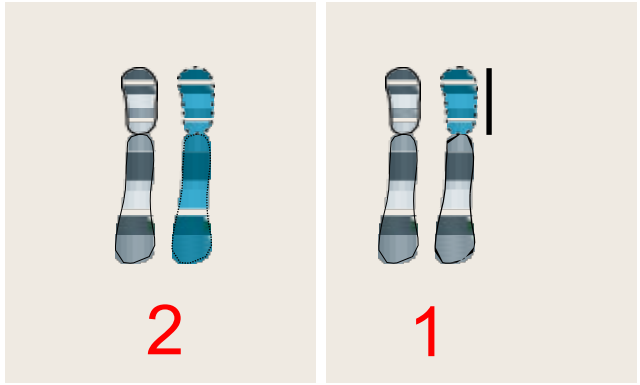
Aneuploidy score: count the number of chromosome arm events, corrected for ploidy

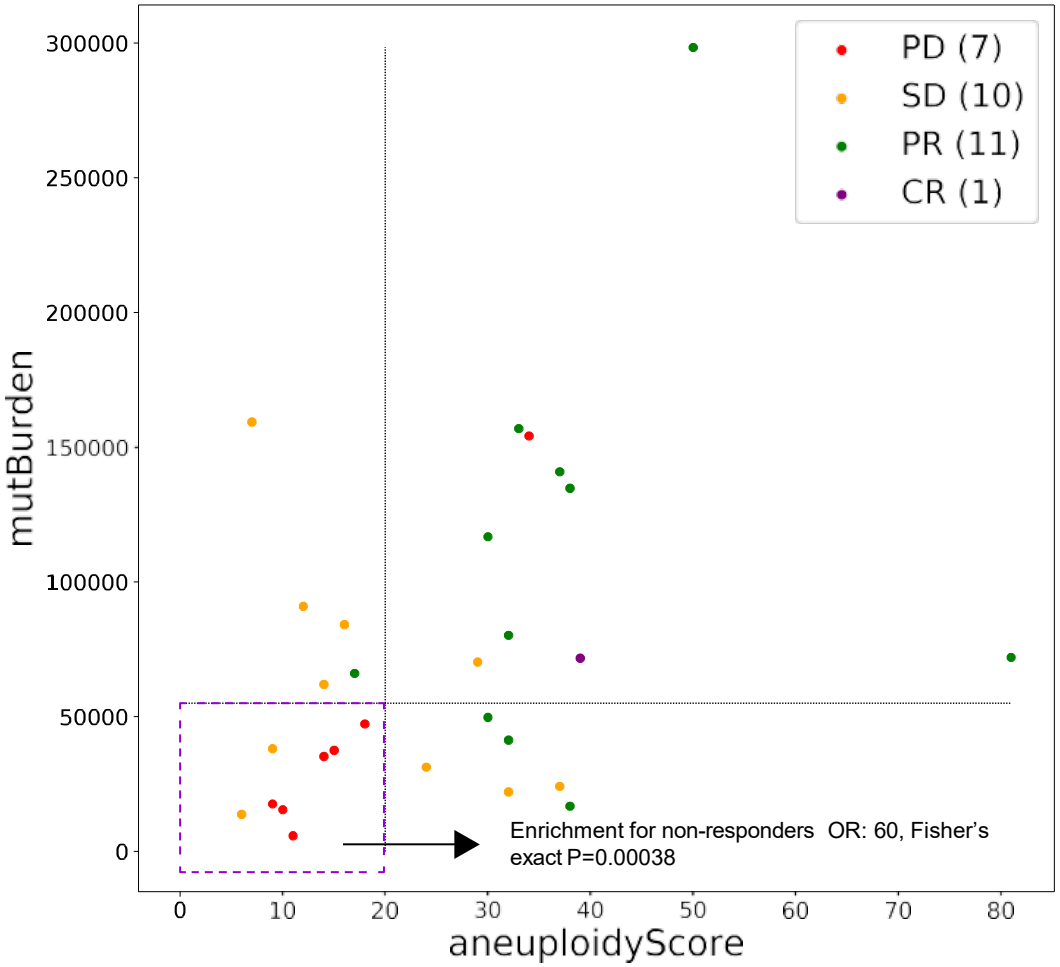
Gains

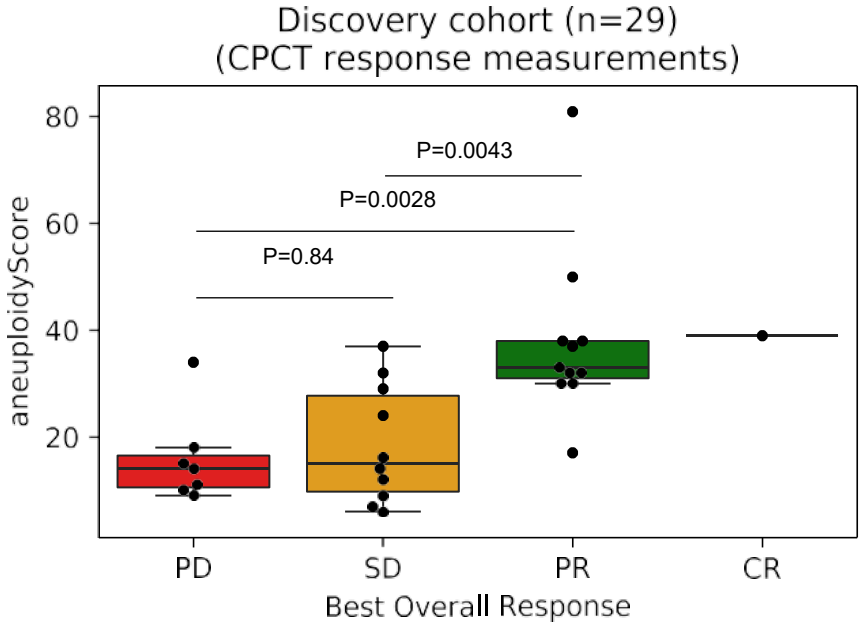


Losses



Discovery cohort (n=29) combined biomarker of TMB and aneuploidy score





Aneuploidy score =
Total number of large-scale copy number events at whole chromosomes and chromosome arms

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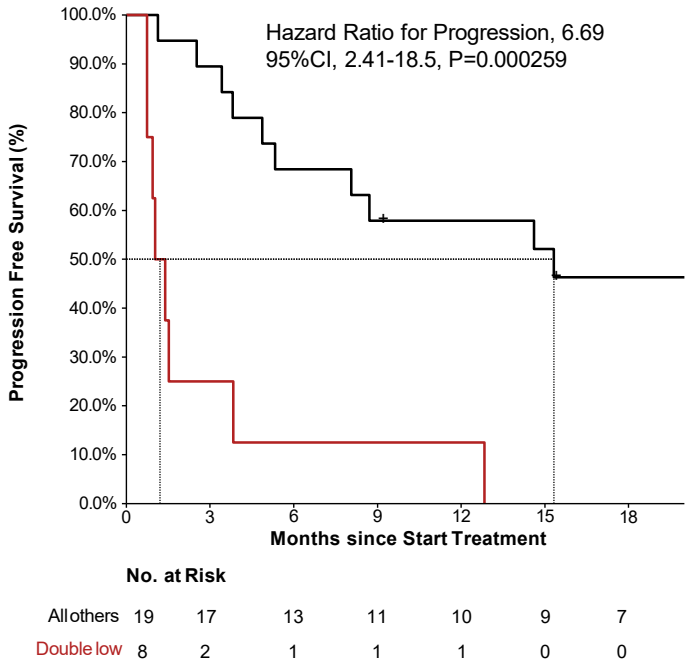
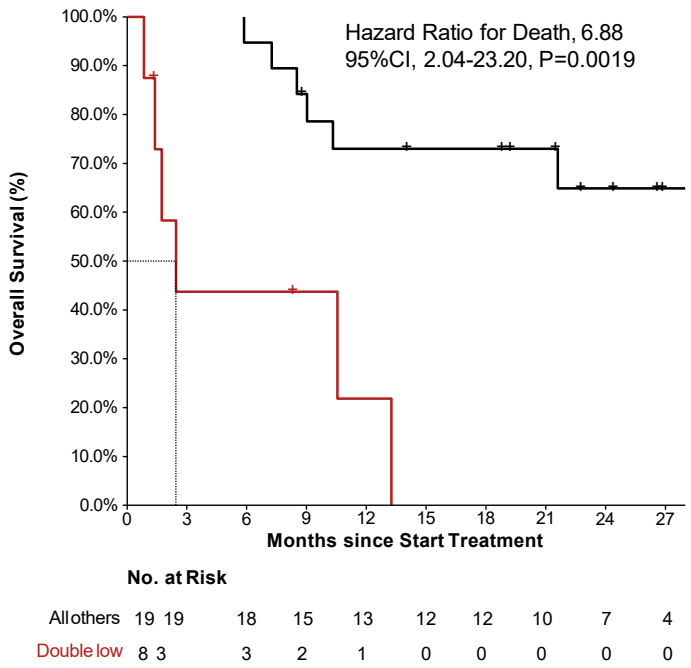
‘Double low’ biomarker patients had a significanlty shorter PFS and OS in the discovery cohort





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Power calculation for validation of combined biomarkers (TMB and aneuploidy score)

- 20% marker negative patients (TMB low, aneuploidy low):

- 50 patients in validation cohort:
  - 10 marker negative patients
  - 40 marker positive patients

  - 79.296% power to find a difference of 50% in response rate between marker positives and marker negatives (p=0.0328)

  - H0 = response rate of 70% in marker negatives
  - H1 = reponse rate of 20% in marker negatives

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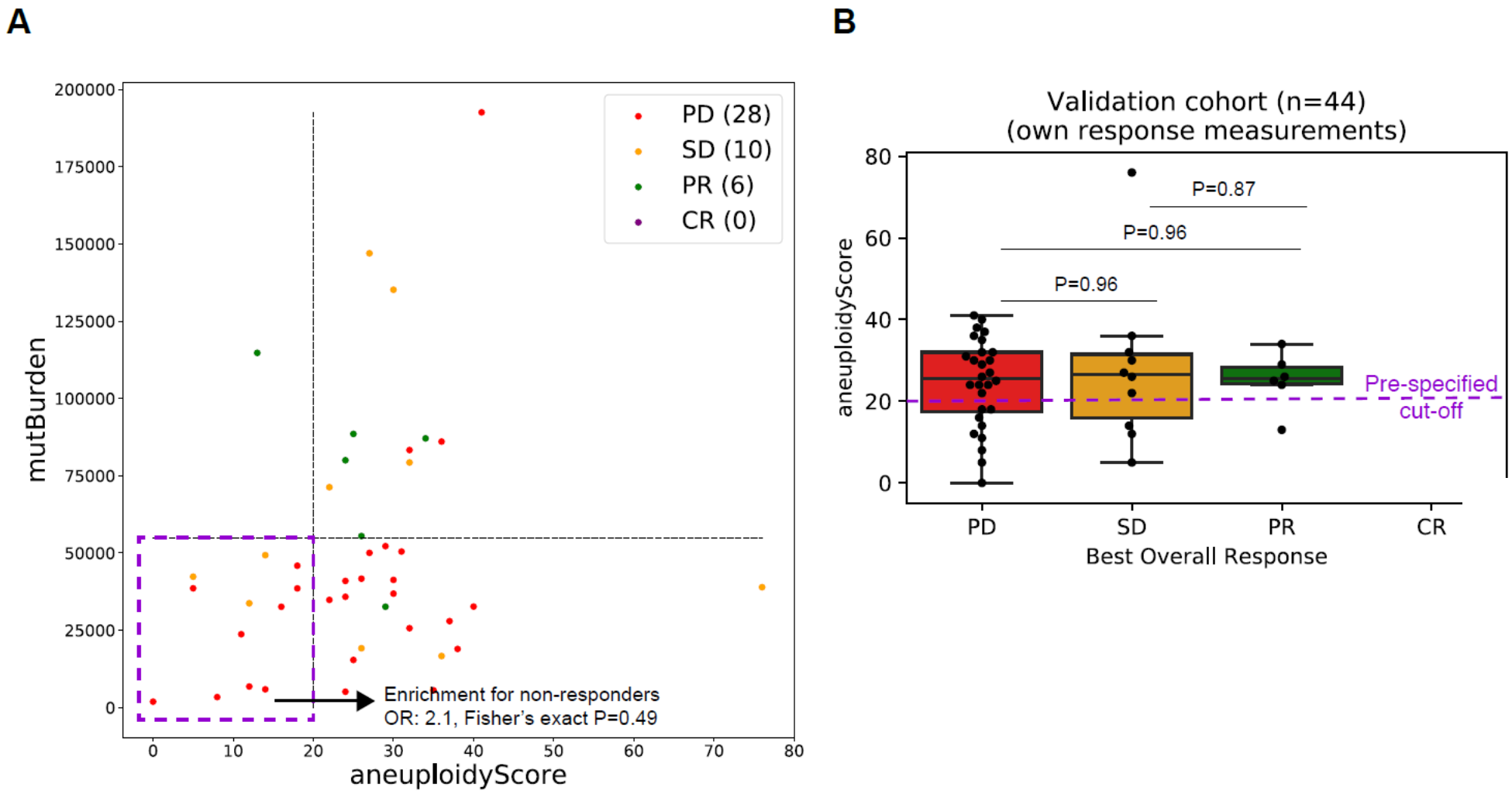
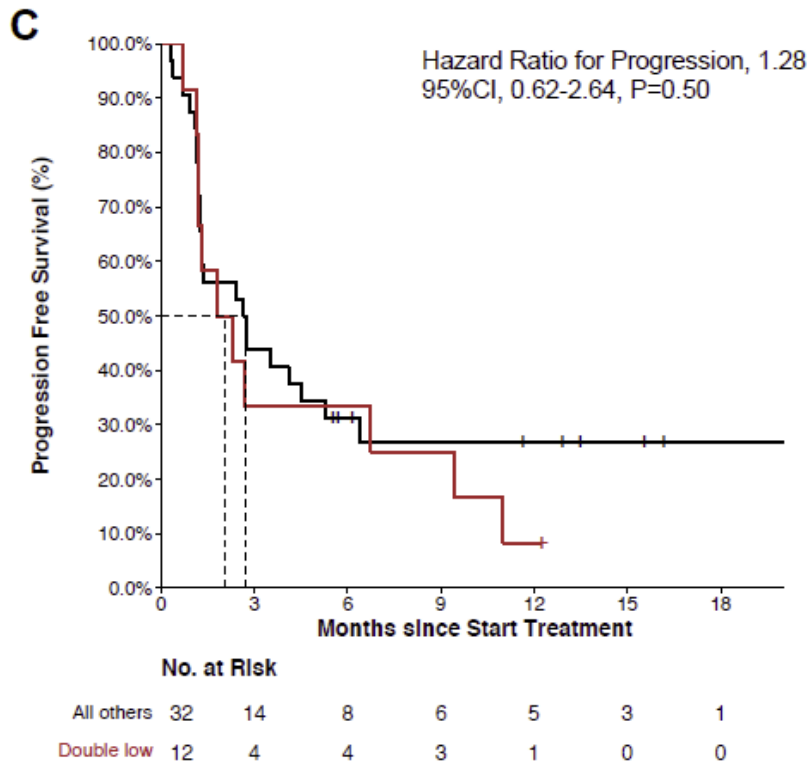
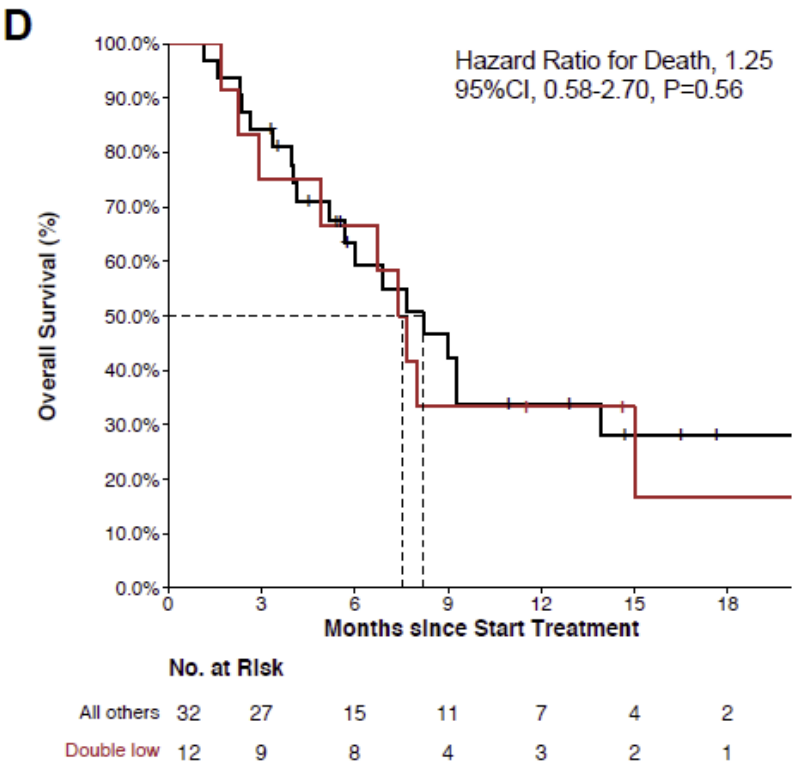
Validation cohort (n=50, analysed n =44) combined biomarker of TMB and aneuploidy score



‘Double low’ biomarker patients did not have a different PFS or OS in the validation cohort





Baseline characteristics discovery and validation cohorts

Variable	discovery	validation	p
n	**29**	**44**	
Smoking (%)			0.692
current	8 (28.6)	8 (18.2)	
former	14 (50.0)	27 (61.4)	
never	2 (7.1)	2 (4.5)	
unknown	4 (14.3)	7 (15.9)	
Pack_years (mean (SD))	34.81 (24.14)	26.30 (13.94)	0.149
ECOG (%)			0.712
>2	0 (0.0)	1 (2.4)	
0	6 (22.2)	12 (29.3)	
1	17 (63.0)	24 (58.5)	
2	4 (14.8)	4 (9.8)	
Prior_treatment_cat (%)			0.456
Chemotherapy	21 (75.0)	21 (60.0)	
Chemo-RT	0 (0.0)	1 (2.9)	
None	5 (17.9)	6 (17.1)	
Other	0 (0.0)	2 (5.7)	
TKI	2 (7.1)	5 (14.3)	
Treatment (%)			0.42
pembrolizumab	11 (39.3)	12 (27.3)	
nivolumab	18 (60.7)	36 (72.7)	
Tx line (%)			0.167
1	5 (17.9)	6 (14.0)	
2	23 (82.1)	30 (69.8)	
3	0 (0.0)	5 (11.6)	
4	0 (0.0)	2 (4.7)	

Variable	discovery	validation	p
n	**29**	**44**	
ICI cycles (mean (SD))	16.93 (14.71)	8.89 (10.39)	0.014
Biopsy_location (%)			0.665
NA	0 (0.0)	1 (2.8)	
M	20 (74.1)	25 (69.4)	
P	7 (25.9)	10 (27.8)	
Histology (%)			0.991
adeno	17 (65.4)	21 (63.6)	
NOS	4 (15.4)	6 (18.2)	
other	1 (3.8)	1 (3.0)	
squamous	4 (15.4)	5 (15.2)	
PD L1 status (%)			0.498
	07 (41.2)	21 (55.3)	
	16 (35.3)	8 (21.1)	
	24 (23.5)	9 (23.7)	
DCB = YES (%)	13 (48.1)	12 (27.3)	0.126
aneuploidyScore (mean (SD))	25.48 (14.42)	25.11 (12.23)	0.907
TMB (mean (SD))	74376.00 (63592.66)	49227.14 (40170.32)	0.042
BOR (%)			0.034
NE	2 (6.9)	0 (0.0)	
PD	11 (37.9)	28 (63.6)	
PR	10 (34.5)	6 (13.6)	
SD	6 (20.7)	10 (22.7)	

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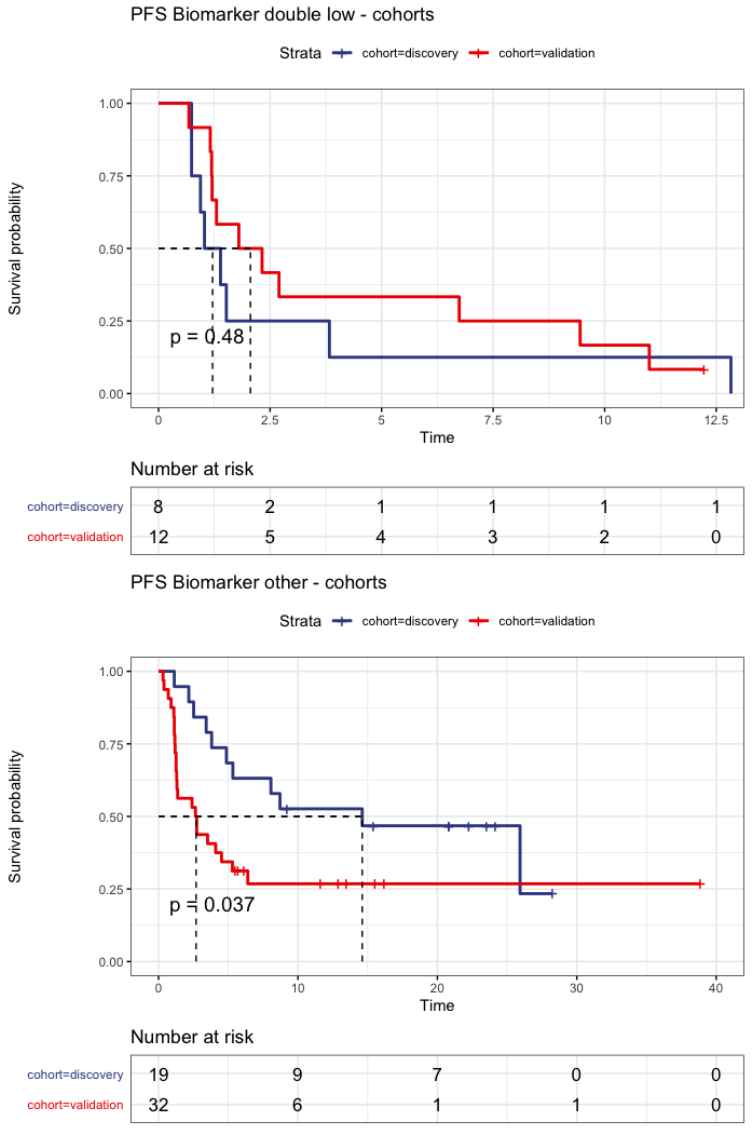
Small number of patients experienced benefit in the Validation CH, compared to the Discovery CH



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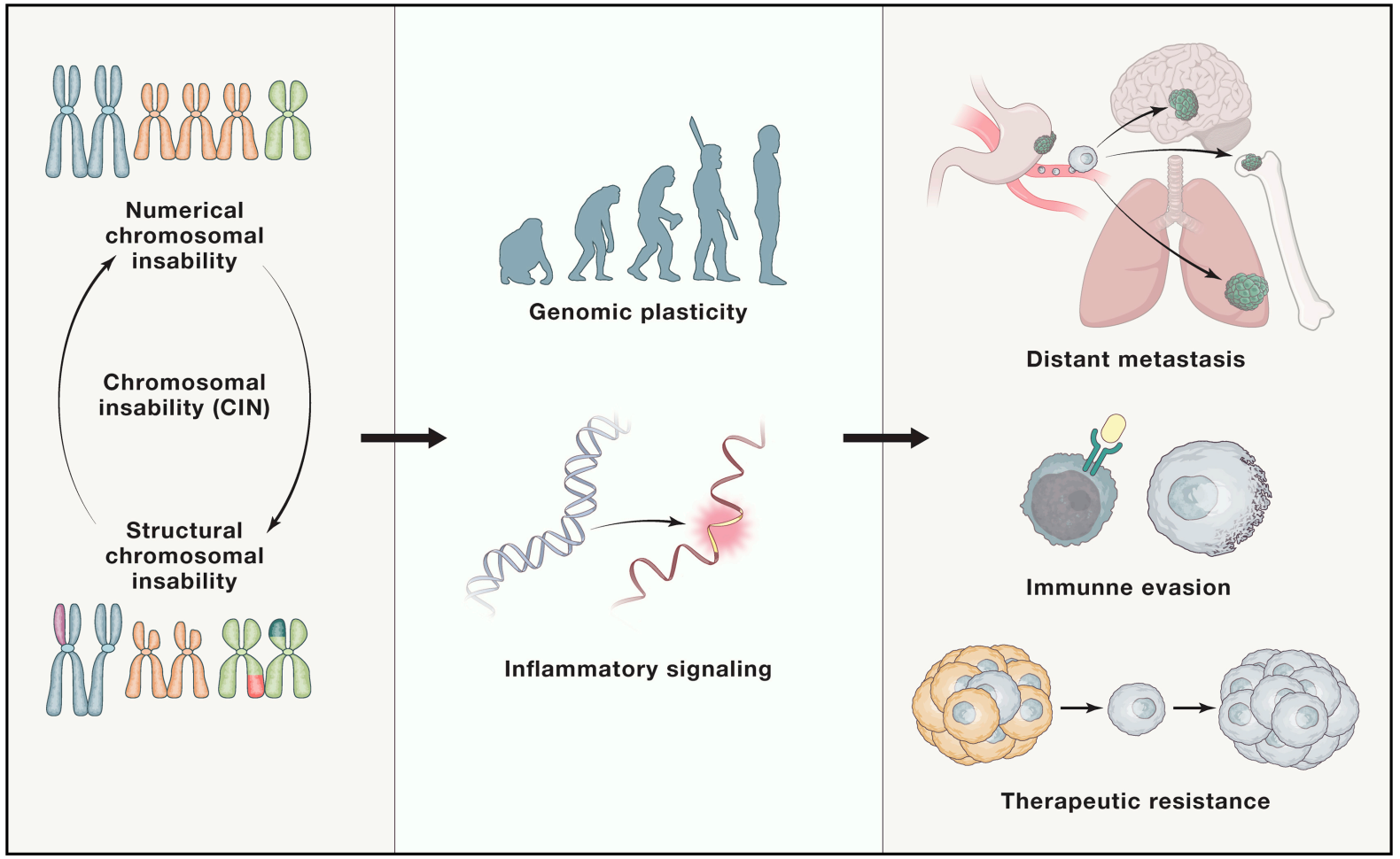
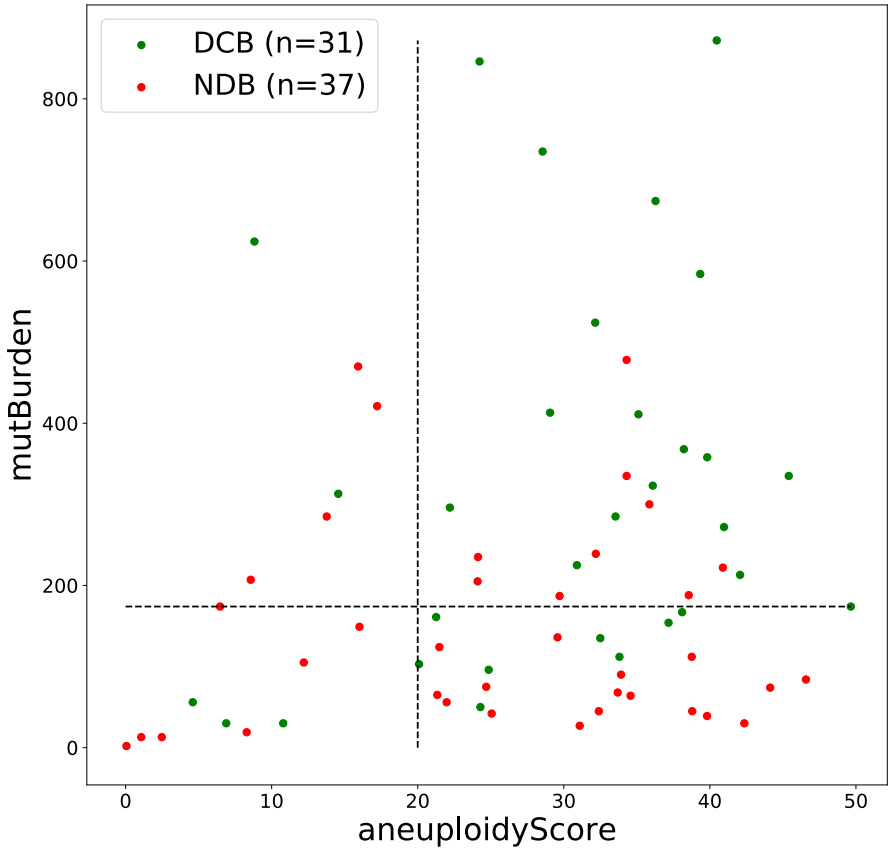
Aneuploidy can induce anti-tumor immune responses but also facilitate immune escape



Bakhoum et al. Cell. 2018

Validation in an independent (WES based, n=68) cohort from Anagnostou et al. (JHU)



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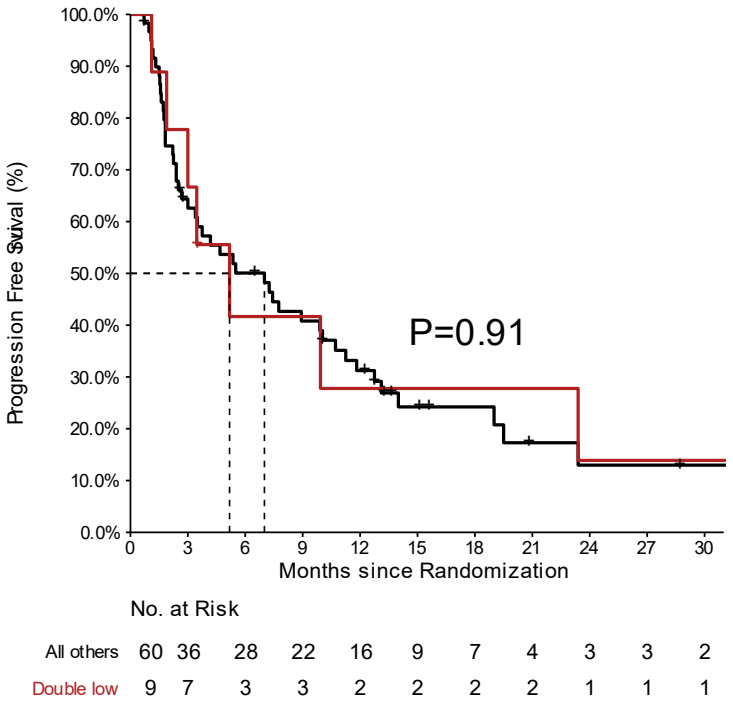
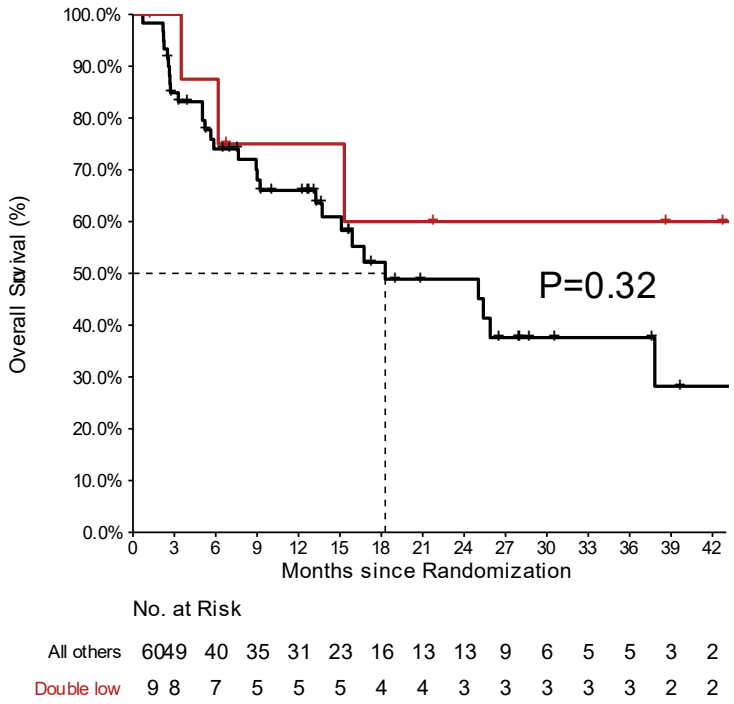
Cohort of Anagnostou et al: PFS and OS stratified by biomarker ‘double low’ and others





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Conclusions part I

- We were not able to confirm the predictive role of a combined biomarker of aneuploidy and TMB for aPD-1 responses in NSCLC
- In an independent cohort of 68 WES samples, no clear relationship between the combined biomarker and response was found
- Validation in our own dataset could be abbrogated by differences in the two patient cohorts

- We then analyzed the full cohort to (1) perform a rigorous external validation of previously published biomarkers, and (2) discover novel biomarkers

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Presentation outline

PART 1: External validation of published biomarkers

1. cTMB, cTML, cFSL, Tobacco signature - *WGS-based*
2. PD-L1 immunohistochemistry
3. Receptor tyrosine kinase mutations
4. KRAS, STK11, KEAP1, PTEN mutations
5. Germline and somatic HLA diversity

PART 2: Discovery of biomarkers

1. HLA loss of heterozygosity
2. Biallelic cTML/cFSL

PART 3: Patient stratification by a combined biomarker

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Baseline characteristics

Characteristic	Value
N	70
Median age (year)	63
Male sex - no (%)	32
ECOG performance score - no (%)	
0	18 (26)
1	40 (57)
2	7 (10)
>2	1 (1.4)
Unknown	4 (5.7)
Smoking status - no (%)	
Never	14 (20)
Current	15 (21)
Former	41 (59)
Pack Years - mean (SD)	29 (19)
Treatment - no (%)	
Nivolumab	47 (67)
Pembrolizumab	23 (33)
Line of treatment	
1	11 (16)
2	51 (73)
3	5 (7.1)
4	2 (2.9)
Unknown	1 (1.4)
Best Overall Response - no (%)	
PR	15 (21)
SD	16 (23)
PD	39 (56)
PD-L1 expression - no (%)	
<1%	27 (39)
1-50%	14 (20)
>50%	13 (19)
Unknown	16 (23)

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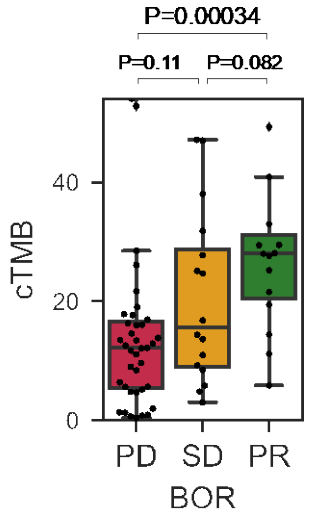
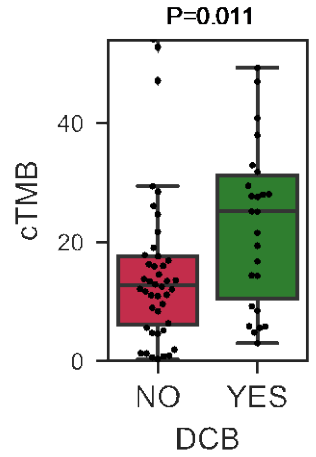
Tumor mutational burden & variants thereof

Best overall response



Clinical benefit (6 mo)



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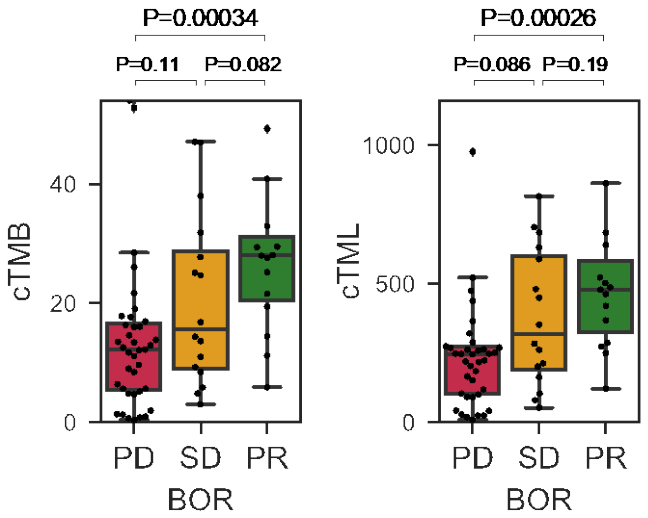

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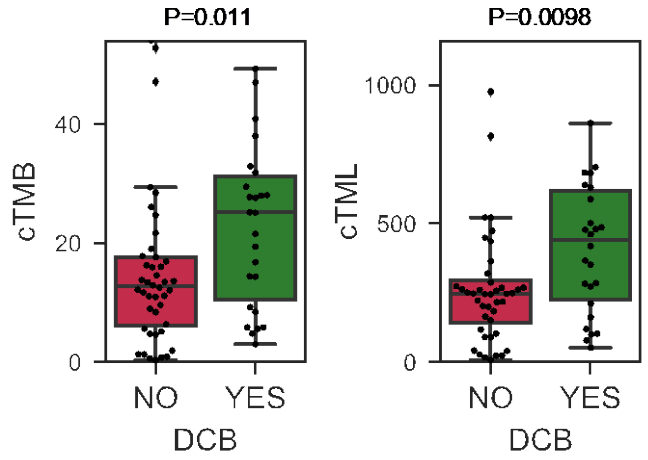
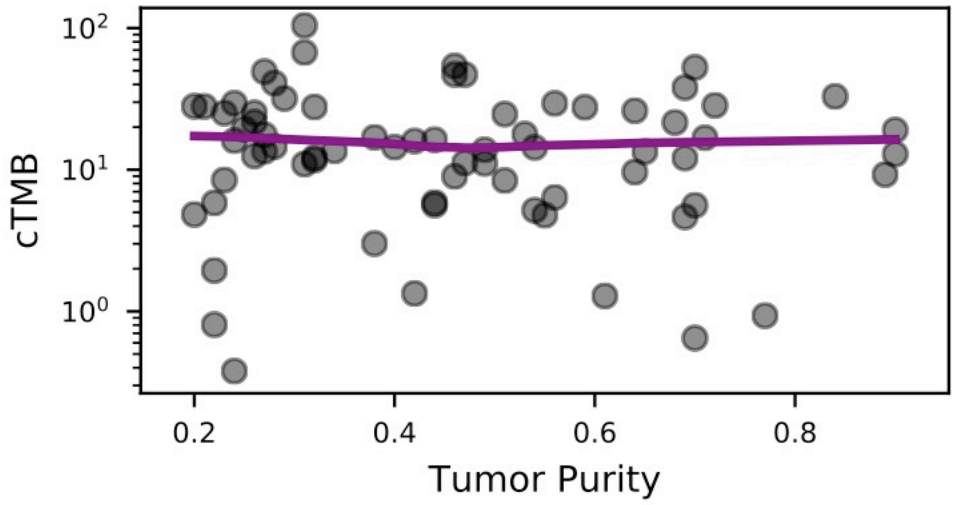
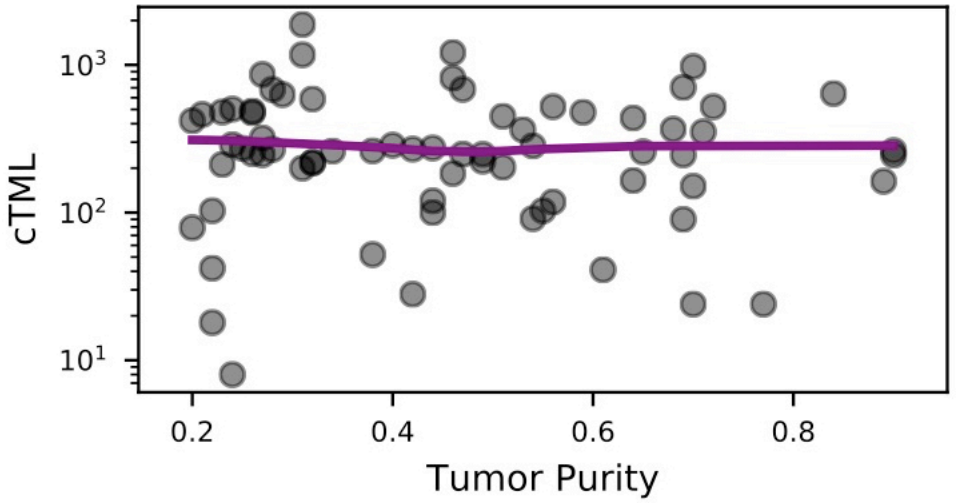


No confounding by tumor purity





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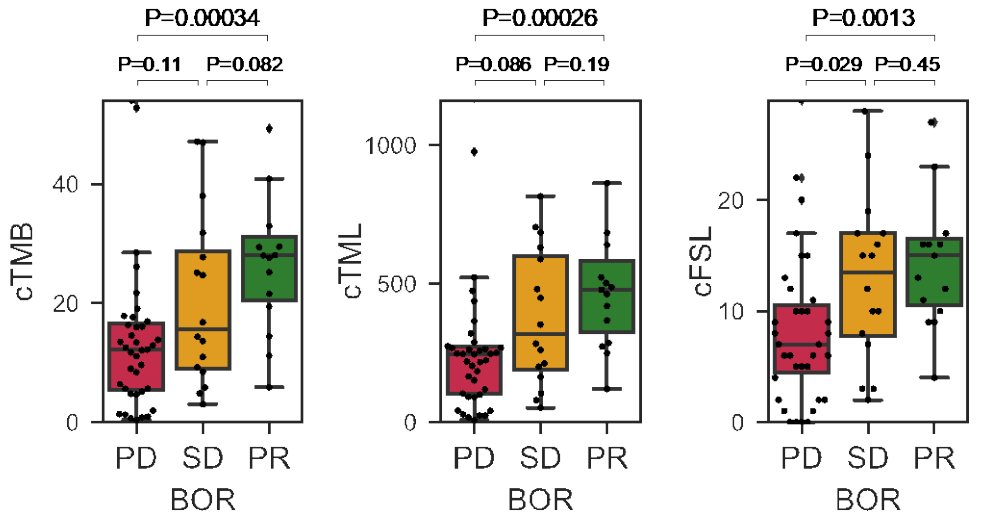

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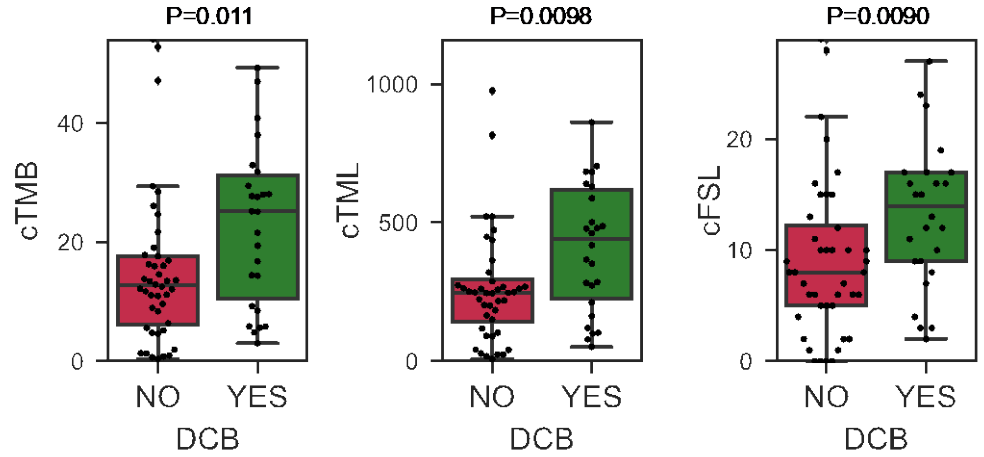

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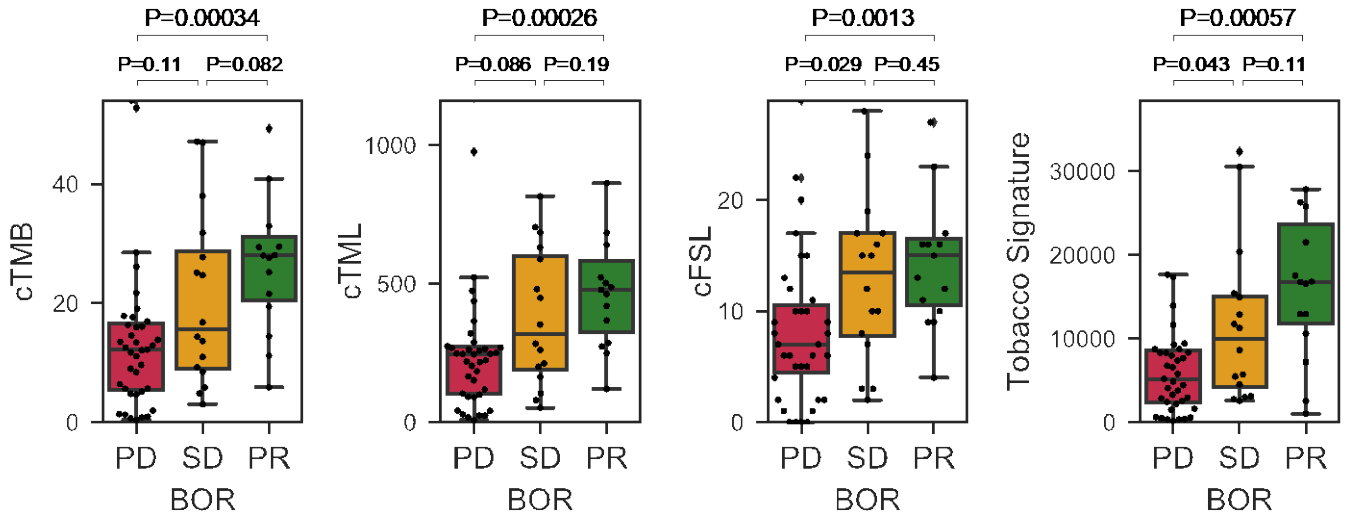
Tumor mutational burden & variants thereof

Best overall response



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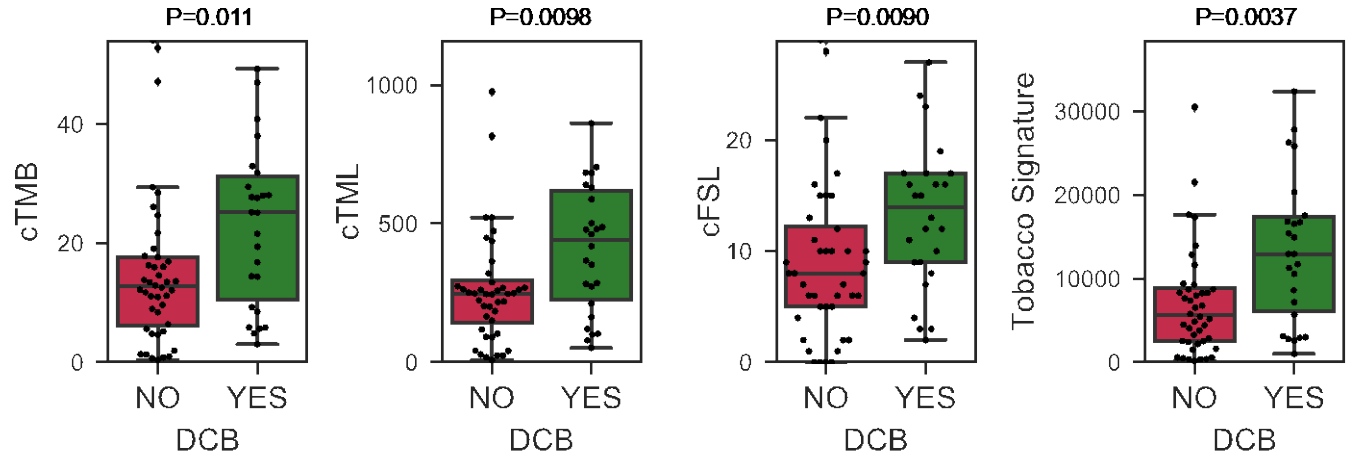

Correlation with Pack years (n=43): rho=0.37, P=0.016

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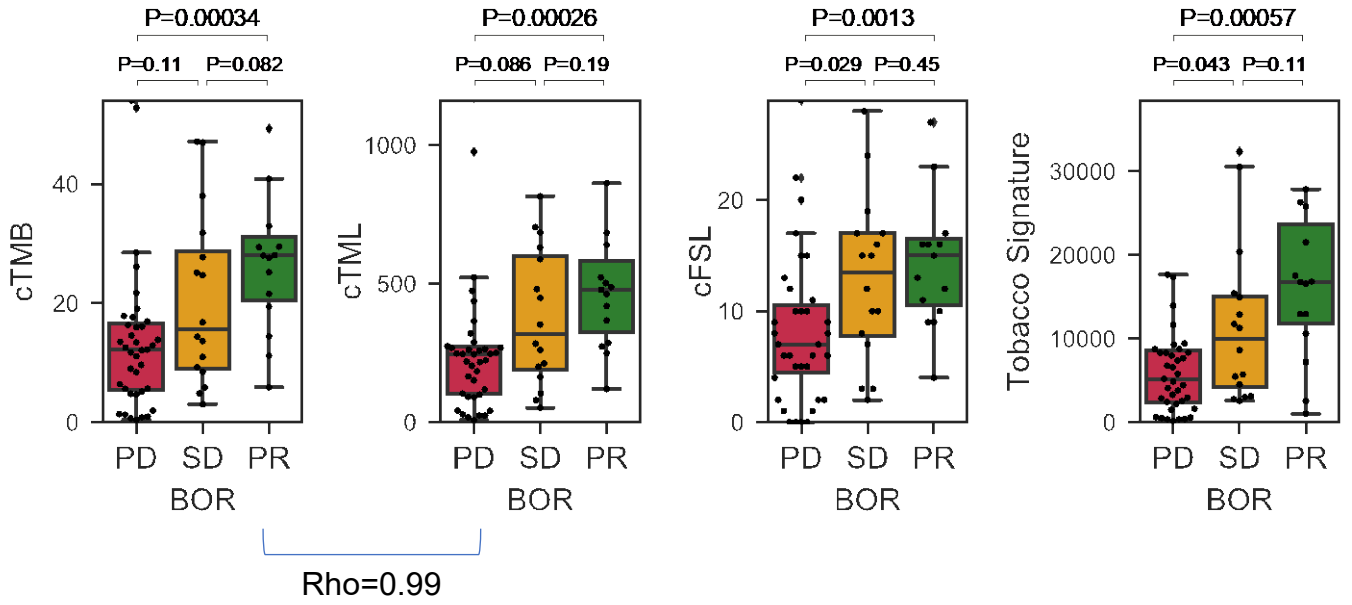
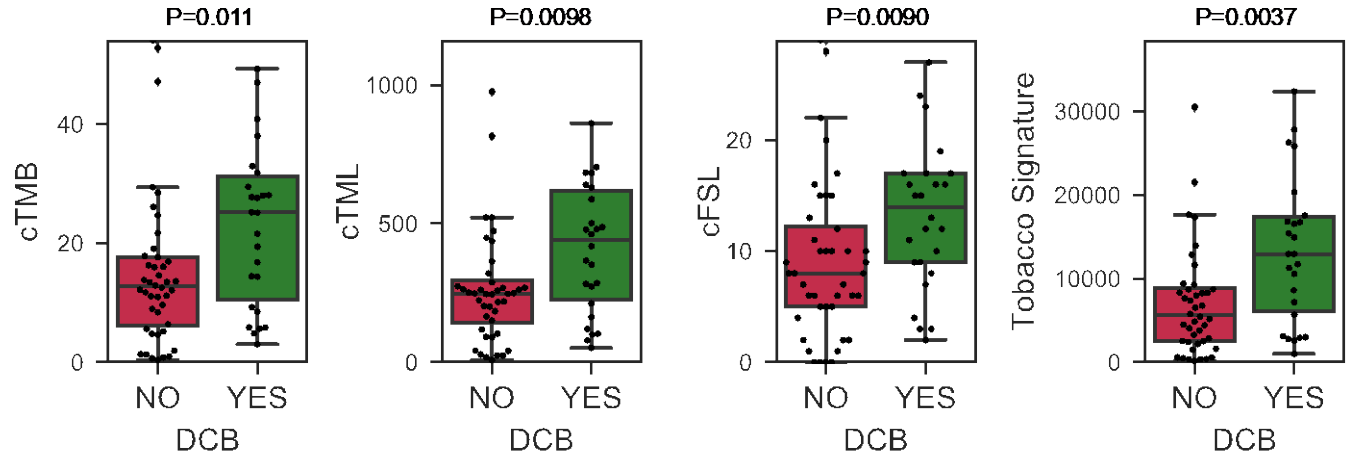
Tumor mutational burden & variants thereof

Best overall response



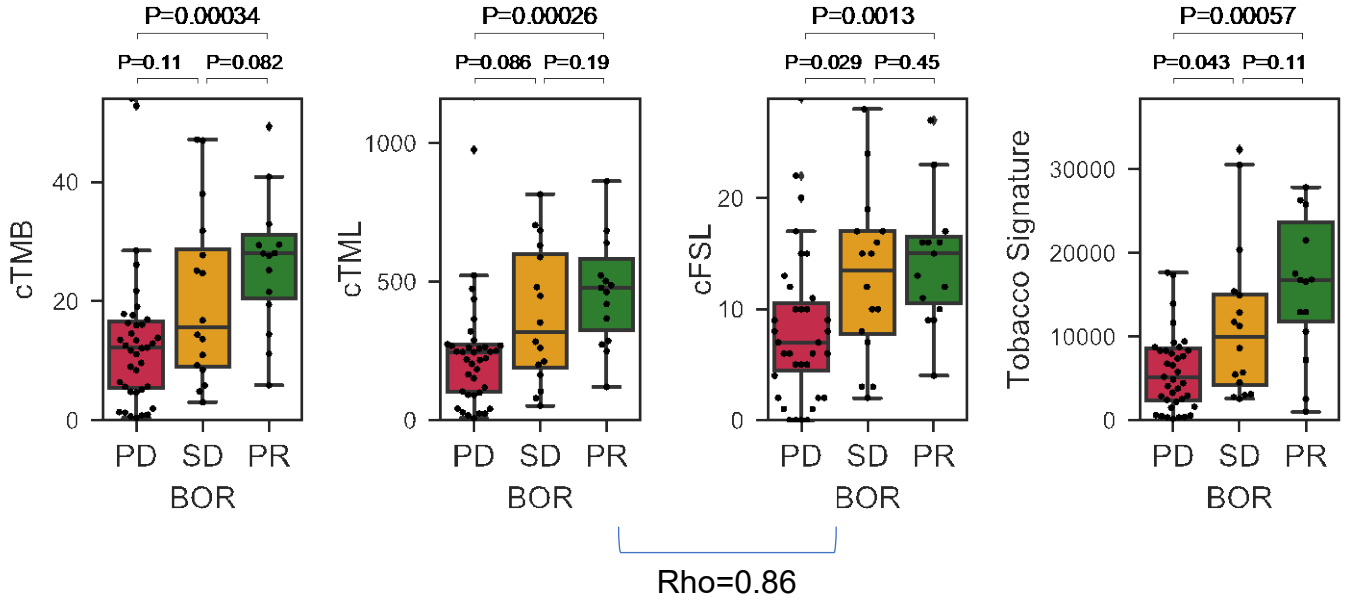
Clinical benefit (6 mo)



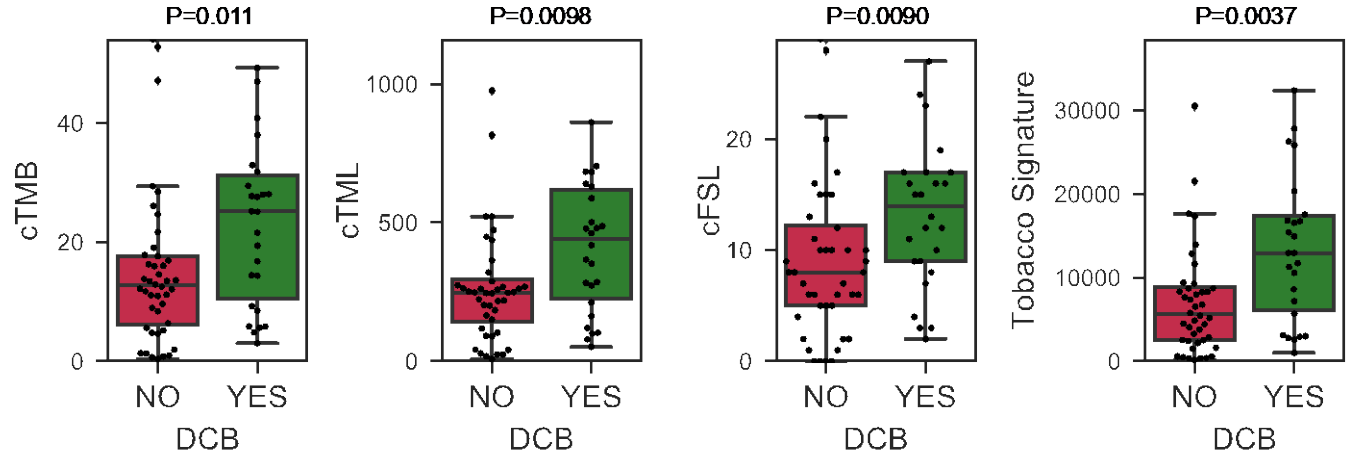
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Tumor mutational burden & variants thereof

Best overall response



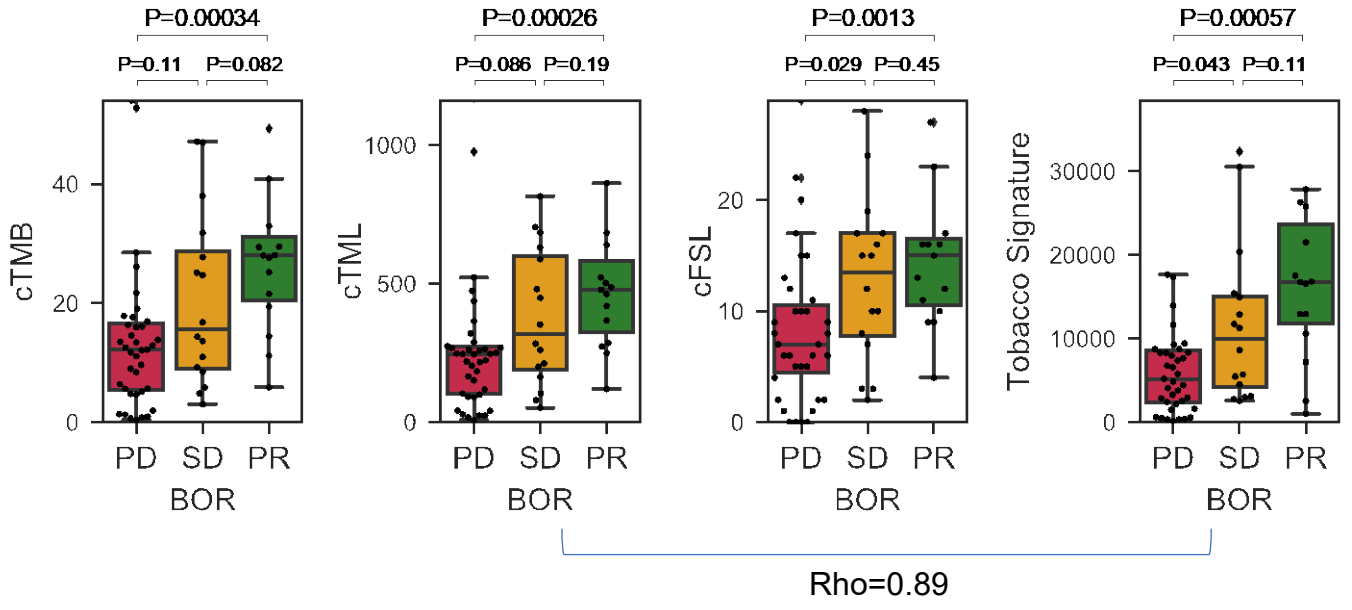
Clinical benefit (6 mo)



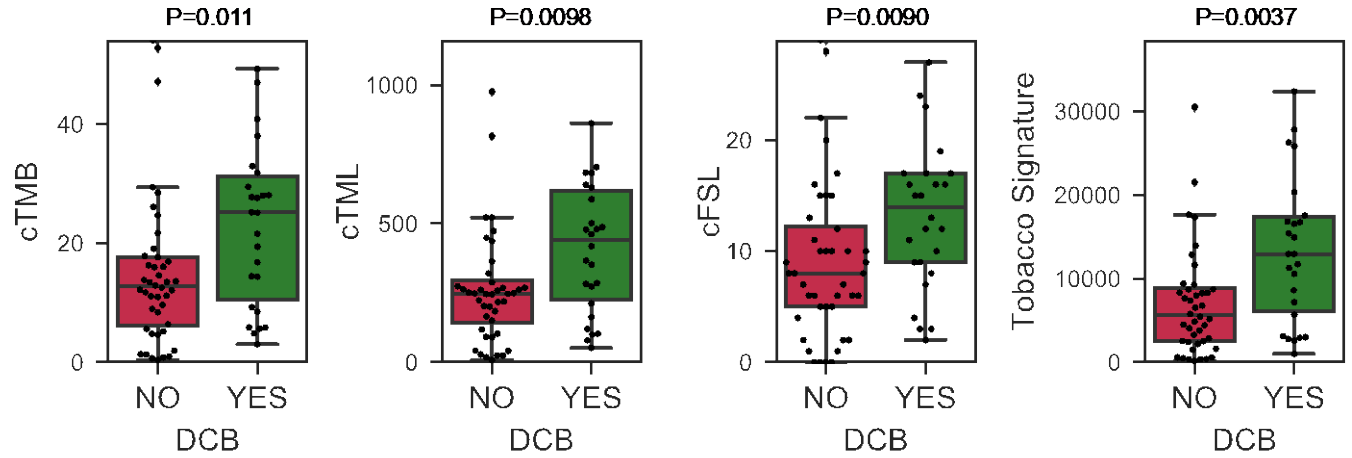
TANGO
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Tumor mutational burden & variants thereof

Best overall response

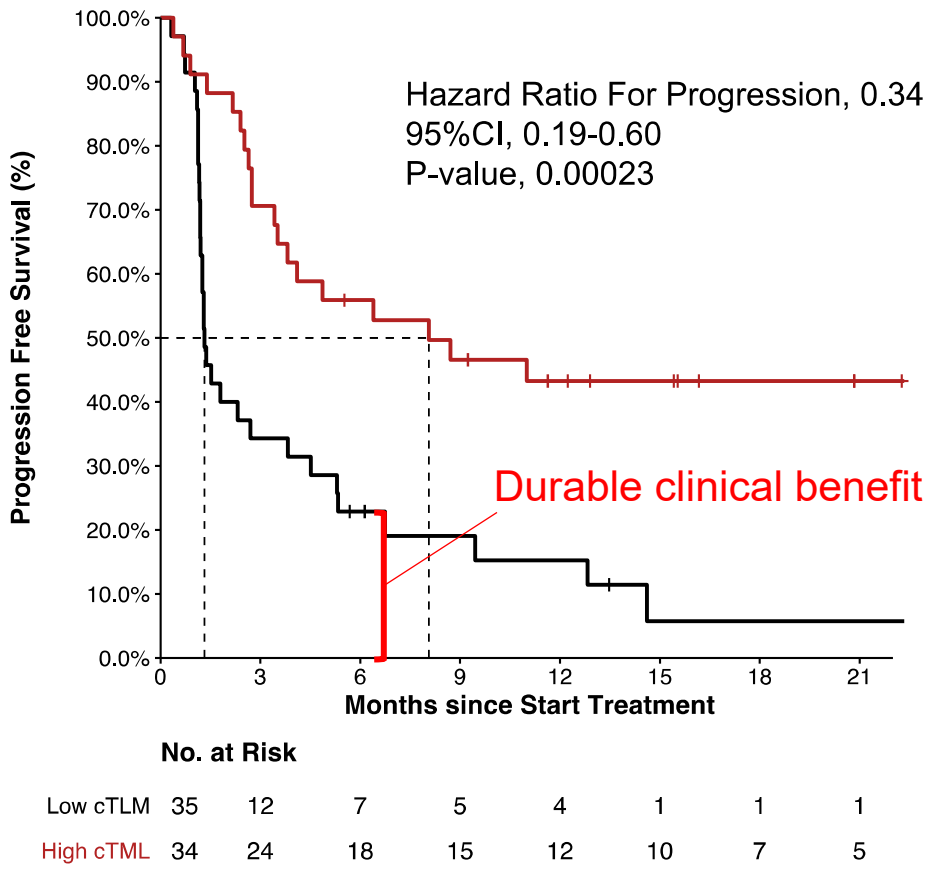


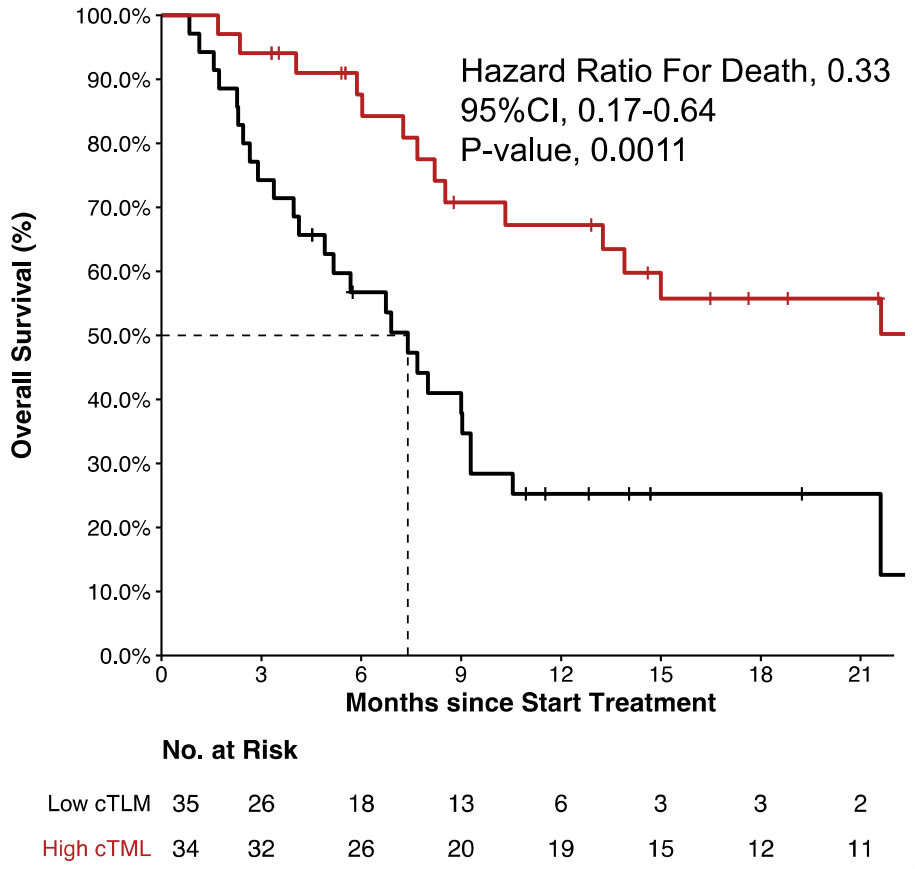
Clinical benefit (6 mo)



Technology Assessment of Next Generation Sequencing in Personalized Oncology

Tumor mutational burden & variants thereof





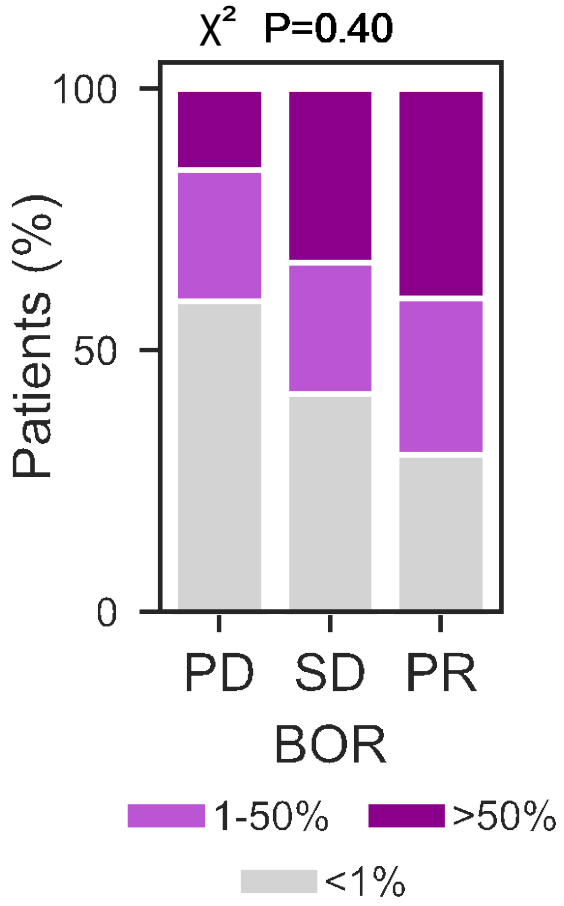
Technology Assessment of Next Generation Sequencing in Personalized Oncology

PD-L1 status on immunohistochemistry

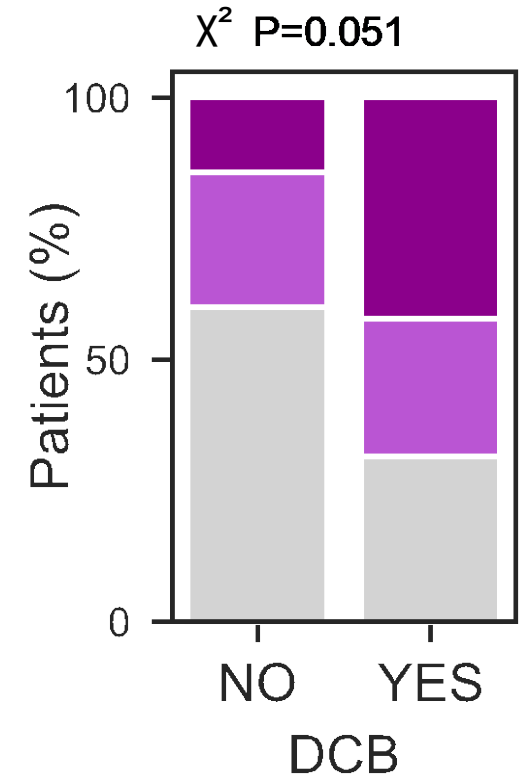
Used in clinical practice

54 patients

Best overall response



Clinical benefit (6 mo)

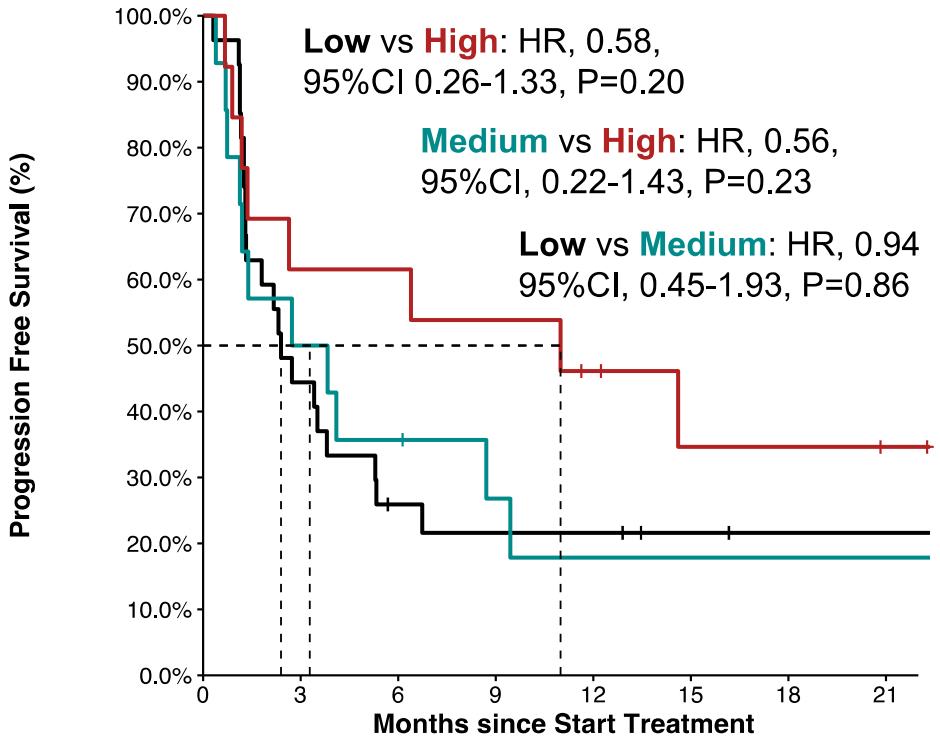


Technology Assessment of Next Generation Sequencing in Personalized Oncology

PD-L1 status on immunohistochemistry

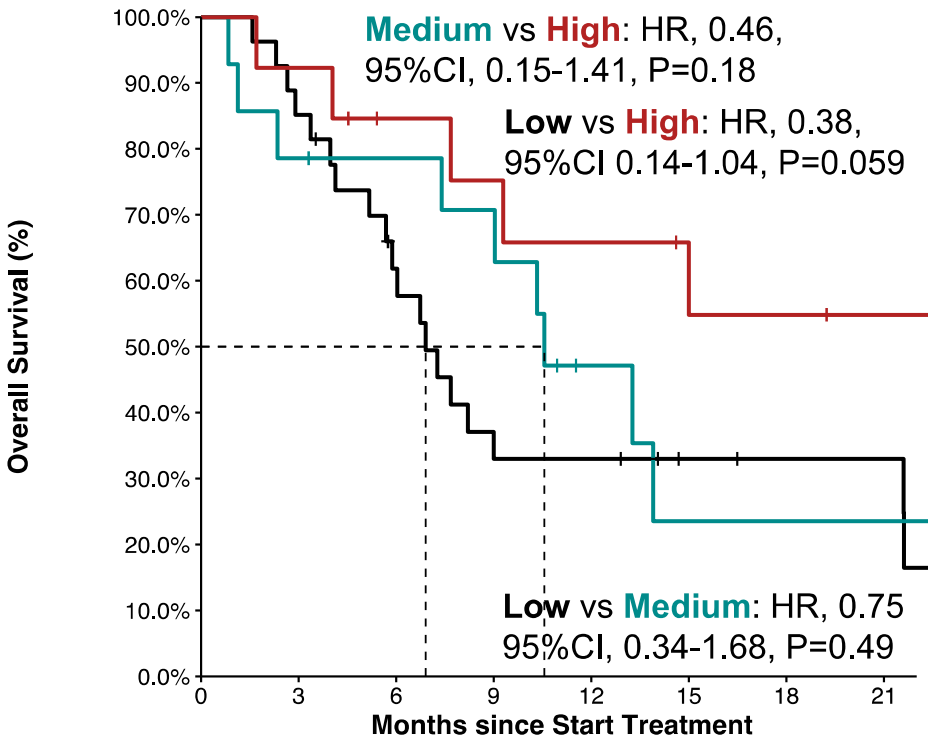
Used in clinical practice

54 patients



No. at Risk

PD–L1 <1%	27	12	6	5	5	3	2	2
PD–L1 1–50%	14	7	5	3	2	2	2	2
PD–L1 >50%	13	8	8	7	5	3	3	2



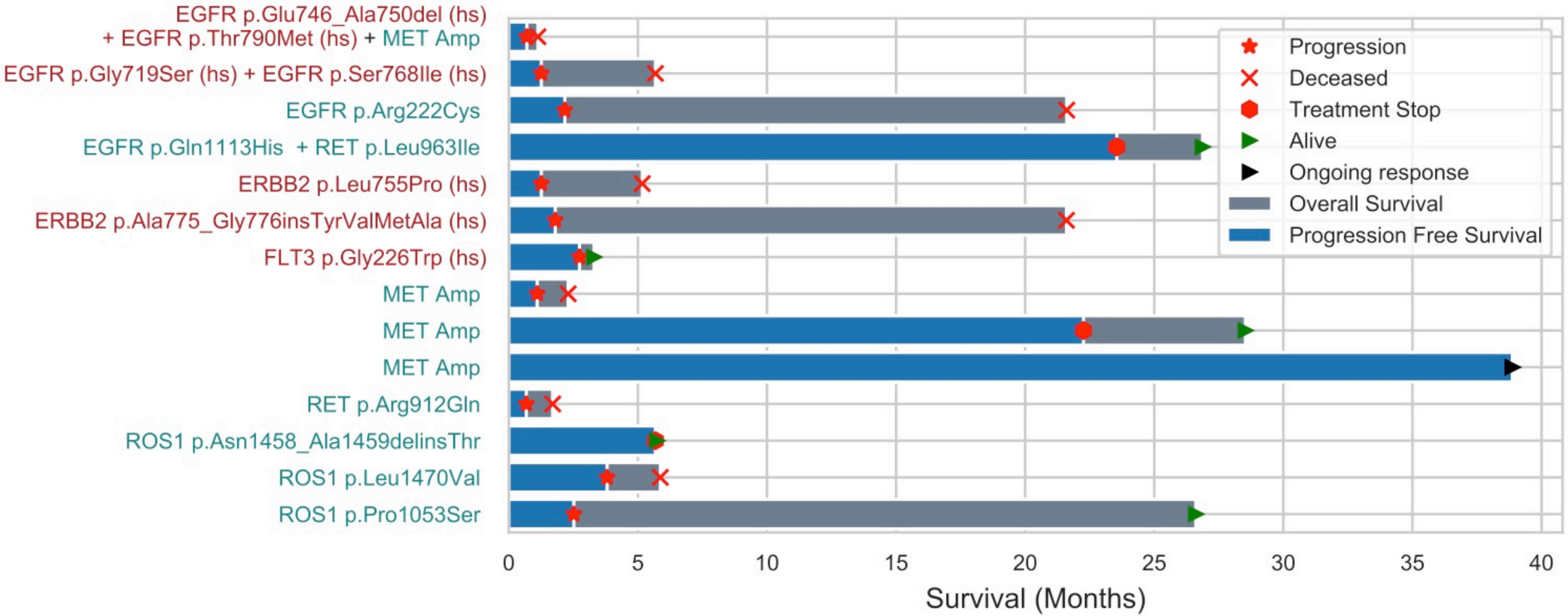
No. at Risk

PD–L1 <1%	27	23	15	9	8	5	4	4
PD–L1 1–50%	14	11	10	9	4	2	2	2
PD–L1 >50%	13	12	9	8	7	6	5	4

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Receptor tyrosine kinase somatic variants

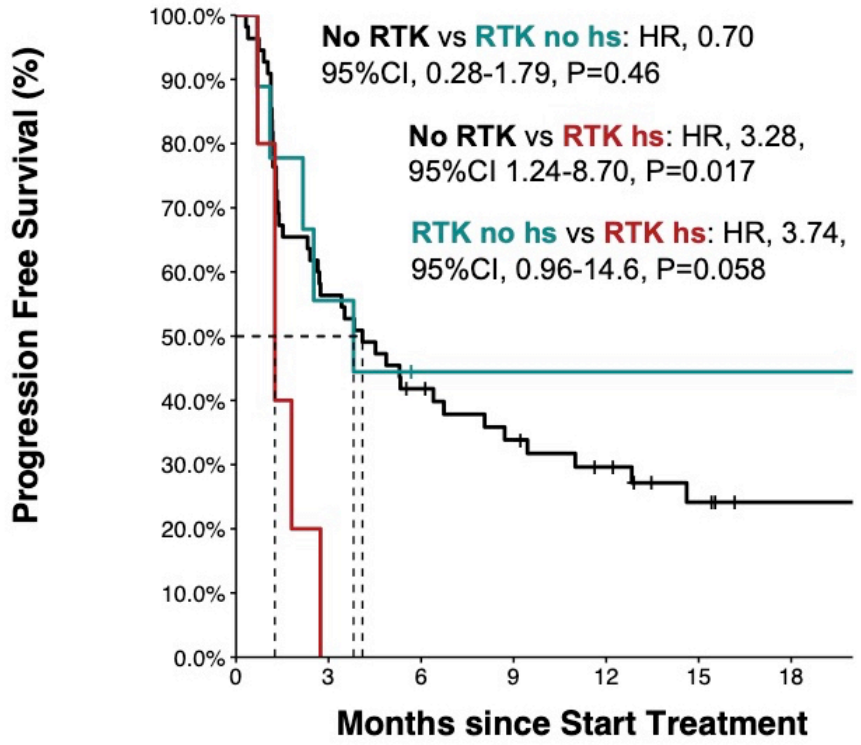
Partly used in clinical practice



…Larger studies needed

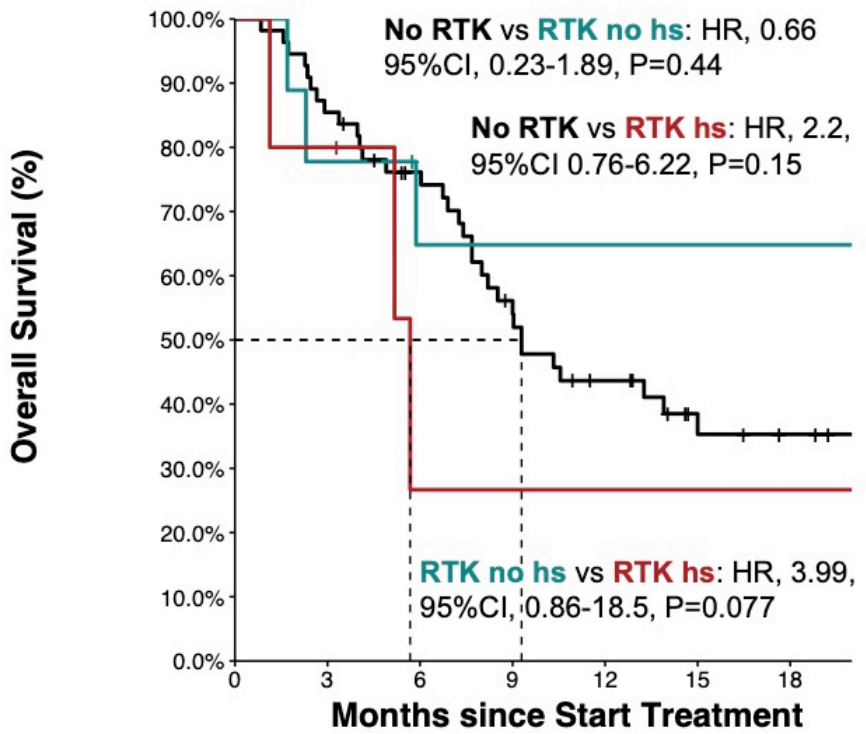
Receptor tyrosine kinase somatic variants

Partly used in clinical practice



No. at Risk

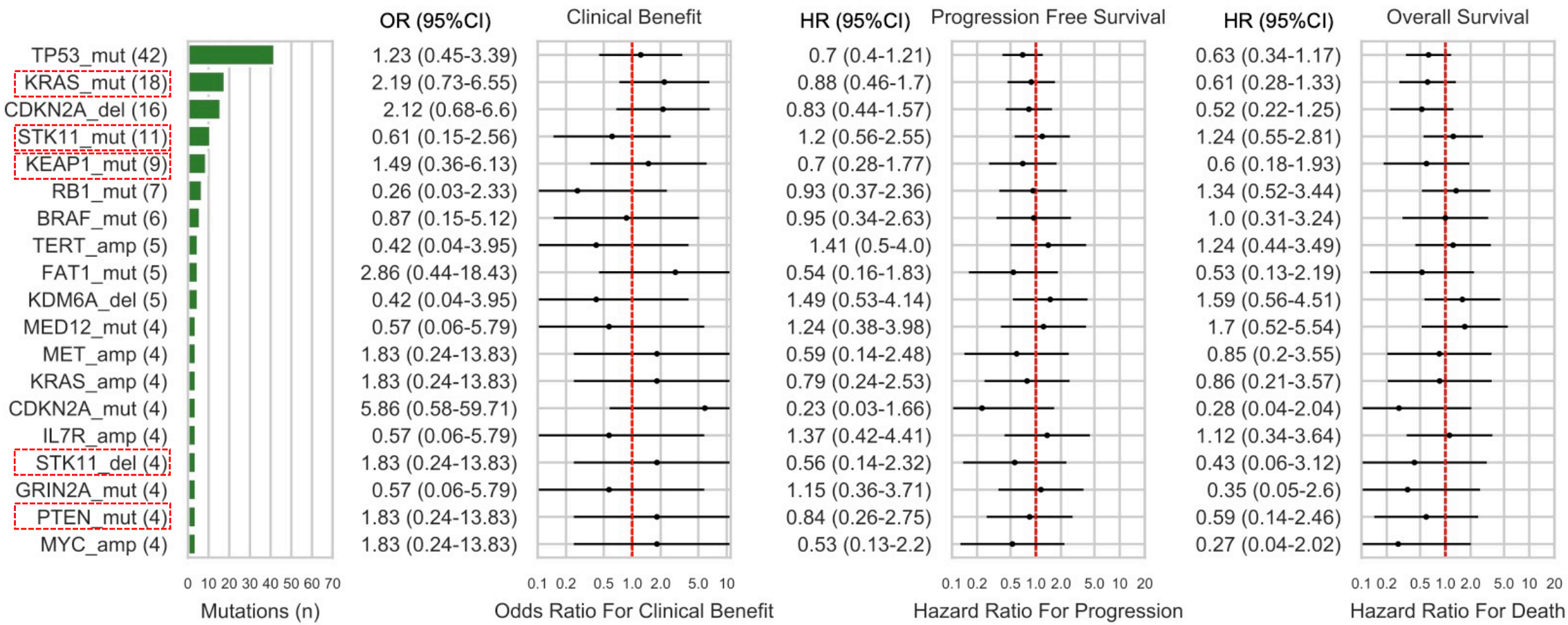
No RTK alteration	55	31	22	17	13	8	5
RTK other than hs mut	9	5	3	3	3	3	3
RTK hs mut	5	0	0	0	0	0	0



No. at Risk

No RTK alteration	55	47	38	27	19	12	9
RTK other than hs mut	9	7	5	5	5	5	5
RTK hs mut	5	4	1	1	1	1	1

KRAS, STK11, KEAP1 & PTEN mutations



Technology Assessment of Next Generation Sequencing in Personalized Oncology

HLA class I diversity

Germline HLA diversity

REPORT

Patient HLA class I genotype influences cancer response to checkpoint blockade immunotherapy

Diego Chowell[1,2], Luc G. T. Morris[2,3,*], Claud M. Grigg[4,*], Jeffrey K. Weber[5], Robert M. Samstein[1,2], Vladimir M...
+ See all authors and affiliations

Science 02 Feb 2018:
Vol. 359, Issue 6375, pp. 582-587
DOI: 10.1126/science.aao4572

Evolutionary divergence of HLA class I genotype impacts efficacy of cancer immunotherapy

Diego Chowell, Chirag Krishna, Federica Pierini, Vladimir Makarov, Naiyer A. Rizvi, Fengshen Kuo, Luc G. T. Morris, Nadeem Riaz, Tobias L. Lenz ✉ & Timothy A. Chan ✉

Nature Medicine **25**, 1715–1720(2019) | Cite this article

Germline + somatic HLA diversity

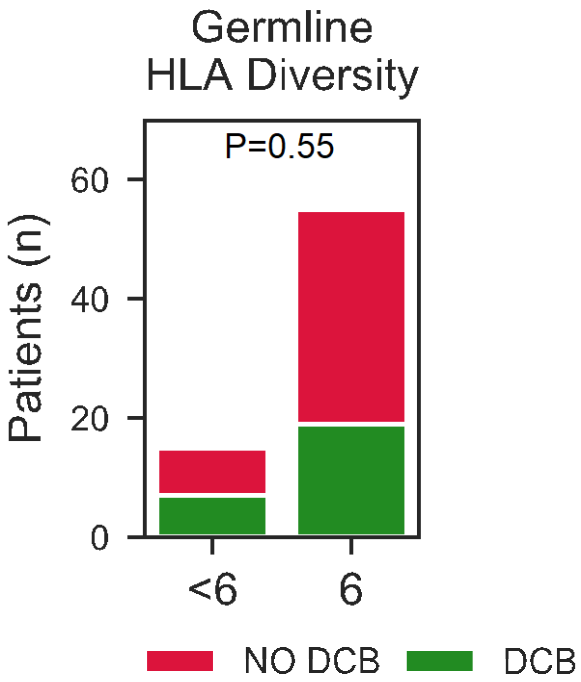
Multimodal genomic features predict outcome of immune checkpoint blockade in non-small-cell lung cancer

Valsamo Anagnostou ✉, Noushin Niknafs, [...] Victor E. Velculescu ✉

Nature Cancer **1**, 99–111(2020) | Cite this article

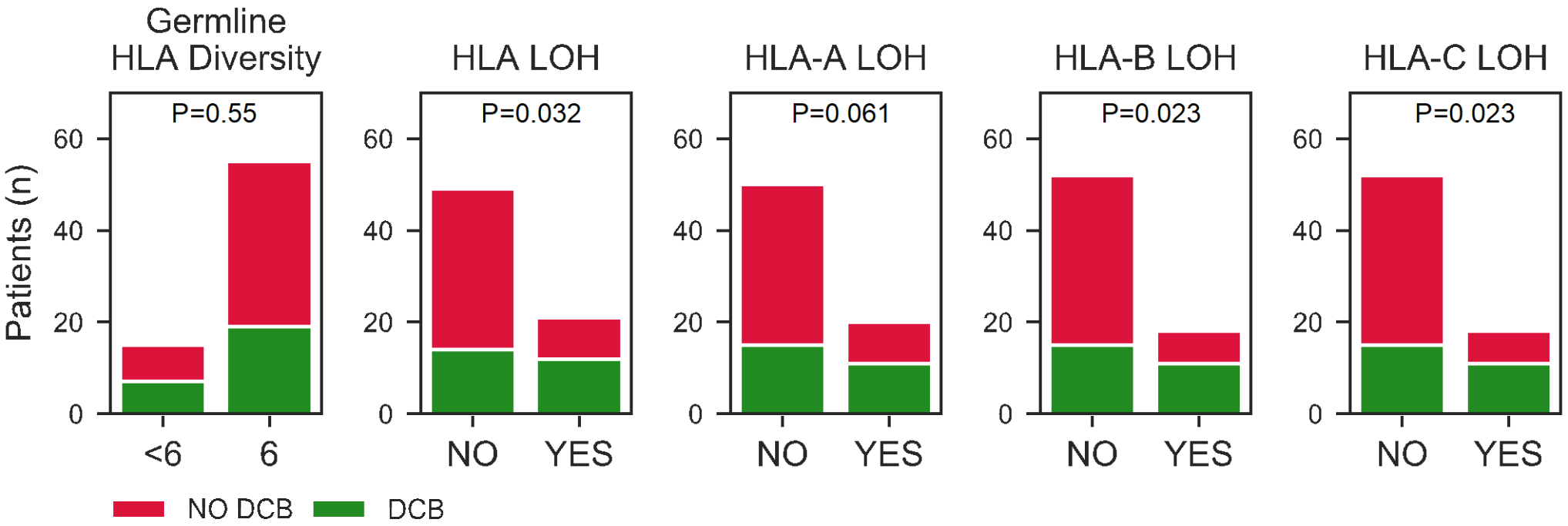
Technology Assessment of Next Generation Sequencing in Personalized Oncology

HLA class I diversity



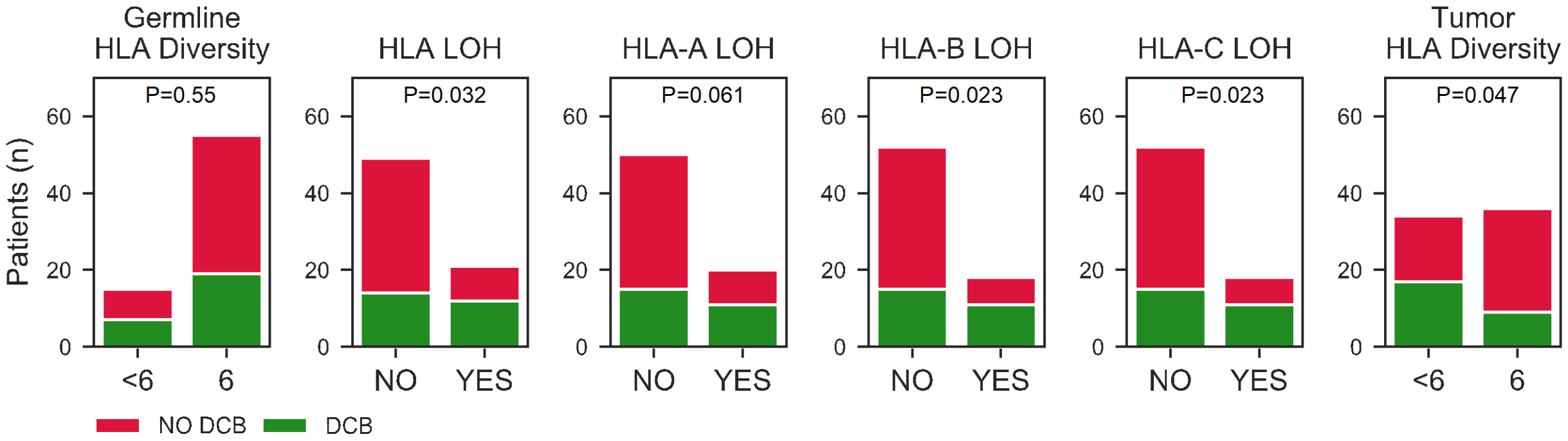
Technology Assessment of Next Generation Sequencing in Personalized Oncology

HLA class I diversity



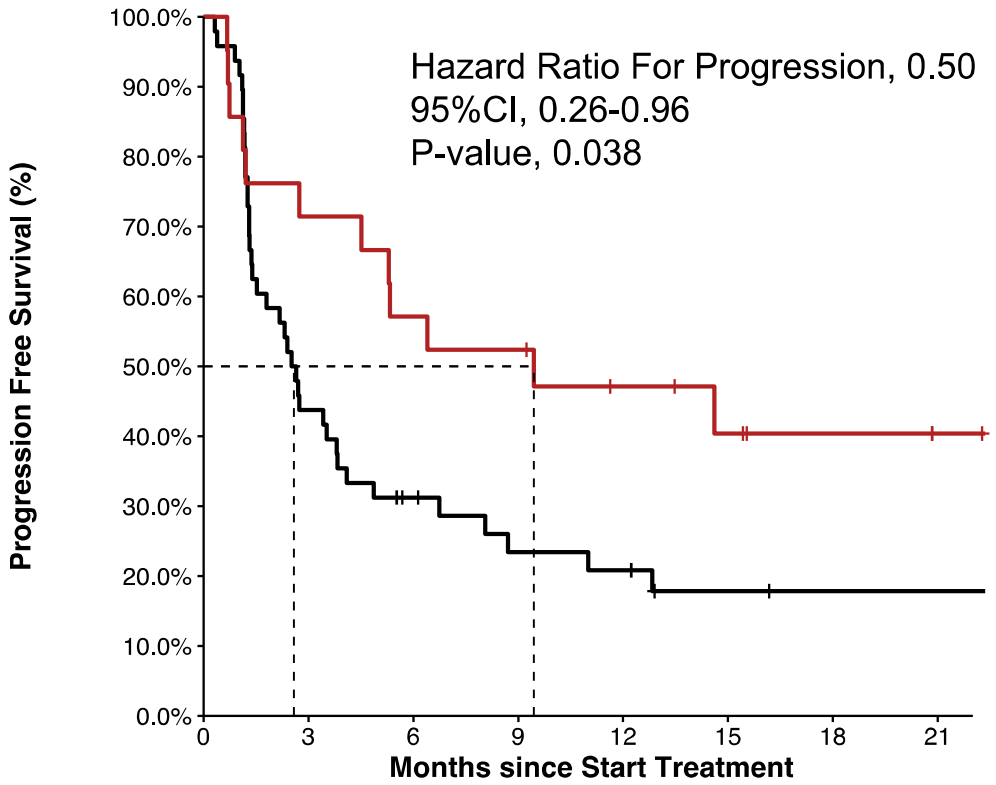
Technology Assessment of Next Generation Sequencing in Personalized Oncology

HLA class I diversity



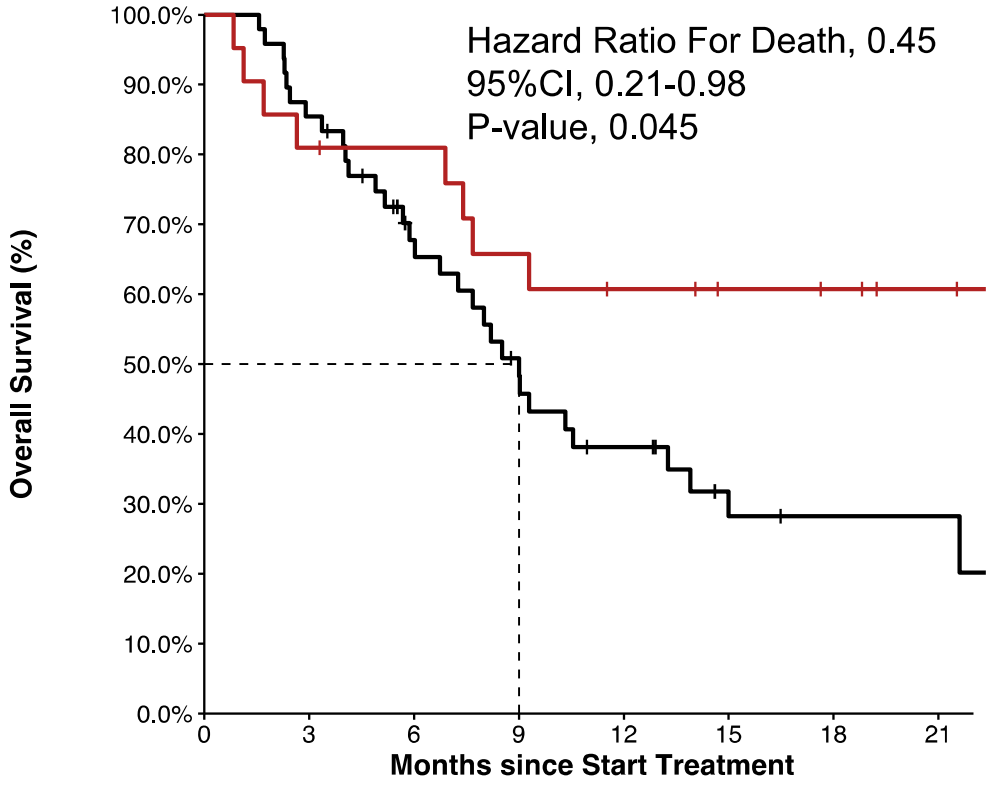
Technology Assessment of Next Generation Sequencing in Personalized Oncology

HLA class I diversity



No. at Risk

NO HLA LOH	48	21	13	9	8	5	4	4
HLA LOH	21	15	12	11	8	6	4	2



No. at Risk

NO HLA LOH	48	41	28	20	14	9	7	7
HLA LOH	21	17	16	13	11	9	8	6

External validation ongoing (Kevin Litchfield, Charles Swanton, CRUK Institute, London, UK)

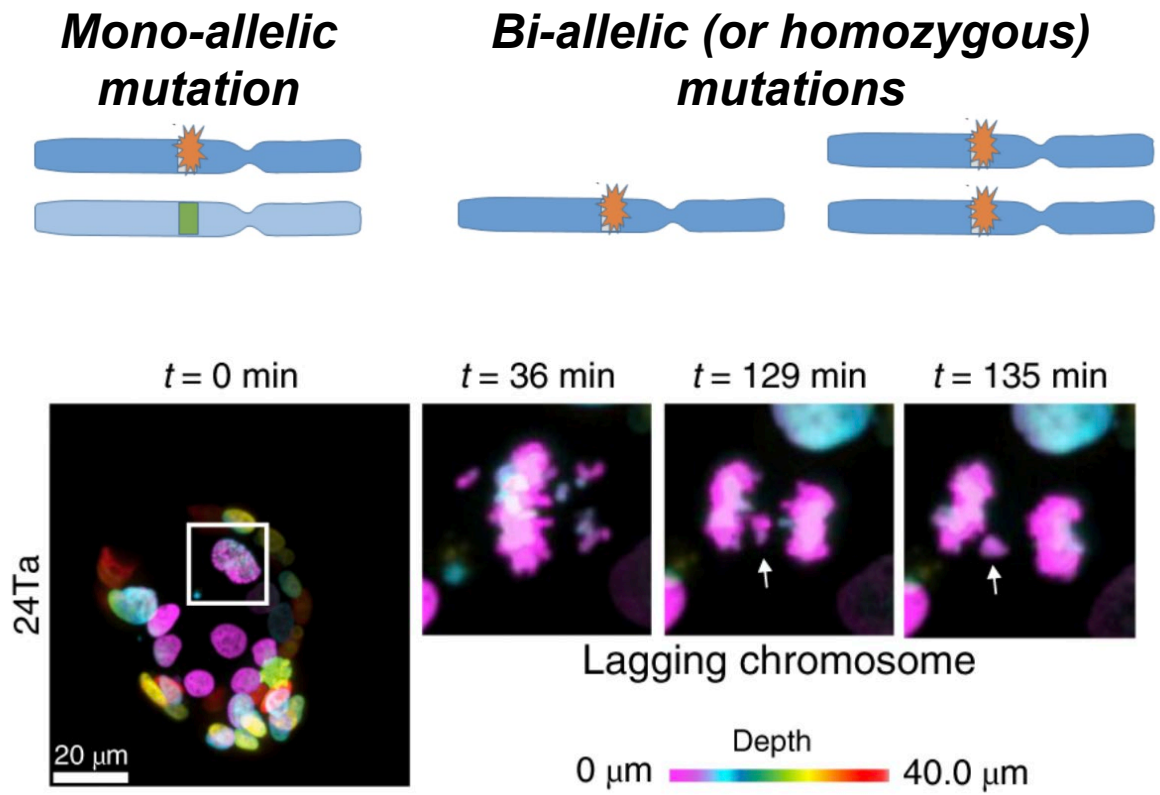
TRACERx

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Neoantigen loss through chromosome missegregation

Bi-allelic tumor mutational load & frameshift load

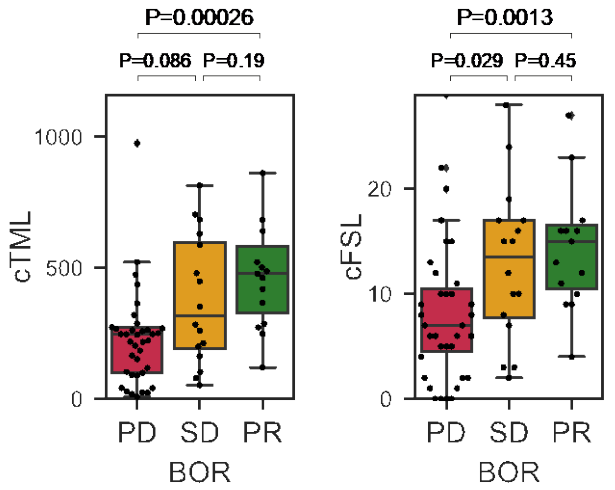
- ~20% of cell divisions have a chromosome missegregation
- 23x3 = 69 chromosomes per tumor cell, on average
- For each cell division, the probability of losing 1 chromosome is 20/69= 0.30%
- 1 cm tumor contains ~100.000.000 cells
- **1 cell division → 289,855 antigen-negative cells**



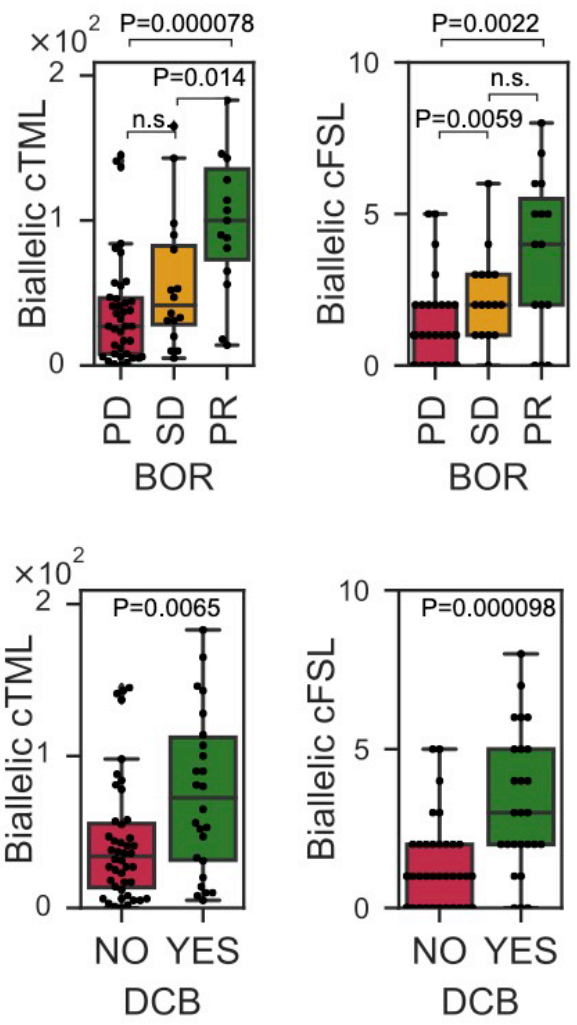
Bolhaqueiro, Nature Genetics, 2019

Bi-allelic tumor mutational load & frameshift load

All variants



Only bi-allelic variants



External validation ongoing (Kevin Litchfield, Charles Swanton, CRUK Institute, London, UK)

Technology Assessment of Next Generation Sequencing in Personalized Oncology

A simple combination of validating biomarkers
cTML+ PD-L1 IHC + RTK hotspots

LOW probability of clinical benefit:

- Low cTML (<median) AND low PD-L1 IHC (<1%)
- OR RTK hotspot mutation

INTERMEDIATE probability of clinical benefit:

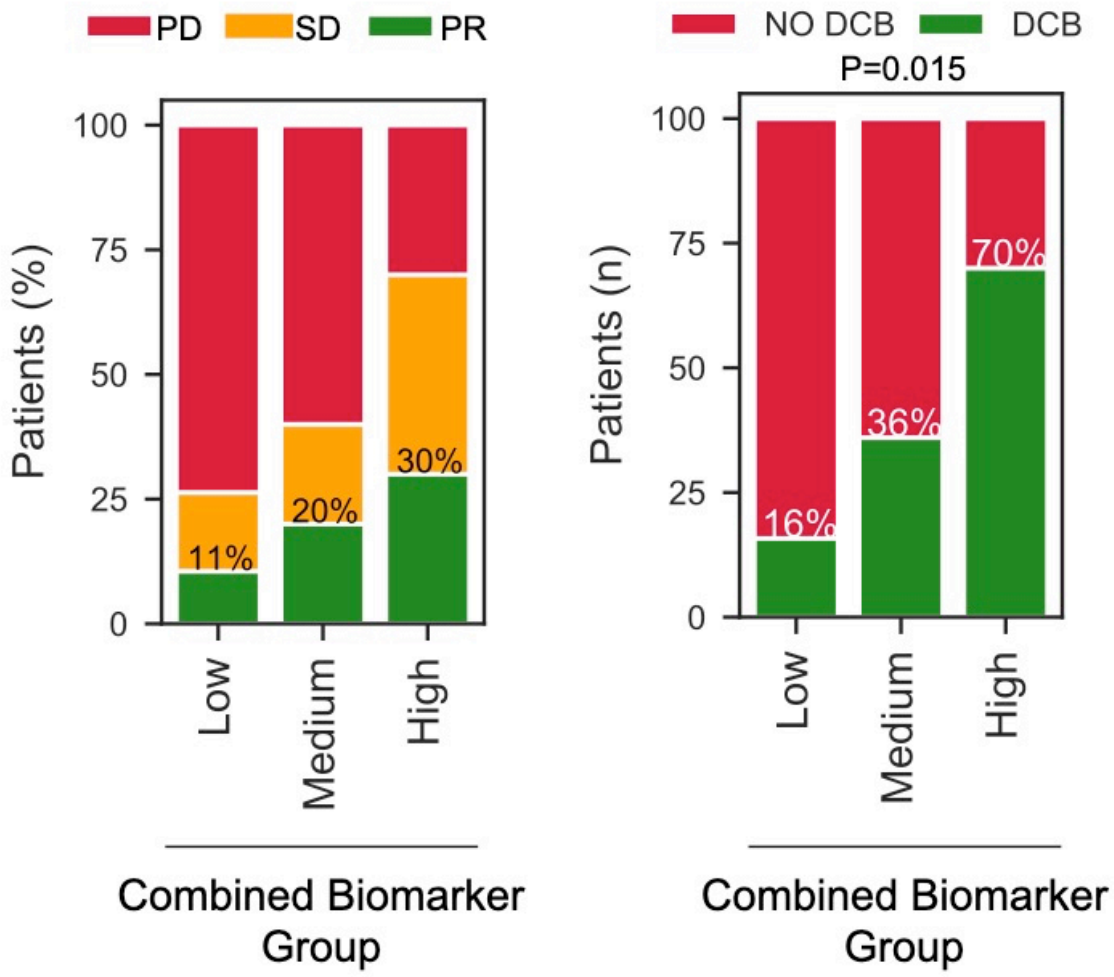
- Low cTML (<median) AND medium/high PD-L1 IHC (>1%)
- OR high cTML (>median) AND low PD-L1 IHC (<1%)
- AND no RTK hotspot mutation

HIGH probability of clinical benefit:

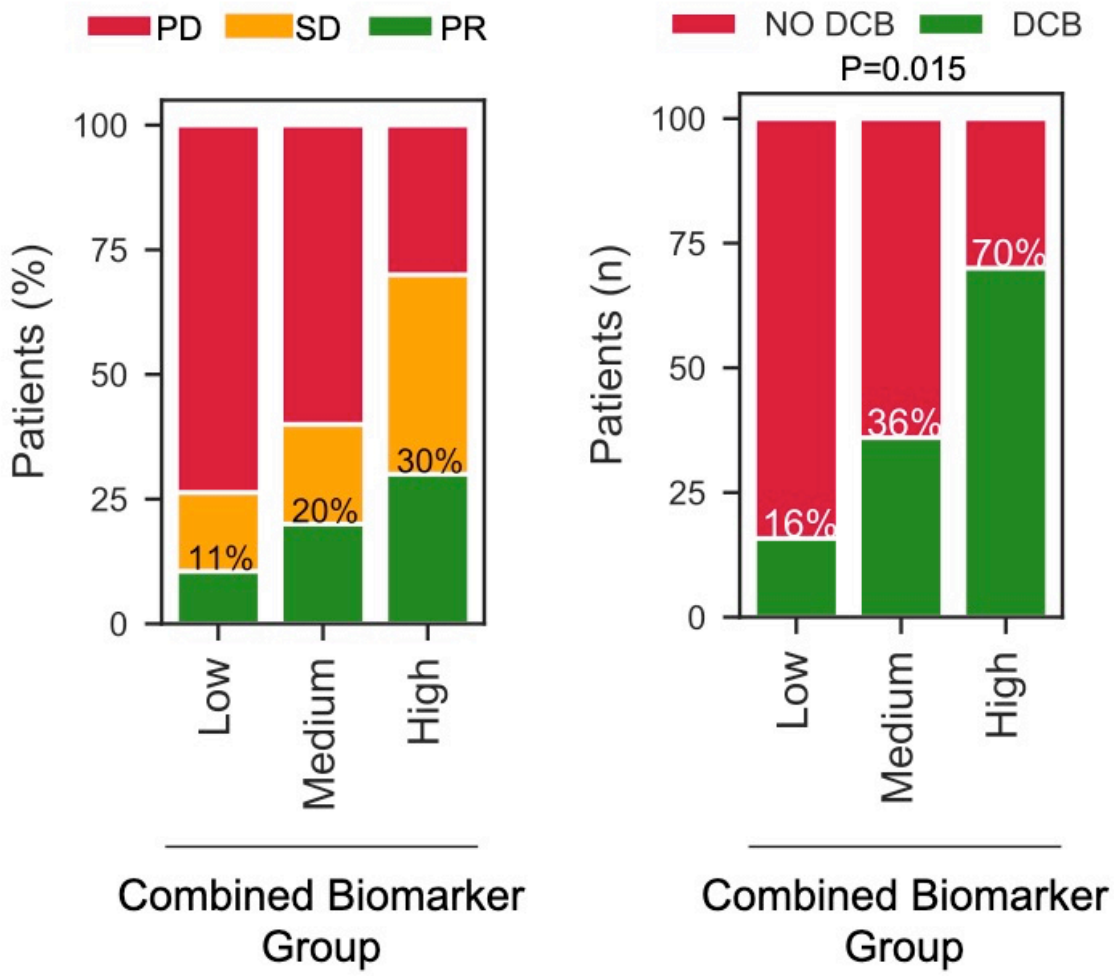
- High cTML (>median) AND medium/high PD-L1 IHC (>1%)
- AND no RTK hotspot mutation

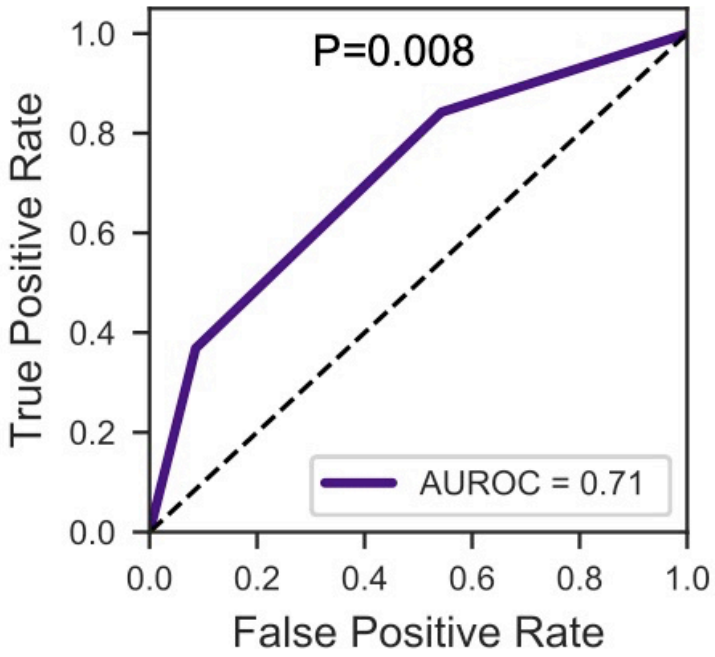
Technology Assessment of Next Generation Sequencing in Personalized Oncology

A simple combination of validating biomarkers
cTML+ PD-L1 IHC + RTK hotspots

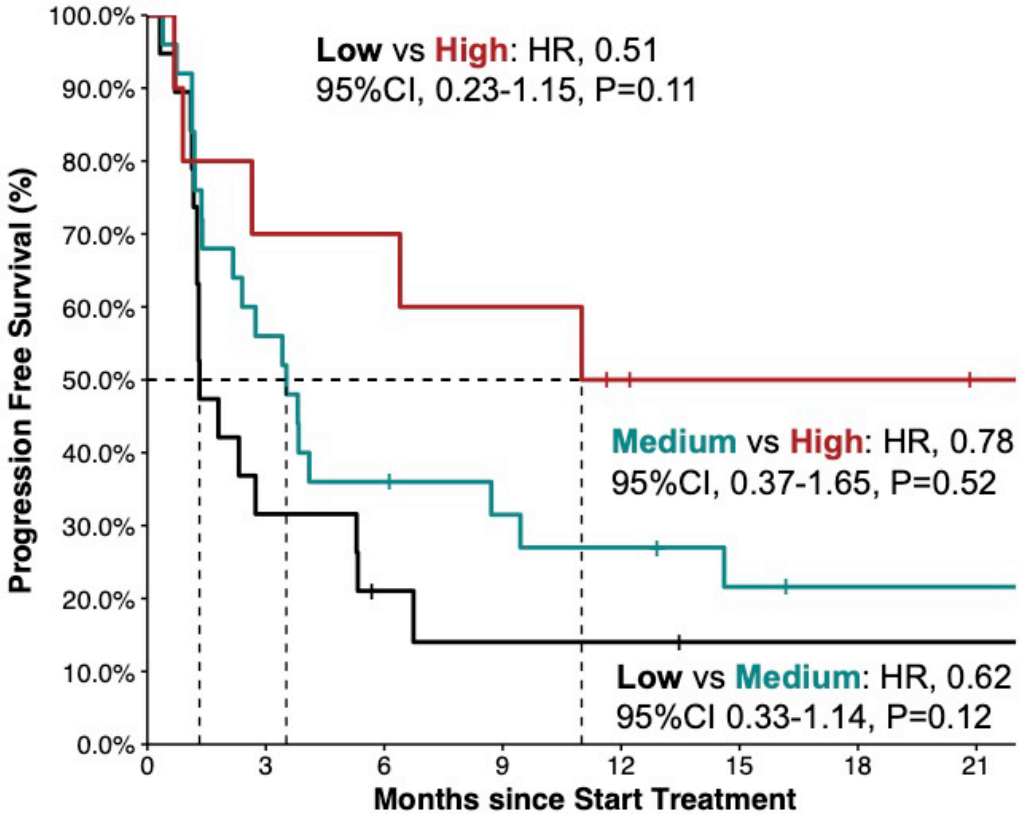


A simple combination of validating biomarkers
cTML+ PD-L1 IHC + RTK hotspots



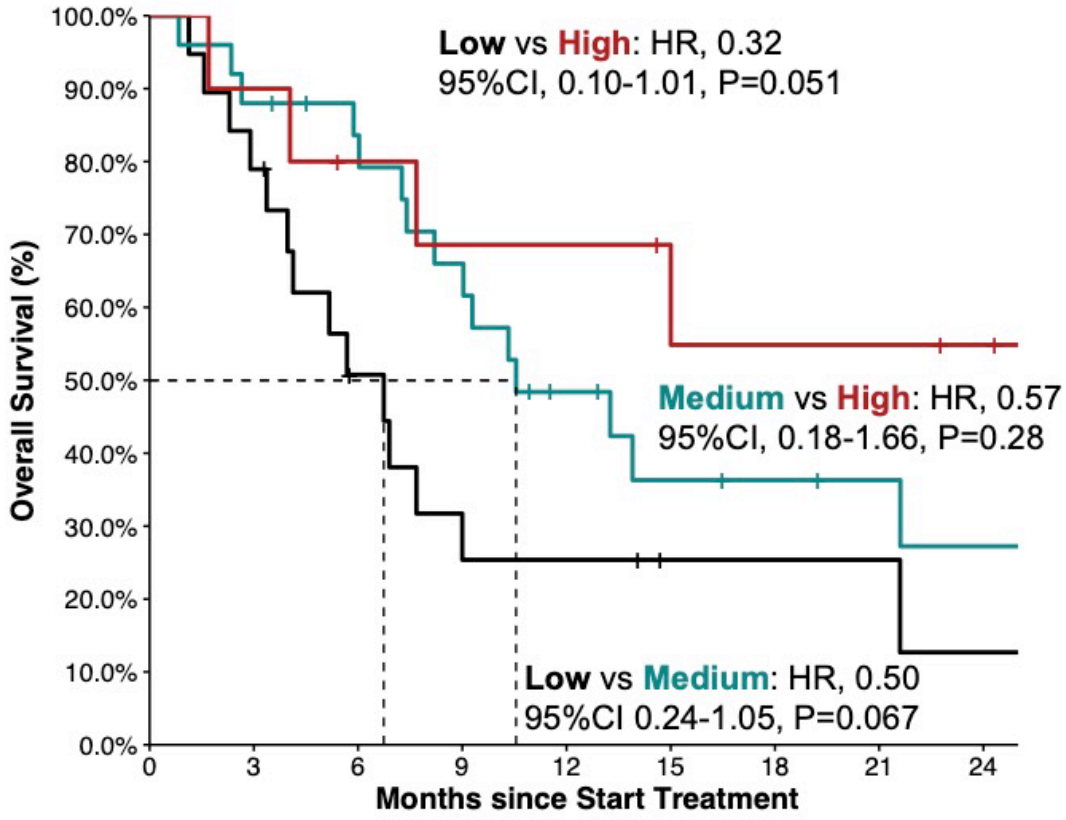


A simple combination of validated biomarkers
cTML+ PD-L1 IHC + RTK hotspots



No. at Risk

Low	19	6	3	2	2	1	1	1
Medium	25	14	9	7	6	4	3	3
High	10	7	7	6	4	3	3	2



No. at Risk

Low	19	15	8	5	4	2	2	2	1
Medium	25	22	19	15	9	6	5	4	3
High	10	9	7	6	6	5	4	4	3

Conclusions

1. We performed an **extensive external validation** of genomic biomarkers for PD-1 blockade in NSCLC
   - ✓ TMB/TML/FSL/tobacco signature (although all same signal)
   - ✓ RTK hotspot mutations
   - ~ PD-L1 IHC
   - X KRAS, STK11, KEAP1, PTEN muts
   - X Germline or somatic HLA diversity

2. We performed **biomarker discovery**, leading to several promising leads
   - Aneuploidy score – Validation failed X
   - Bi-allelic TML & FSL – Validation ongoing
   - HLA LOH – Validation ongoing

3. Genomic biomarkers achieved superior performance as compared to the clinically used PD-L1 immunohistochemistry

4. A simple combination of biomarkers identified ~1/3rd of patients with a low clinical benefit rate (16%)

Technology Assessment of Next Generation Sequencing in Personalized Oncology

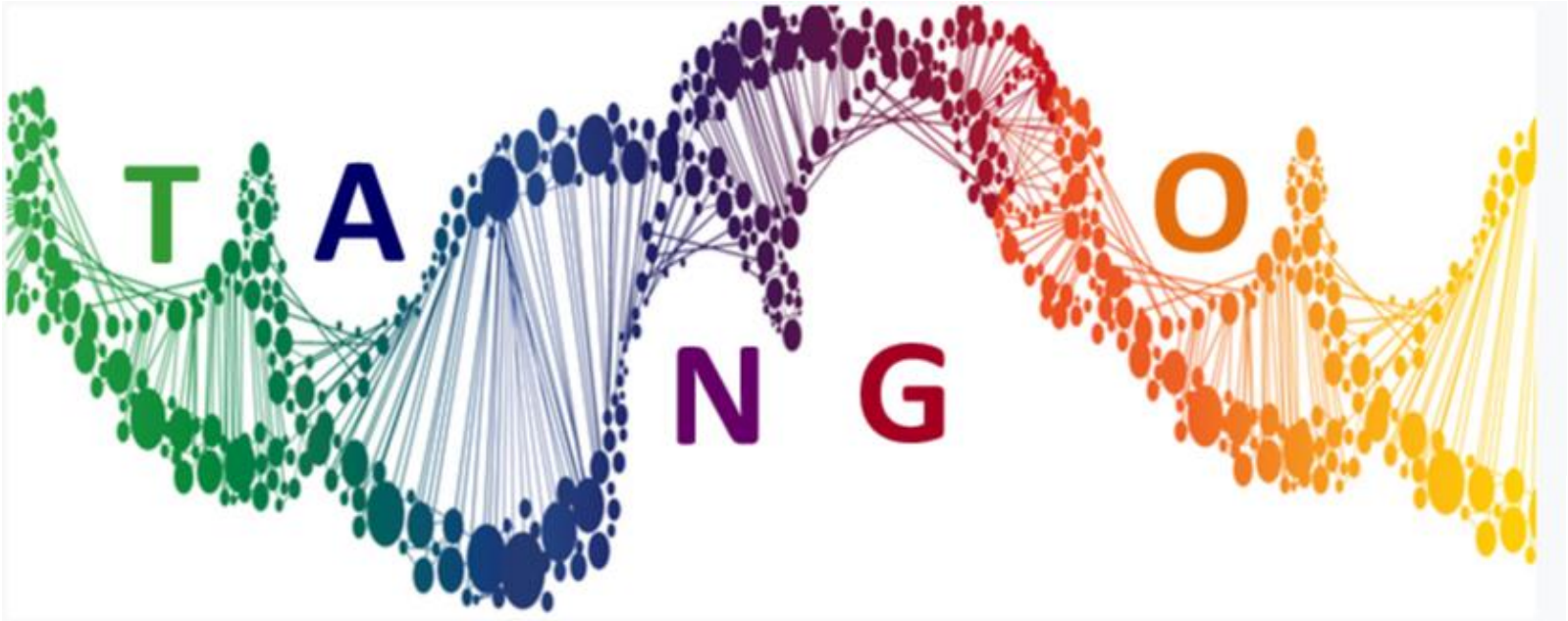
Next steps

1. Await external validation for HLA LOH & biallelic mutations as biomarker
2. Investigate fusion genes as potential biomarkers
3. Include RNA-based immune infiltration estimates as biomarkers
4. Complete manuscript

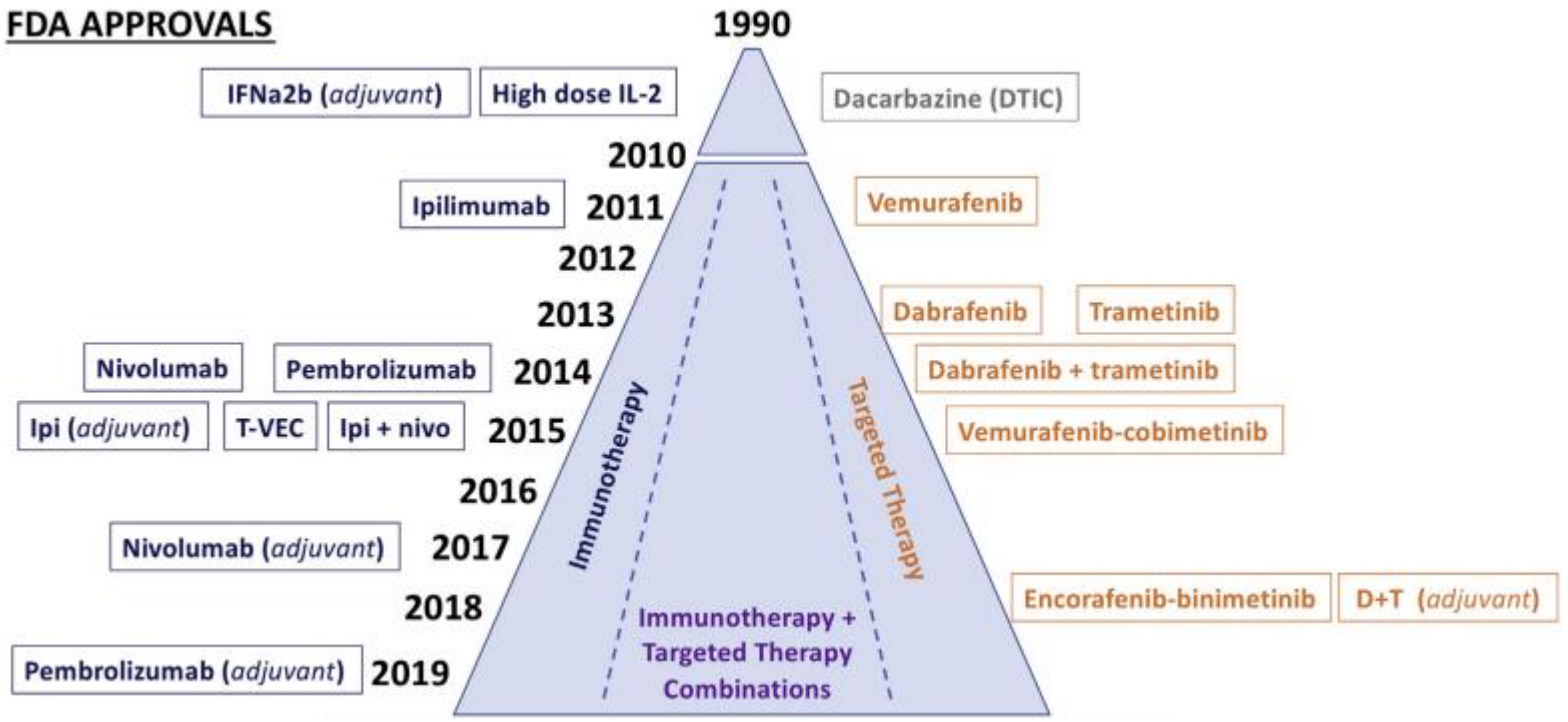
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Clinical response to systemic therapy in metastatic melanoma; towards a WGS-based biomarker

Analysis of the clinical data of immunotherapy treated melanoma patients, as part of the TANGO project (WP2)
PhD: Drs. J.C.L Notohardjo, PI: Prof dr. A.J.M van den Eertwegh
Amsterdam UMC, (VUmc)



FDA-approved therapies for melanoma



[1]Jenkins et al, 2020, Journal of Investigative Dermatology.

Technology Assessment of Next Generation Sequencing in Personalized Oncology

FDA-approved therapies for melanoma

Agent	Mechanism	FDA-approved indications
Targeted Therapies		
Vemurafenib	BRAF inhibitor	- Unresectable/metastatic melanoma harboring BRAF V600E/K mutation
Cobimetinib	MEK inhibitor	- Unresectable/metastatic melanoma harboring BRAF V600E/K mutation
Dabrafenib + trametinib	BRAF inhibitor + MEK inhibitor	- Unresectable/metastatic melanoma harboring BRAF V600E/K mutation - Adjuvant treatment of resected stage III BRAF V600E/K mutant melanoma
Vemurafenib + cobimetinib	BRAF inhibitor + MEK inhibitor	- Unresectable/metastatic melanoma harboring BRAF V600E/K mutation
Encorafenib + binimetinib	BRAF inhibitor + MEK inhibitor	- Unresectable/metastatic melanoma harboring BRAF V600E/K mutation
Immunotherapies		
Ipilimumab	Anti–CTLA-4 monoclonal antibody	- Unresectable/metastatic melanoma (regardless of BRAF status) - Adjuvant treatment of resected stage III melanoma (regardless of BRAF status)
Nivolumab	Anti–PD-1 monoclonal antibody	- Unresectable/metastatic melanoma (regardless of BRAF status) - Adjuvant treatment of resected stage III melanoma (regardless of BRAF status)
Pembrolizumab	Anti–PD-1 monoclonal antibody	- Unresectable/metastatic melanoma (regardless of BRAF status) - Adjuvant treatment of resected stage III melanoma (regardless of BRAF status)
Ipilimumab-nivolumab	Anti–CTLA-4 antibody + anti–PD-1 antibody	- Unresectable/metastatic melanoma (regardless of BRAF status)
T-VEC	Modified, injectable oncolytic herpes virus	Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after surgery

Abbreviations: FDA, Food and Drug Administration; MEK, MAPK kinase; T-VEC, talimogene laherpraepvec.

[1]Jenkins et al, 2020, Journal of Investigative Dermatology.

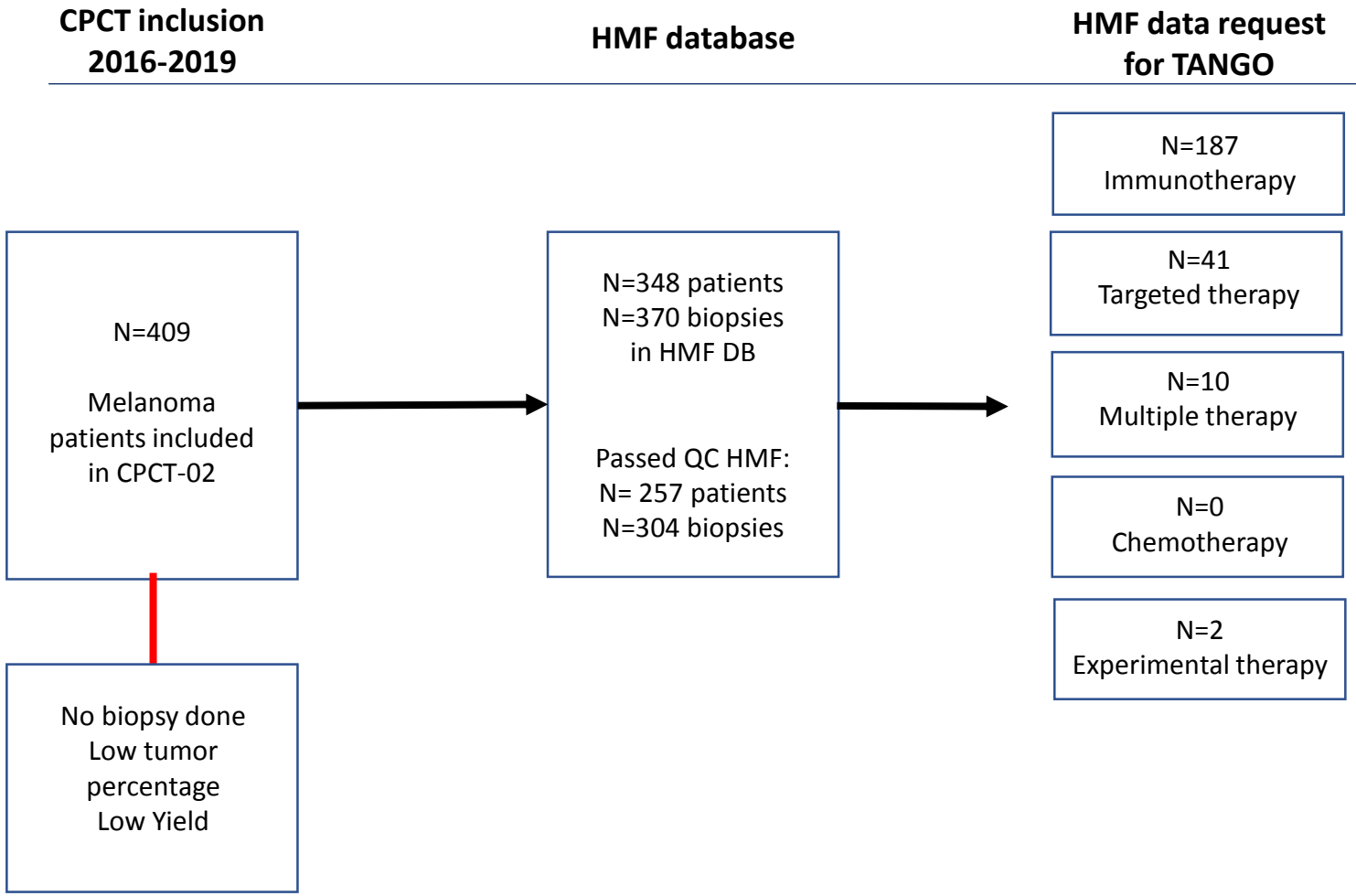
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Objectives work package 2

- Demonstrate the value of whole genome sequencing (WGS) for immunotherapy treatment selection in NSCLC and **melanoma**
  - Discovery of genomic and transcriptomic correlates
  - Identify potential biomarkers for patient stratification

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Patient selection for TANGO (from CPCT-02)



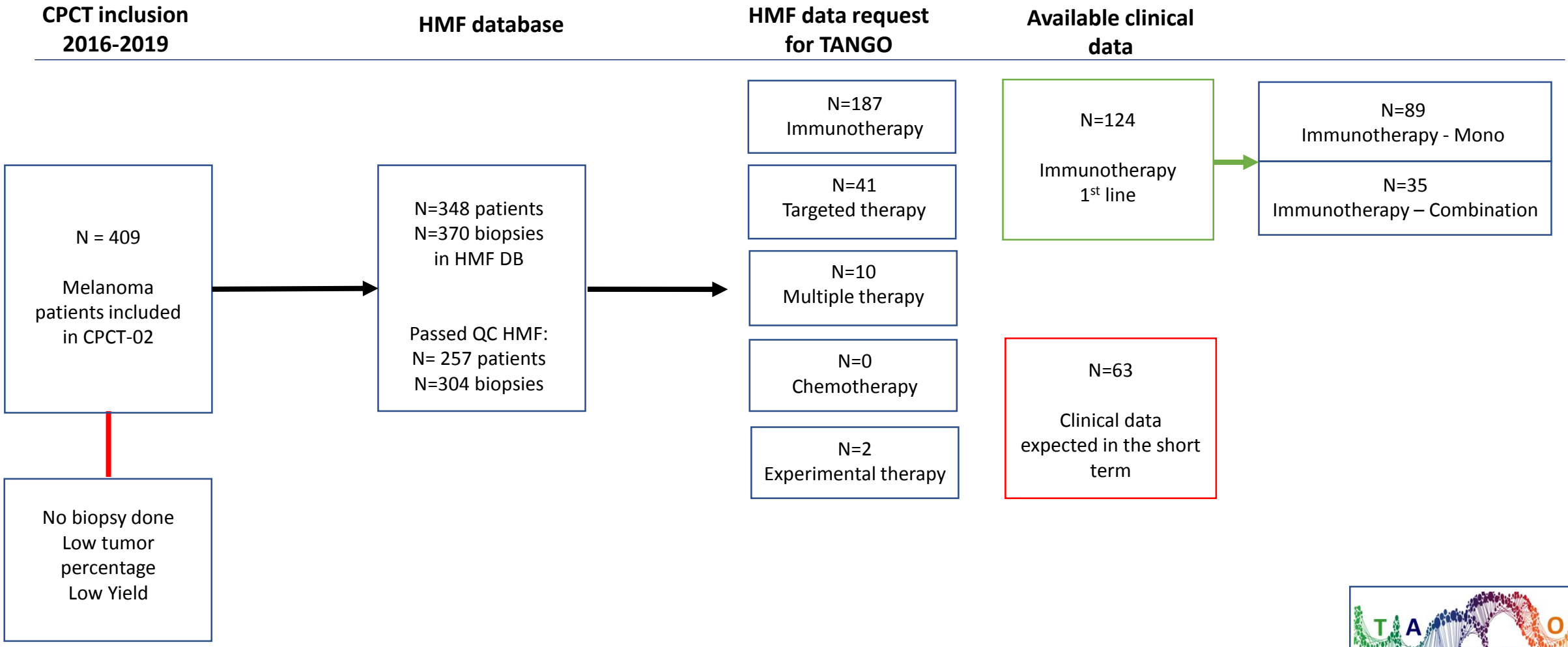
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Clinical data collection

Hospital	METC approval	Data transfer agreement	COVID-19 delay	Data collected
Amsterdam UMC (Vumc)	+	Not needed		+
Amphia Hospital	*Vumc*	Not needed		+
Erasmus MC	+	In progress	+	In progress
Isala	*Vumc*	Not needed		+
Maastricht UMC	+	Not needed	+	+
NKI-AVL	*Vumc*	Not needed	+	+
UMC Utrecht	+	+	+	+

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Patient selection for TANGO (from CPCT-02)



Technology Assessment of Next Generation Sequencing in Personalized Oncology

Baseline Characteristics Immunotherapy (n=124)

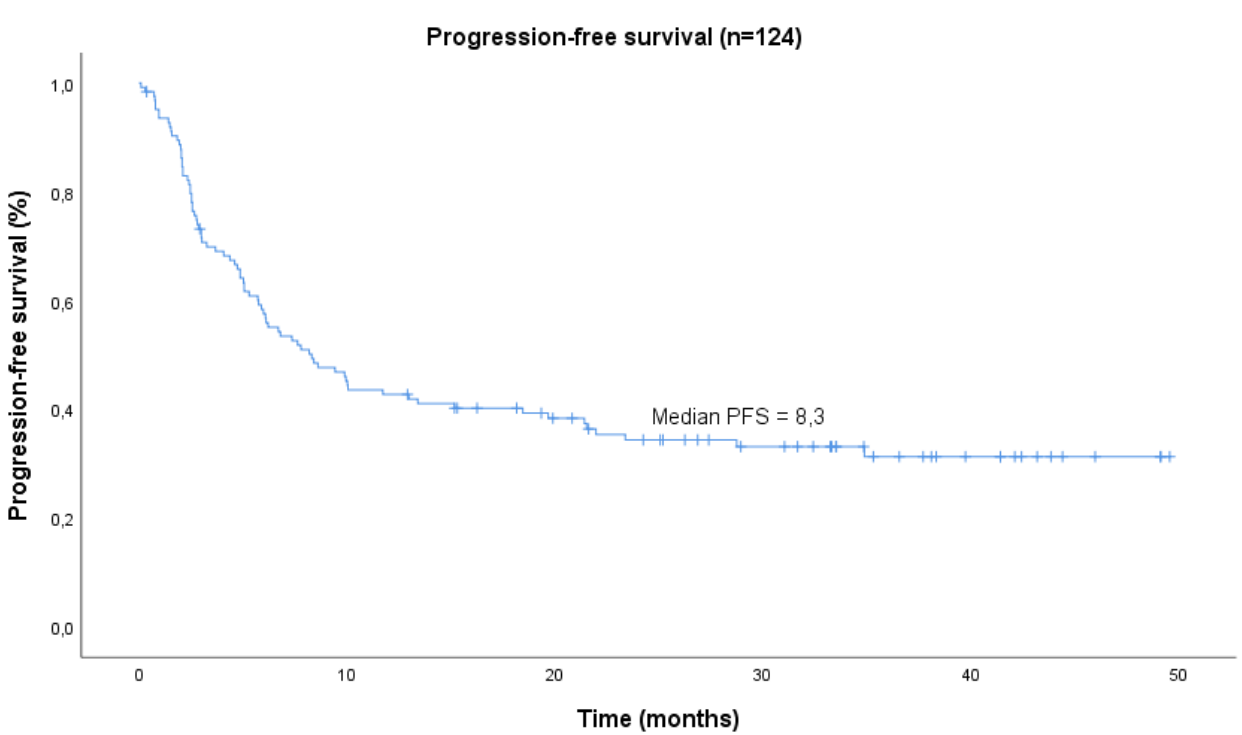
Characteristics	Immuno monotherapy (n=89)	Immuno combination therapy (n=35)	p value
Age (years)	65 ± 12	58 ± 15	0.105
Missing	0	0	
Gender			0.224
Female	40 (44,9)	11 (31,4)	
Male	49 (55,1)	24 (68,6)	
Missing	0	0	
ECOG PS			0.069
0	57 (64,0)	29 (82,9)	
1	30 (33,7)	5 (14,3)	
≥2	2 (2,2)	1 (2,9)	
Missing	0	0	
Histology			0.336
SSM	14 (15,7)	11 (31,4)	
Nodular	12 (13,5)	1 (2,9)	
Other	20 (22,5)	5 (14,3)	
Missing	43 (48,3)	18 (51,5)	
Prior systemic treatment			0.294
No	76 (85,4)	27 (77,1)	
Yes	13 (14,6)	8 (22,9)	
Missing	0	0	
Lactate dehydrogenase (U/l)	223 [184-264]	218 [182-289]	0.650
Normal	63 (70,8)	22 (62,9)	
250-500	18 (21,3)	10 (28,6)	
>500	7 (7,9)	3 (8,6)	
Missing	0	0	

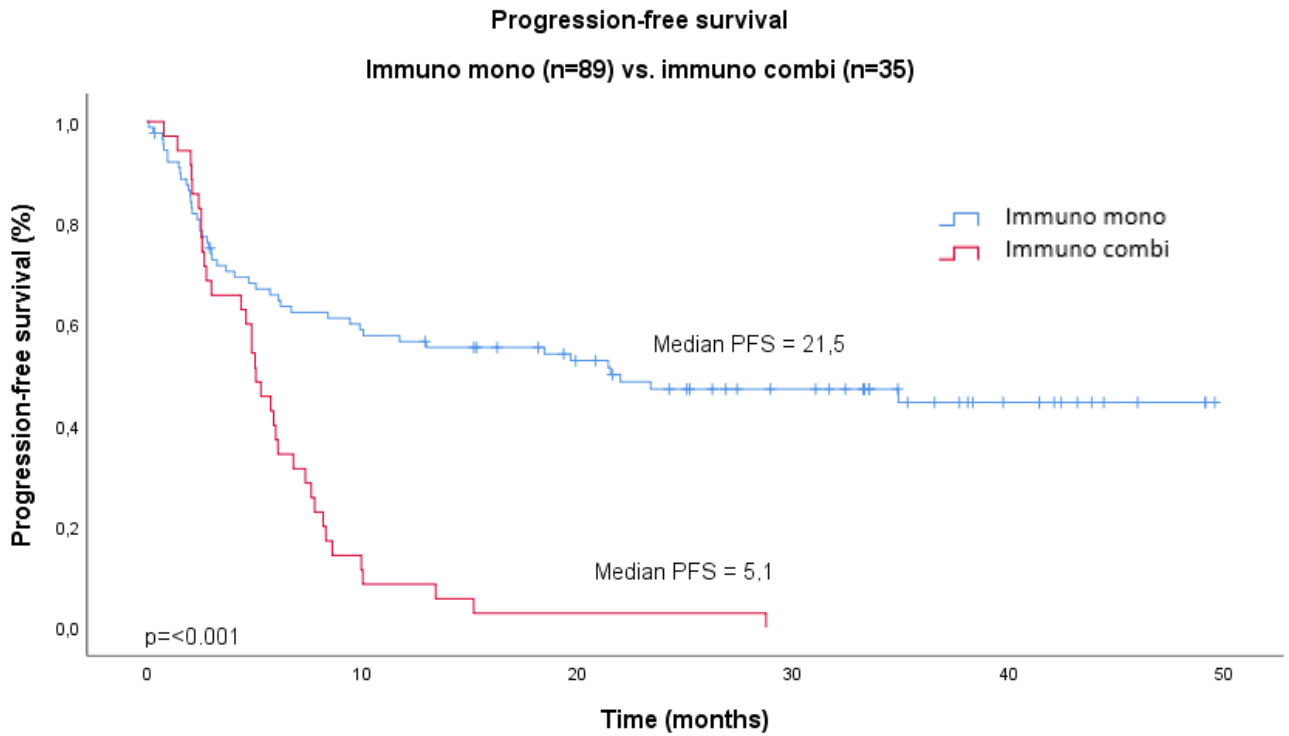
NOTE. Data are presented as mean ± SD, median [interquartile range] or number of patients (%).

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Perfomance Score; SSM, Superfical Spreading Melanoma

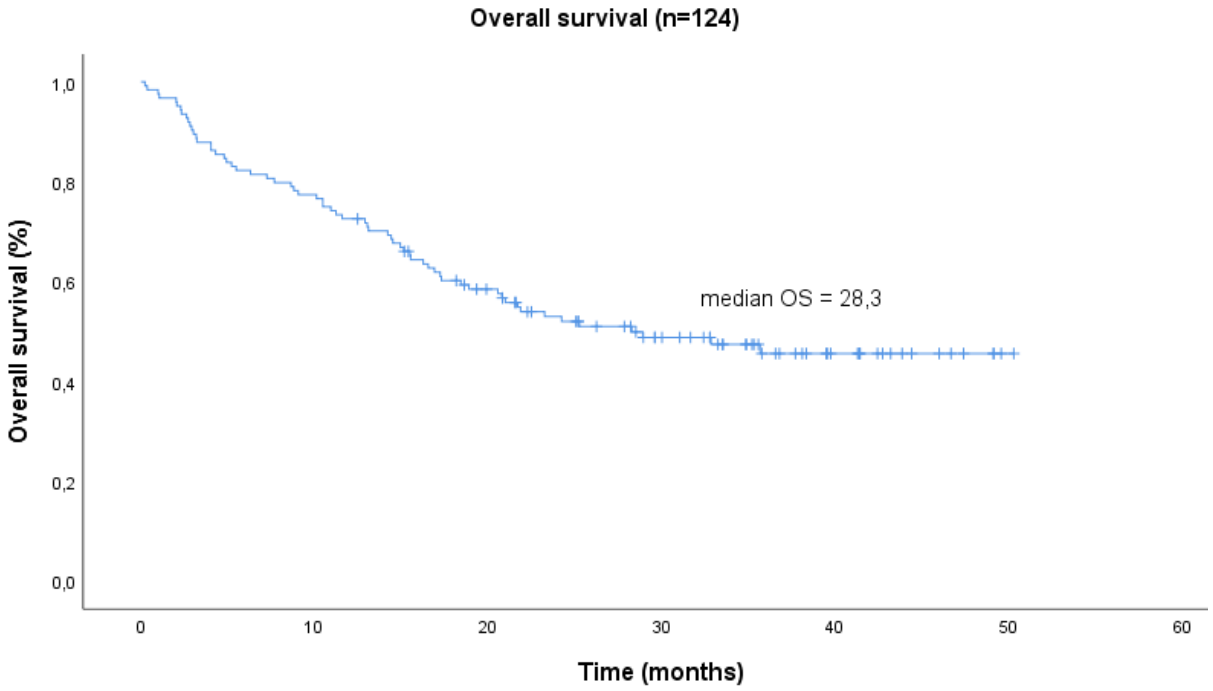
Technology Assessment of Next Generation Sequencing in Personalized Oncology

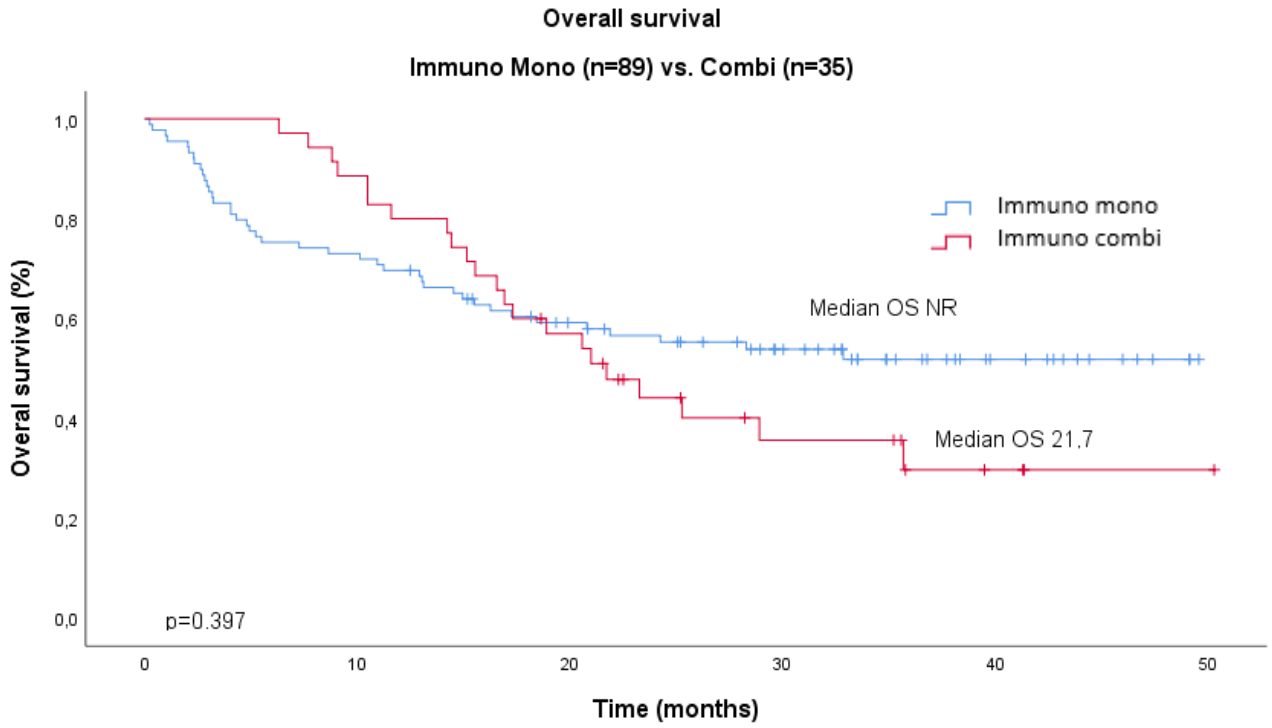
PFS TANGO melanoma cohort



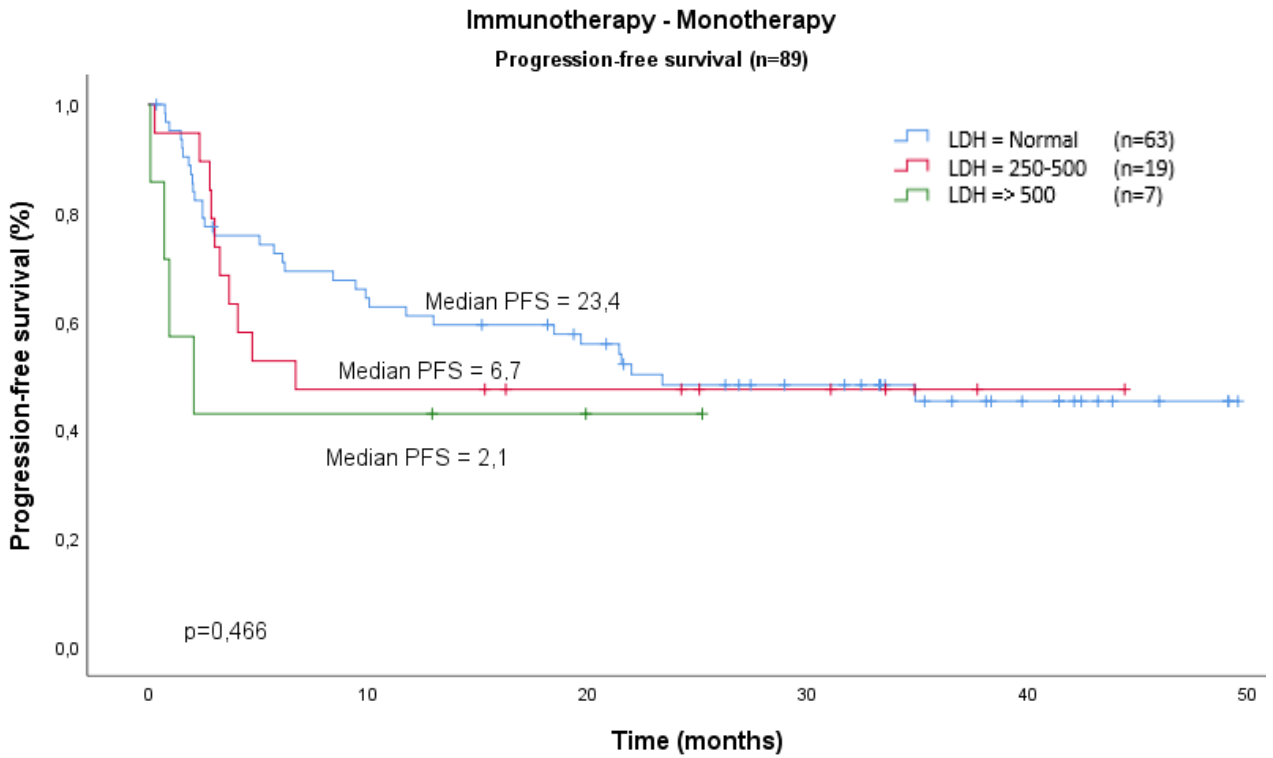


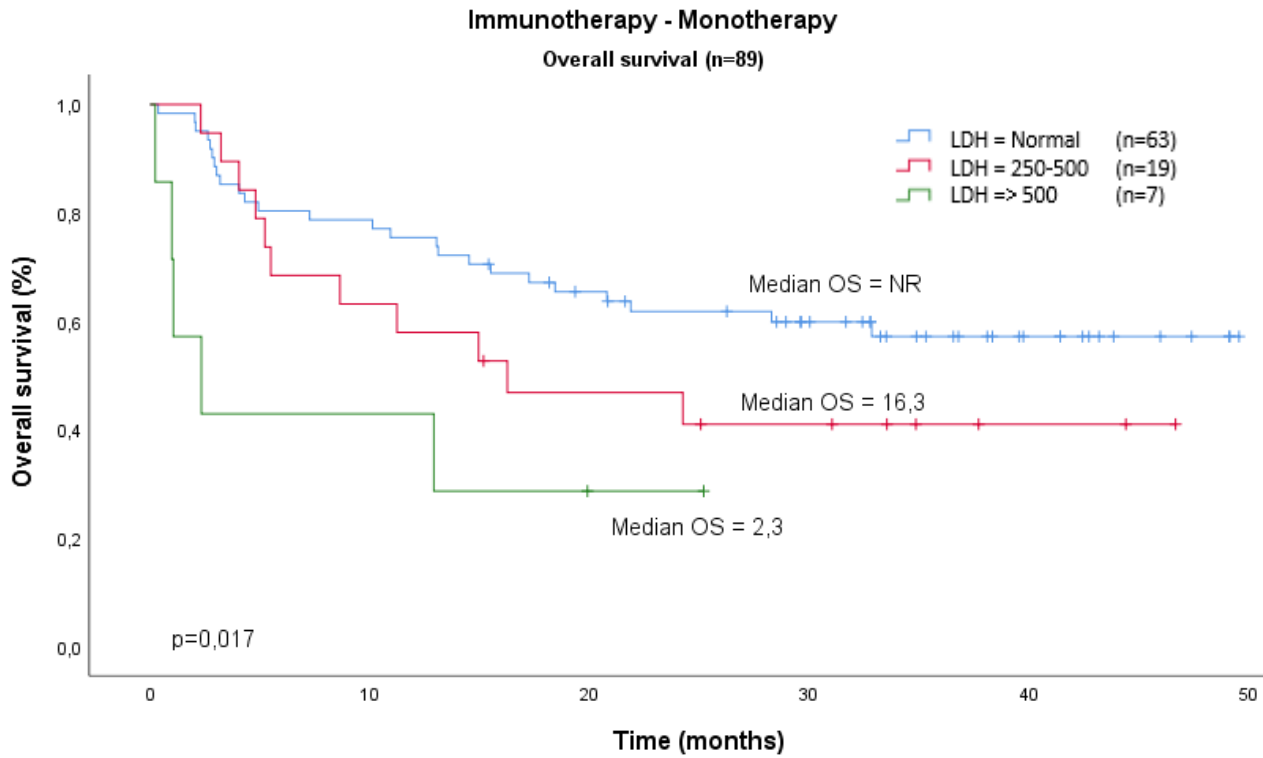
OS TANGO melanoma cohort



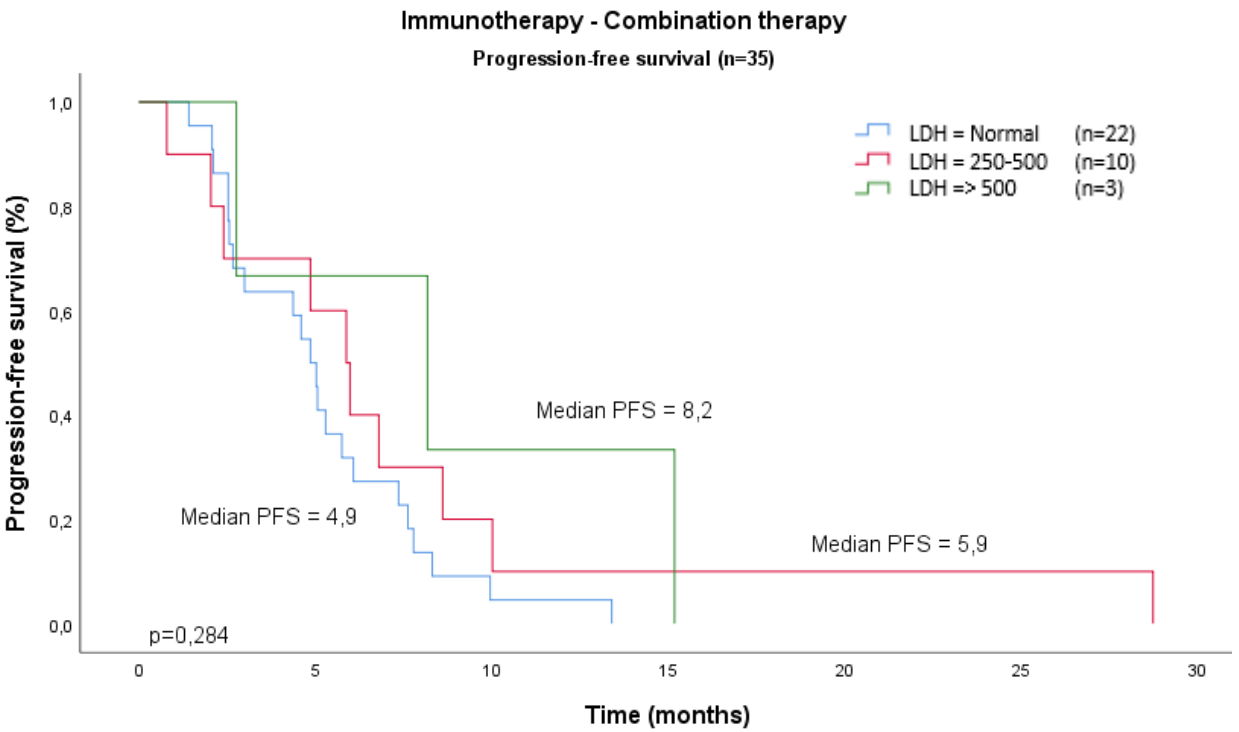


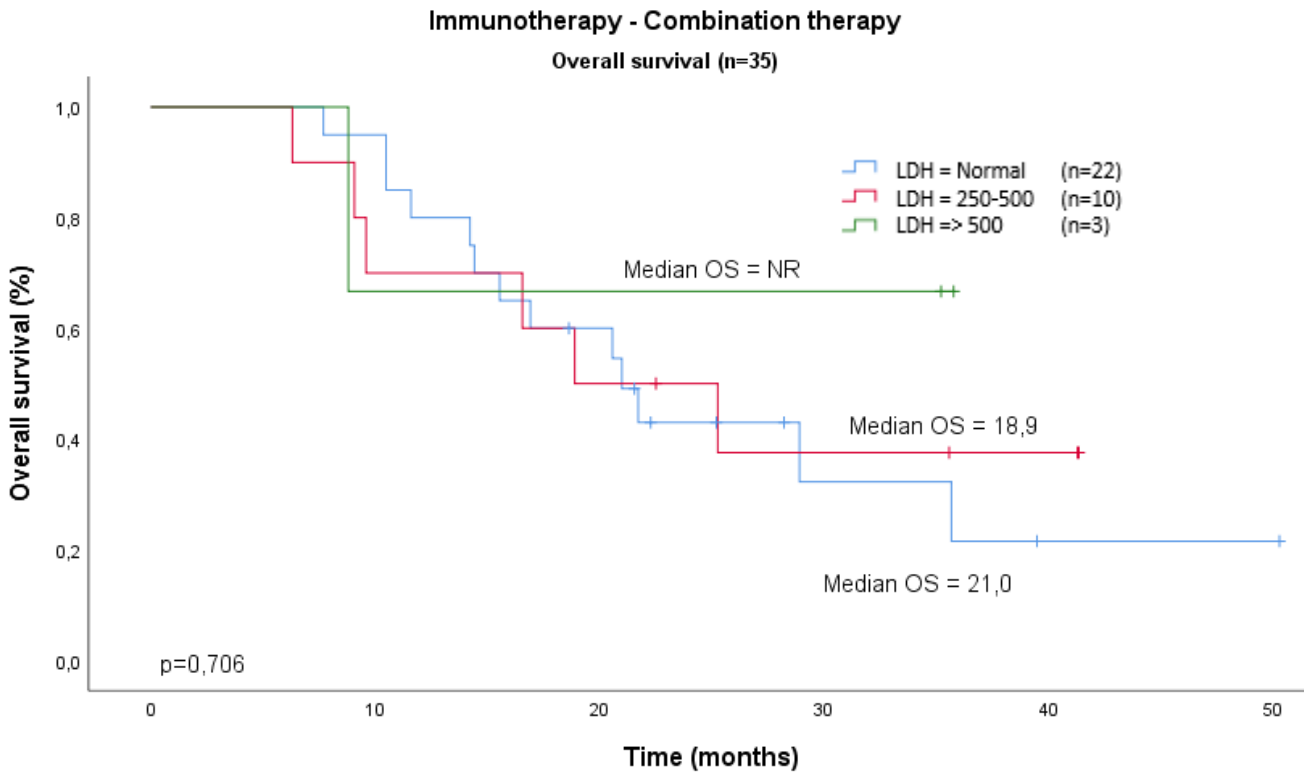
PFS and OS compared to LDH baseline Immuno – Monotherapy (n=83)



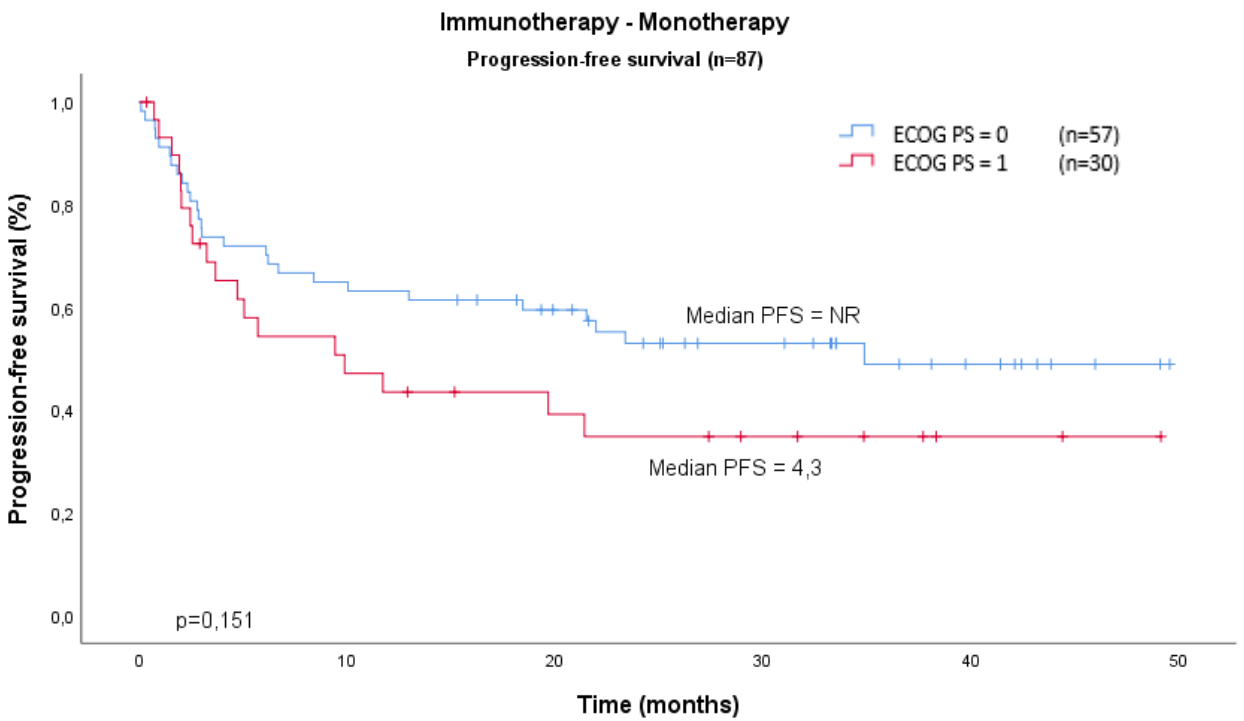


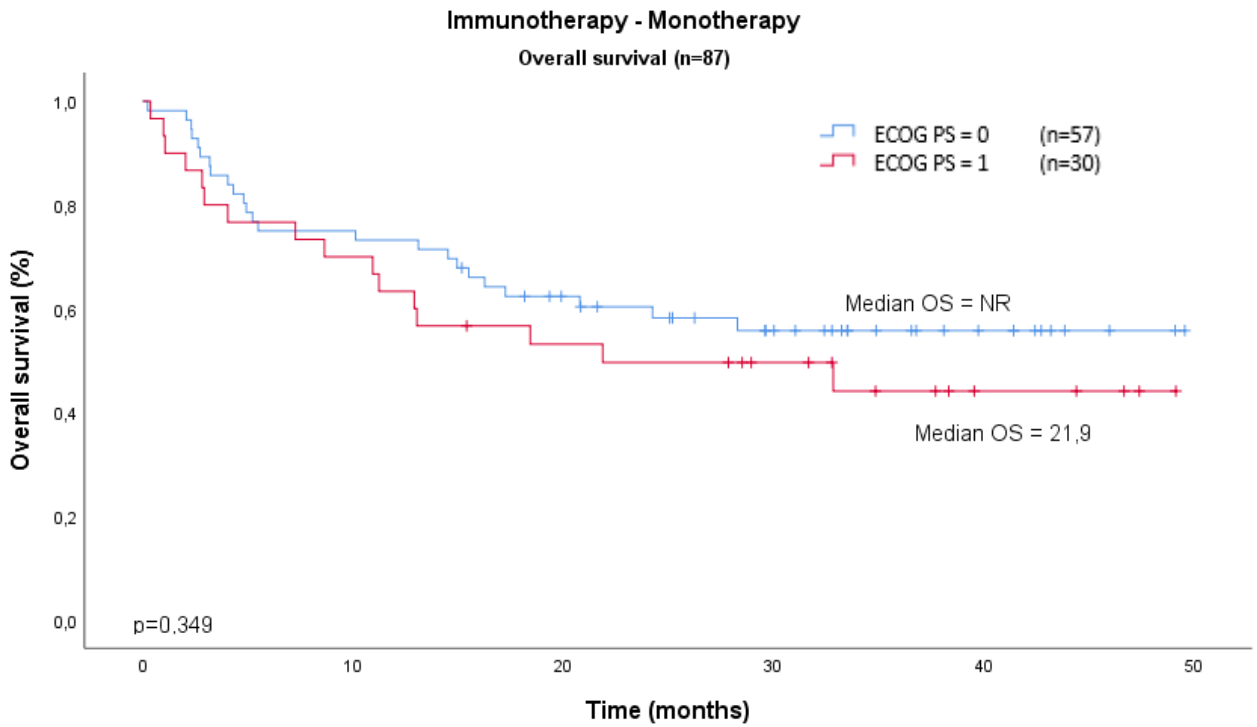
PFS and OS compared to LDH baseline Immuno – Combination therapy (n=35)



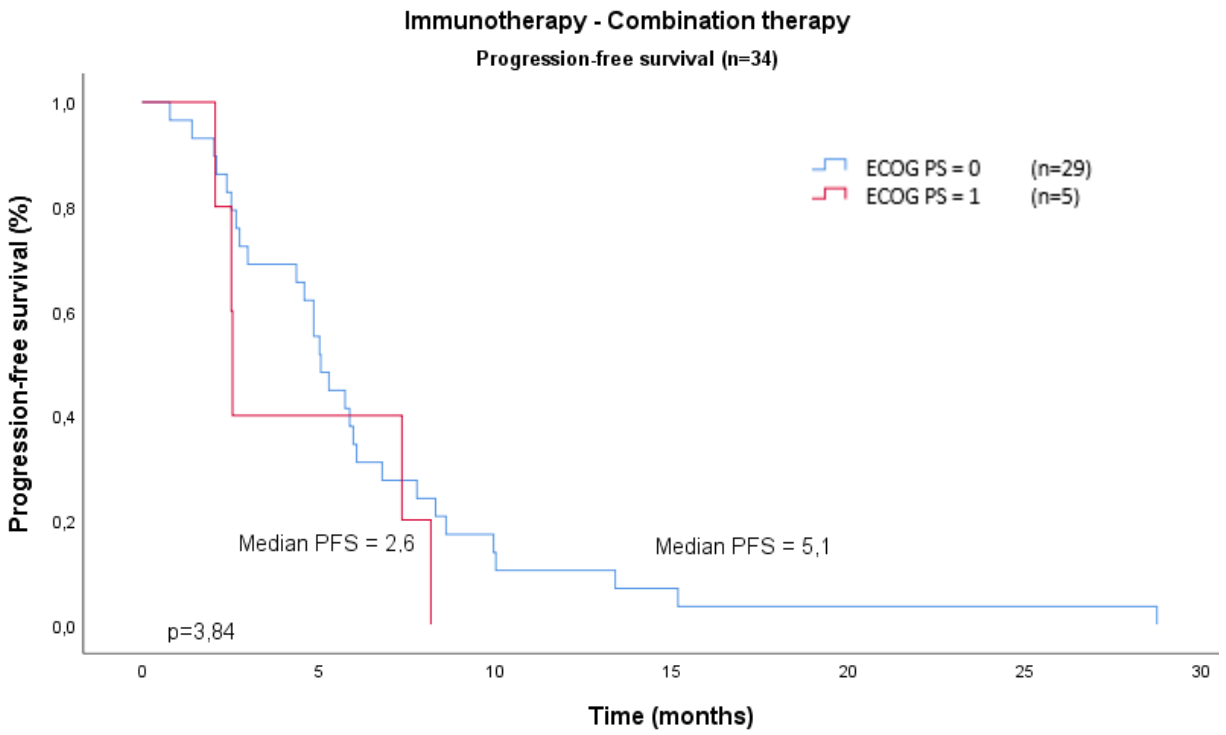


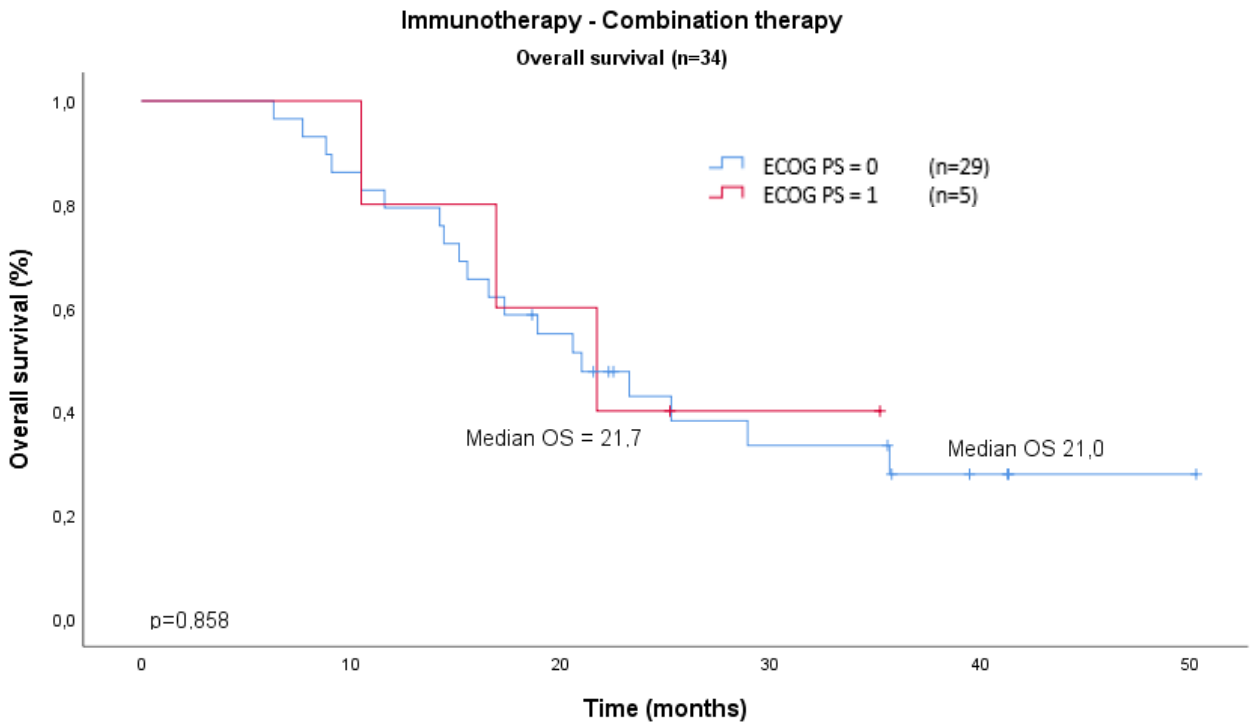
PFS and OS compared to ECOG PS baseline Immuno – Monotherapy (n=87)





PFS and OS compared to ECOG PS baseline Immuno – Combination therapy (n=34)





What's next?

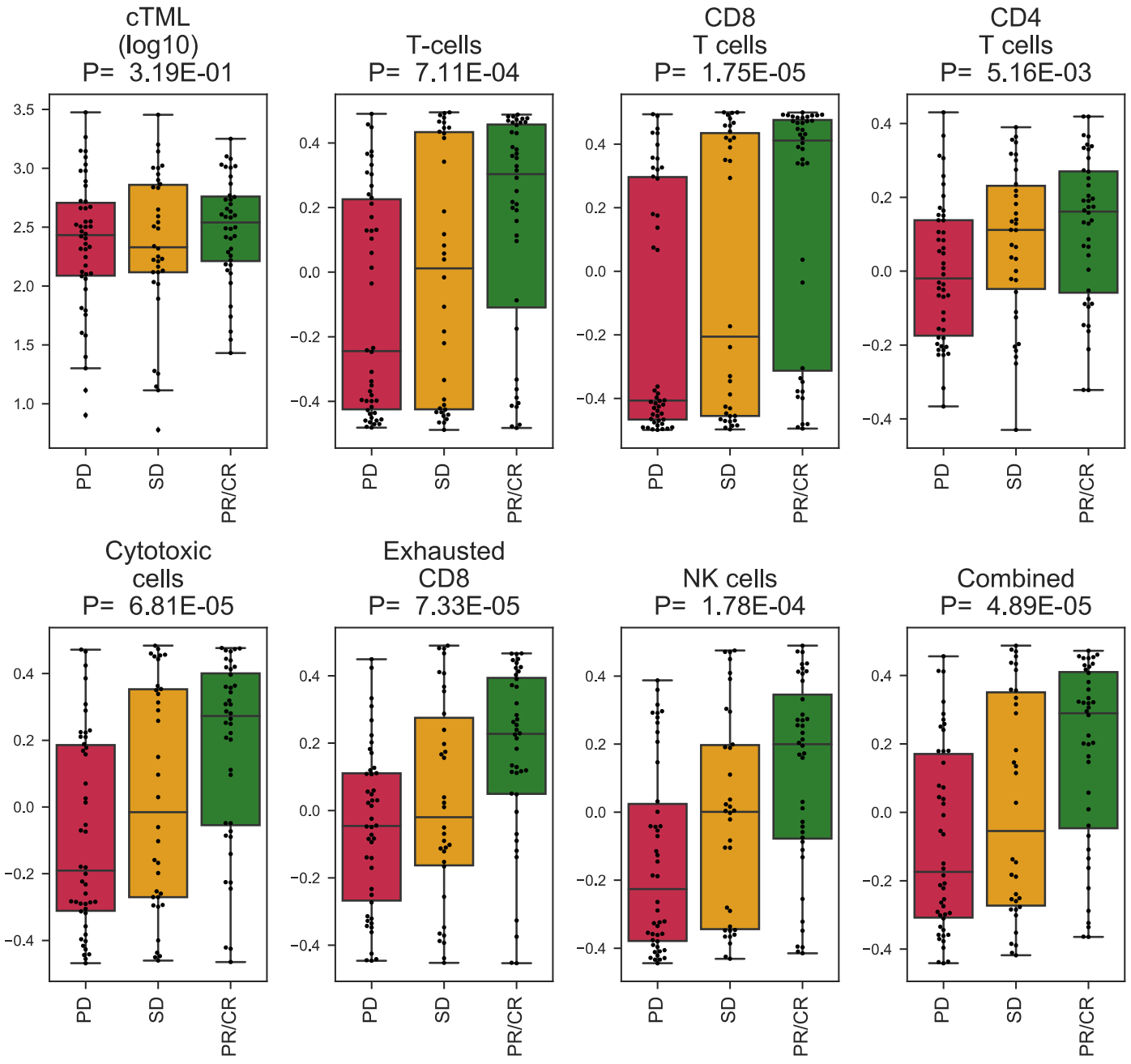
- Completing the data collection (DTA Erasmus MC)
- Genomic and transcriptomic analysis
- Identification potential biomarkers for patient stratification

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Preliminary result

N=120

- Clonal TML (WGS)
- Immune cell infiltration (RNA)



Development and validation of patient-level micro-simulation model for cost-effectiveness analysis of immunotherapy in the Netherlands

Prospect of WGS – Biomarkers in Clinical practice

Tango Mini-Symposium 2020
Tango WP3

PI's: V. Coupé, M. Joore and J. Wilschut

PhD student: Zakile A. Mfumbilwa

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Objectives

1. To **develop and validate a patient-level micro-simulation model** of the treatment trajectory of patients with metastatic non-small cell lung cancer in the Netherlands.

   → Paper 1

2. To assess the **cost-effectiveness of immunotherapy biomarker** for patients with metastatic non-small cell lung cancer in the Netherlands.

   Using model developed in 1.

   → Paper 2

T A O N G

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Tasks

Paper 1 **Goal: Externally validated micro-simulation model of metastatic NSCLC**	**Paper 2** **Goal: CEA of biomarker based immunotherapy for metastatic NSCLC**
Task 1: Analyse data for treatment pattern and the distribution of baseline characteristics.	**Task 8:** Inclusion of cost and utilities.
Task 2: Model conceptualization.	**Task 9:** Simulation of different diagnostic and immunotherapy strategies.
Task 3: Fit parametric survival model for all transitions.	**Task 10:** Assess the impact of uncertainties.
Task 4: Building a micro-simulation model.	**Task 11:** Threshold analyses.
Task 5: Internal validation (Santeon data 2008 -2014).	
Task 6: Inclusion of literature based molecular characteristics and treatment effects of novel treatment.	
Task 7: External validation.	

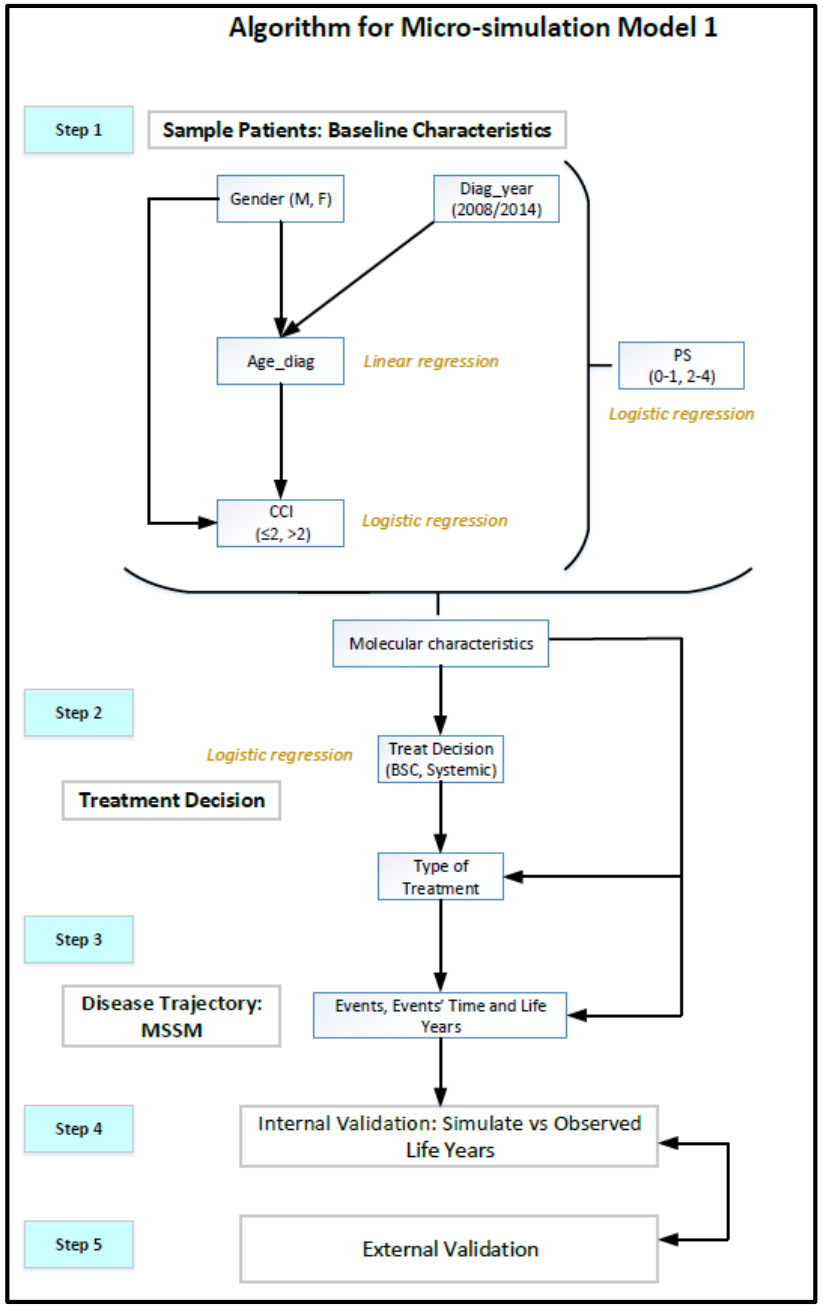
Technology Assessment of Next Generation Sequencing in Personalized Oncology

1st Objective

To develop and validate a patient-level micro-simulation model

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Model Building



Target Population: Dutch population of metastatic NSCLC

Patients population simulated according to Santeon lung cancer registry 2008 – 2014

Dataset

- Nu. Total patients: 2318
- Nu. Treated Chemo: 882
- Baseline characteristics
  - ECOG performance status
  - Charlson comorbidity index
  - Age at diagnosis
  - Gender
  - Year of diagnosis

***BSC** – best supportive care

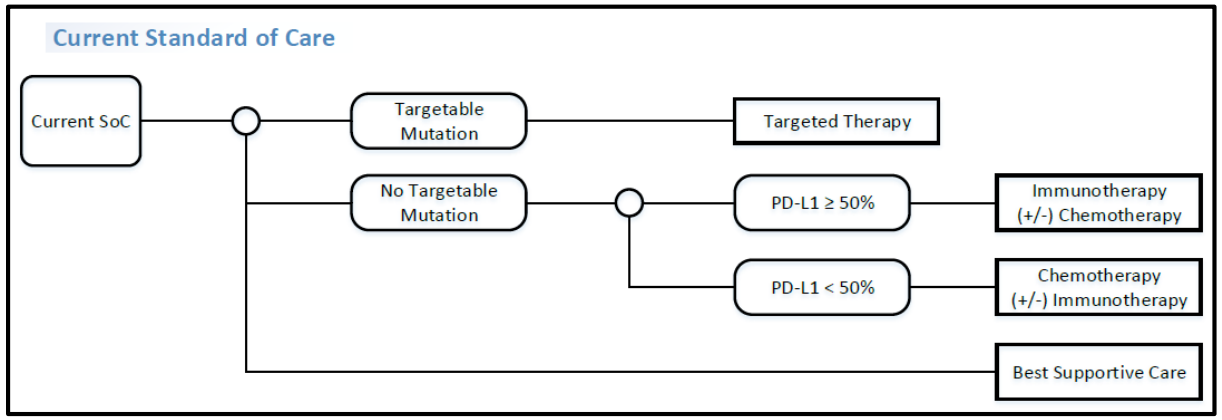
Technology Assessment of Next Generation Sequencing in Personalized Oncology

Simulating molecular biomarker and novel treatment

- Molecular subgroups
  Simulated independently according to the distribution of each subgroup in the literature.

- Treatment based on molecular biomarkers: simulated according to “current standard of care in the Netherlands”.

- Treatment effects taken from RCTs (systematic review)



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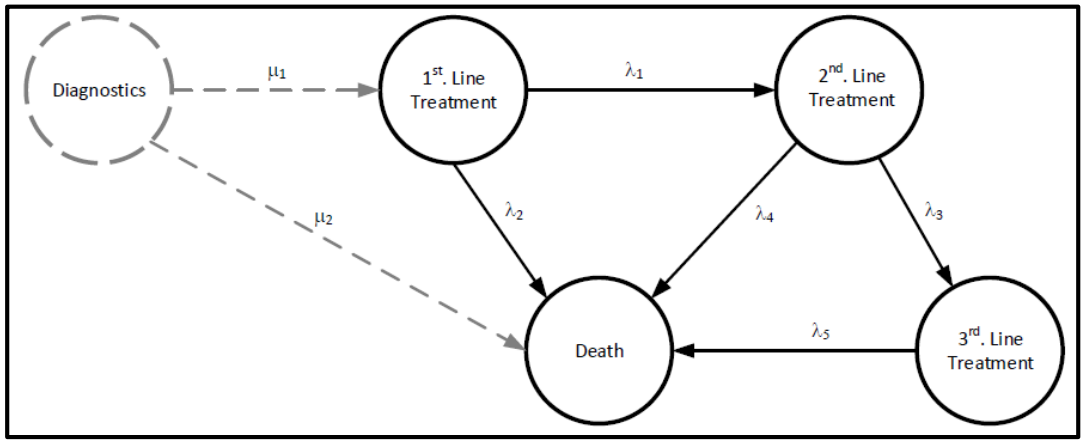
Patients trajectory after treatment

From 1st Line treatment to death was fitted with parametric multistate statistical model (MSSM).

For novel treatments, transition rates will be adjusted by RCTs treatment effects.



Compare the modelled life years (assuming RCT efficacy) with observed real-world life years.

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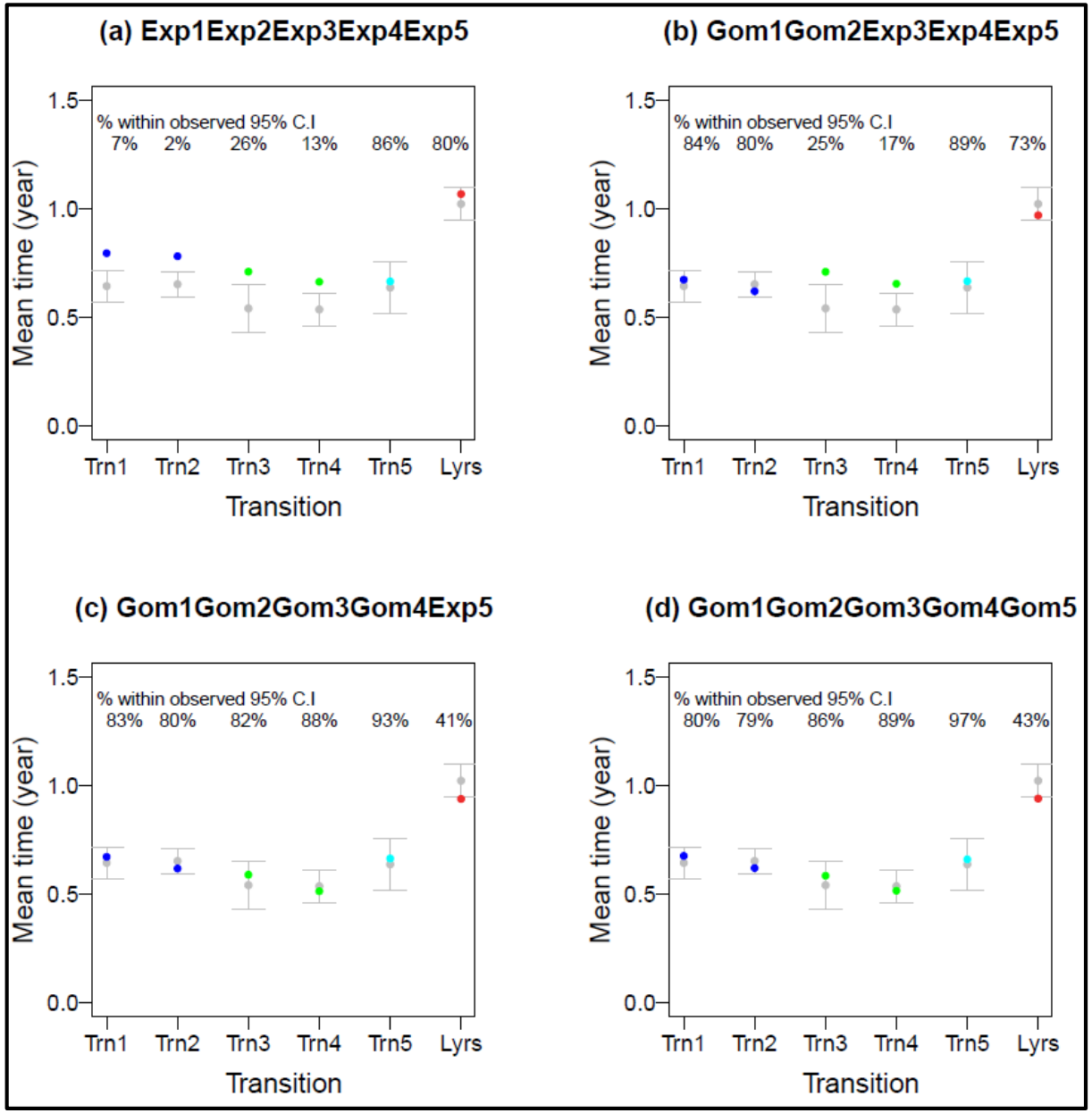
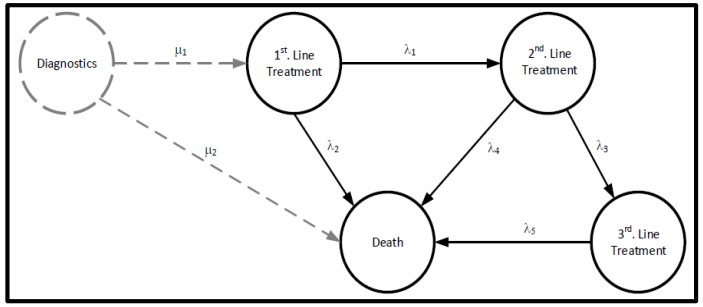
Preliminary results: Internal validation





Key:
Exp – Exponential distribution
Gom – Gompertz distribution

- **1 / Trn1** – Transition 1 (L1Treat → L2Treat)
- **2 / Trn2** – Transition 2 (L1Treat → Death)
- **3 / Trn3** – Transition 3 (L2Treat → L3Treat)
- **4 / Trn4** – Transition 4 (L2Treat → Death)
- **5 / Trn5** – Transition 5 (L3Treat → Death)
- **Lyrs** - simulated mean life years

Observed mean and 95% confidence Limits

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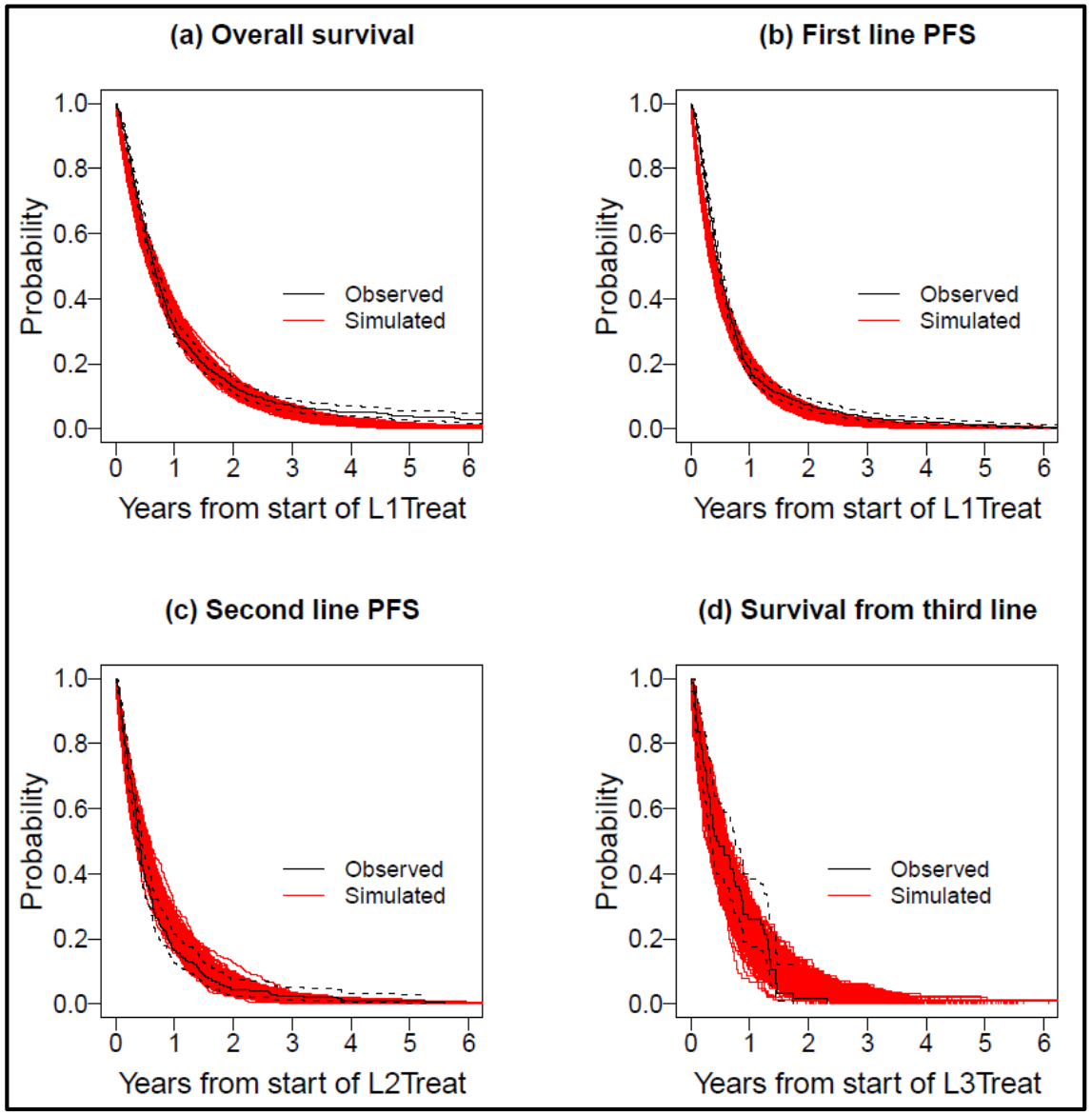
Preliminary results: Internal validation….



Next step:

Using the model with **Gom1Gom2Exp3Exp4Exp5**

- Simulate "novel treatment strategy" where treatment decision depends on simulated "molecular markers"
- External validation of the model output.

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2st Objective

To assess the cost-effectiveness of immunotherapy biomarker

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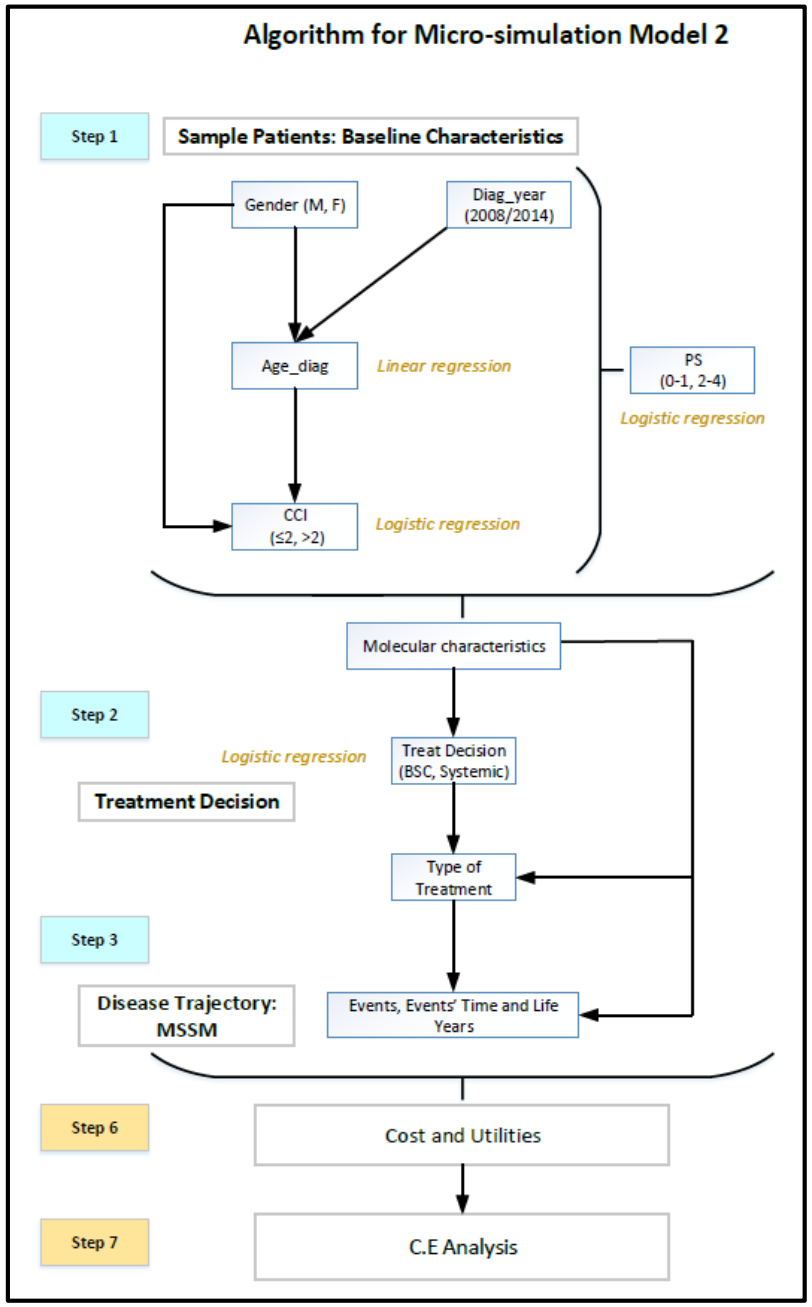

Objective:

- C.E of Immunotherapy biomarker
- Using validated model in 1st Objective

Cost and Utilities

- Medical & non-medical cost
- Utility of being in each health state

Output

- Cost per QALYs

Strategies and threshold analysis

- Comparing different plausible strategies
- Assess when are C.E

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Tasks

Paper 1 Goal: Externally validated micro-simulation model of metastatic NSCLC	Paper 2 Goal: CEA of biomarker based immunotherapy of metastatic NSCLC
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Technology Assessment of Next Generation Sequencing in Personalized Oncology

Work Package 4

Early cost-effectiveness modelling of whole genome sequencing compared to standard diagnostics in non-small cell lung cancer

prof. dr. Manuela Joore

dr. Valesca Retèl

prof. dr. Carin Uyl-de Groot

prof. dr. Wim van Harten

drs. Martijn Simons

Maastricht UMC+

T A O N G

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Main goal WP4

Potential value of whole genome sequencing (WGS) as molecular diagnostic compared to standard diagnostics in advanced cancer patients

- Cost-effectiveness analysis in Non-small cell lung cancer (NSCLC)
- Future scenario drafting
- Future scenario modelling
- Wider benefits WGS
- Quality of life of personalised treatment

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Technology Assessment of Next Generation Sequencing in Personalized Oncology

Cost-effectiveness analysis

Non-small cell lung cancer

Objective

- To determine the early cost-effectiveness of using WGS in diagnostic strategies versus currently used molecular diagnostics in patients with inoperable stage (IIIB,C/IV) NSCLC

Approach

- Model-based, lifetime time horizon, societal perspective
- Data from literature
- Systematic review → survival input

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journal homepage: www.elsevier.com/locate/critrevonc

Observed versus modelled lifetime overall survival of targeted therapies and immunotherapies for advanced non-small cell lung cancer patients – A systematic review

Martijn Simons[a,b], Bram Ramaekers[a], Andrea Peeters[a], Joanne Mankor[c], Marthe Paats[c], Joachim Aerts[c], Wim van Harten[d,e], Valesca Retèl[d,e], Manuela Joore[a,b,*]

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[d] Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Department of Psychosocial Research and Epidemiology, Plesmanlaan 121, 1066 CX, Amsterdam, the Netherlands
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ARTICLE INFO

Keywords:
Non-small cell lung cancer
Targeted therapies
Immunotherapies
Survival analysis
Overall survival

ABSTRACT

Outcomes used for the effectiveness (median) and cost-effectiveness (mean) on overall survival (OS) are different and can vary from one another. Therefore, we compared median and mean OS gains of targeted therapies and immunotherapies for stage IIIB/IV Non-small cell lung cancer and explored underlying aspect. Eligible trials were searched in PubMed, survival curves were digitized, and parametric survival models fitted to model the mean OS. Twenty-seven trials were found for targeted therapies (n = 17) and immunotherapies (n = 10). Differences between median and mean OS gains in months ranged from −2.8 to 6.8 and −4.9 to 0.3 for two different subgroups of targeted therapies, and −2.4 to 11.4 for immunotherapies. The mean OS gain was substantially larger for most immunotherapy trials, due to relatively long survival. Median and mean OS gains did not differ for targeted therapies. Our findings imply a potential discrepancy between the estimates of effectiveness and cost-effectiveness of cancer treatments.

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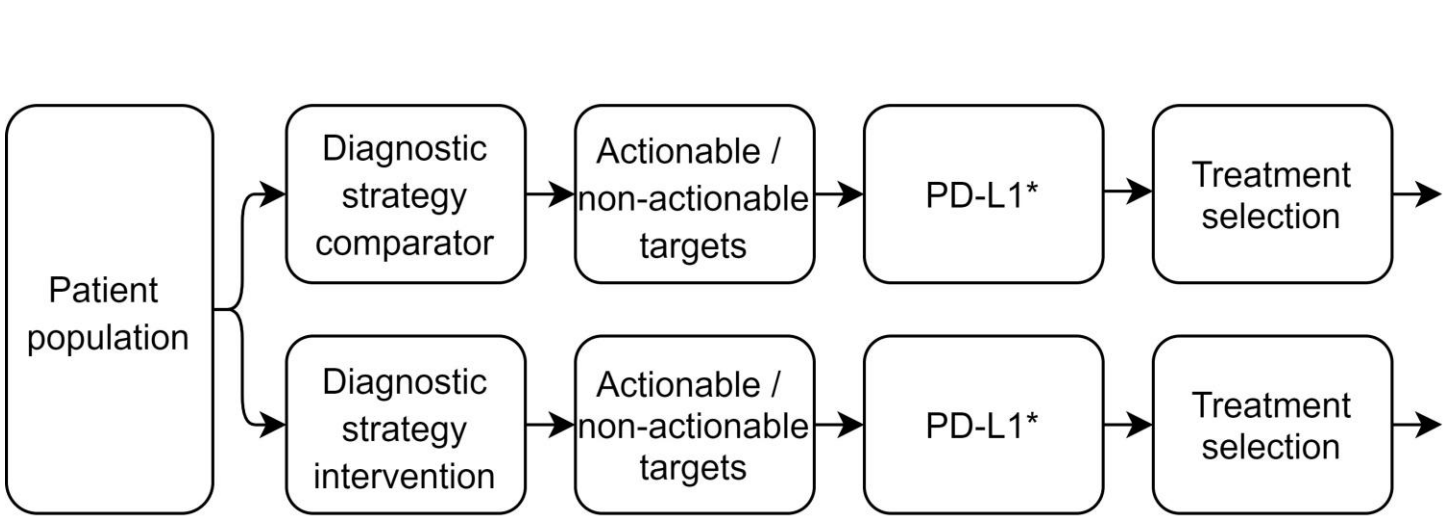
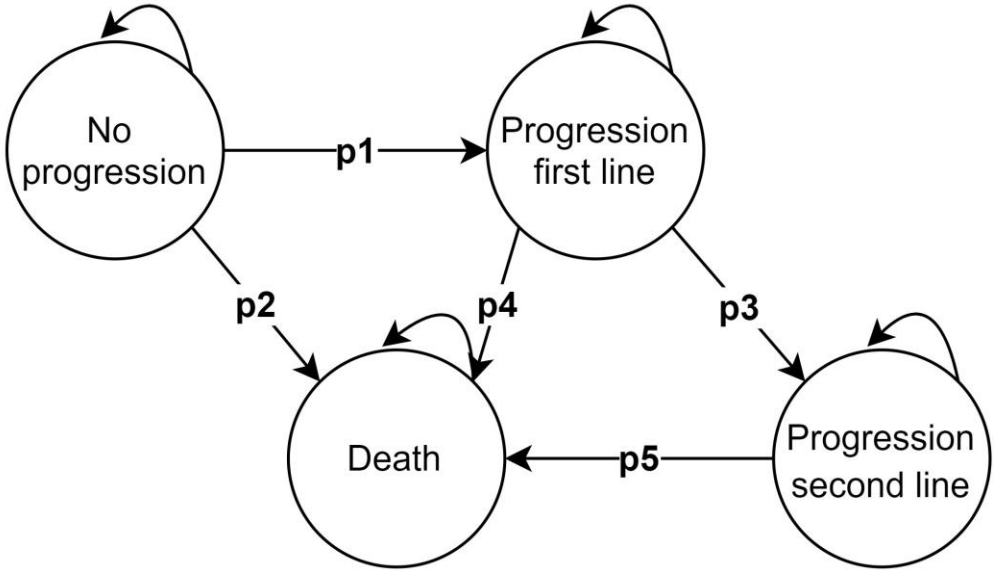
Cost-effectiveness analysis
Model structure





- Decision tree → diagnostic pathway
- State transition model → disease progression

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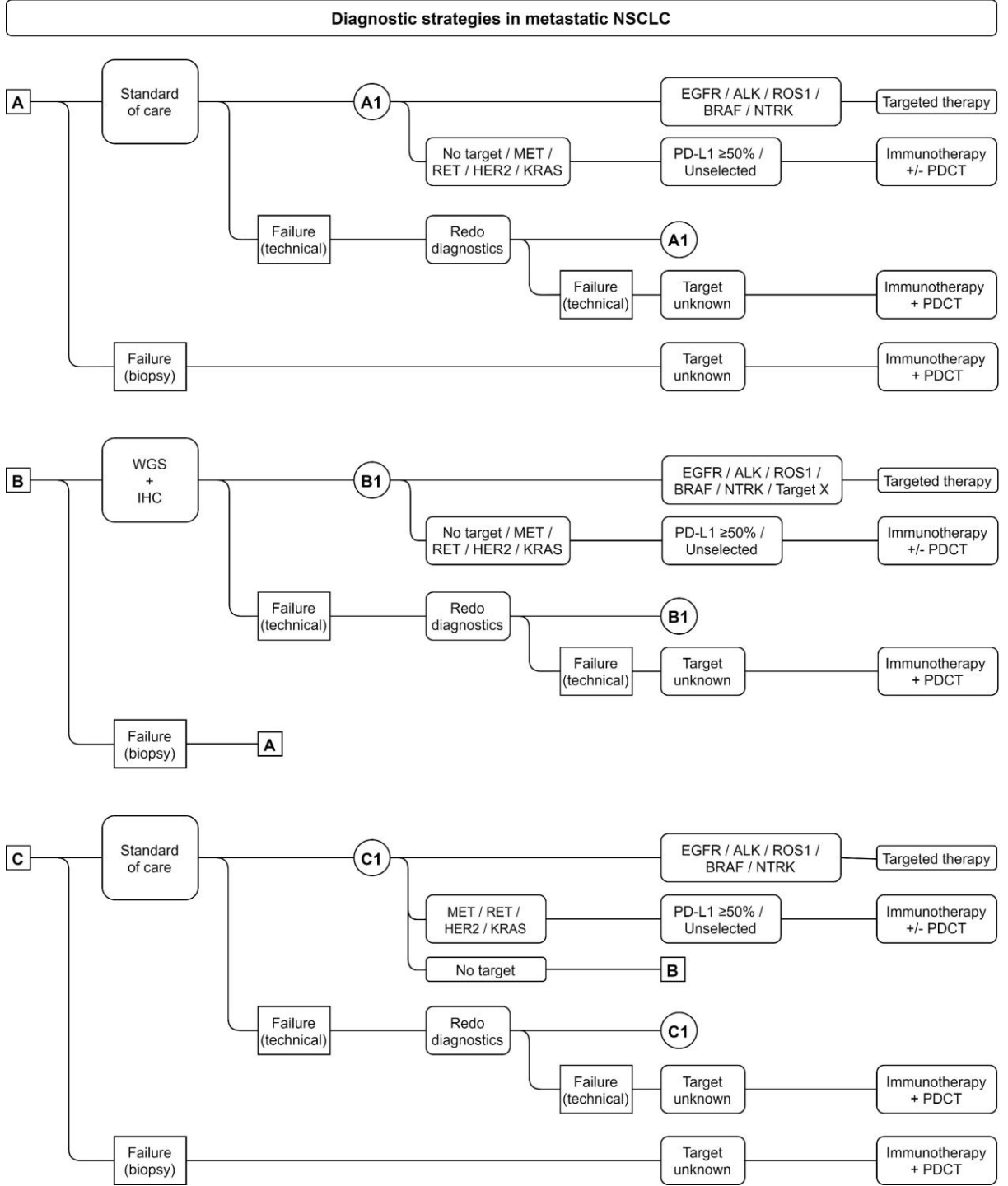
Cost-effectiveness analysis

Comparators

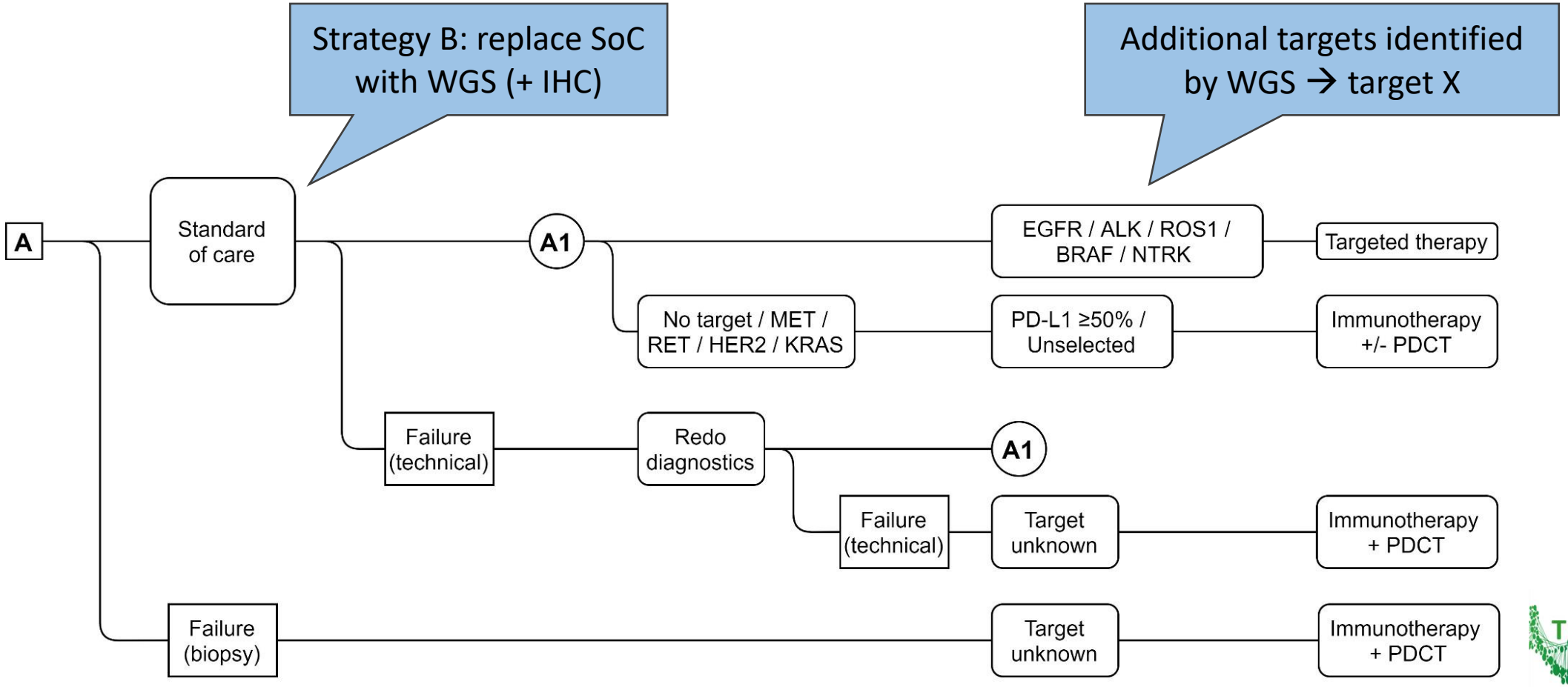
- Strategy A: SoC diagnostics
- Strategy B: WGS (+ SoC)
- Strategy C: SoC + WGS



Cost-effectiveness analysis

Comparators

- Strategy A: SoC diagnostics (optimal test strategy)



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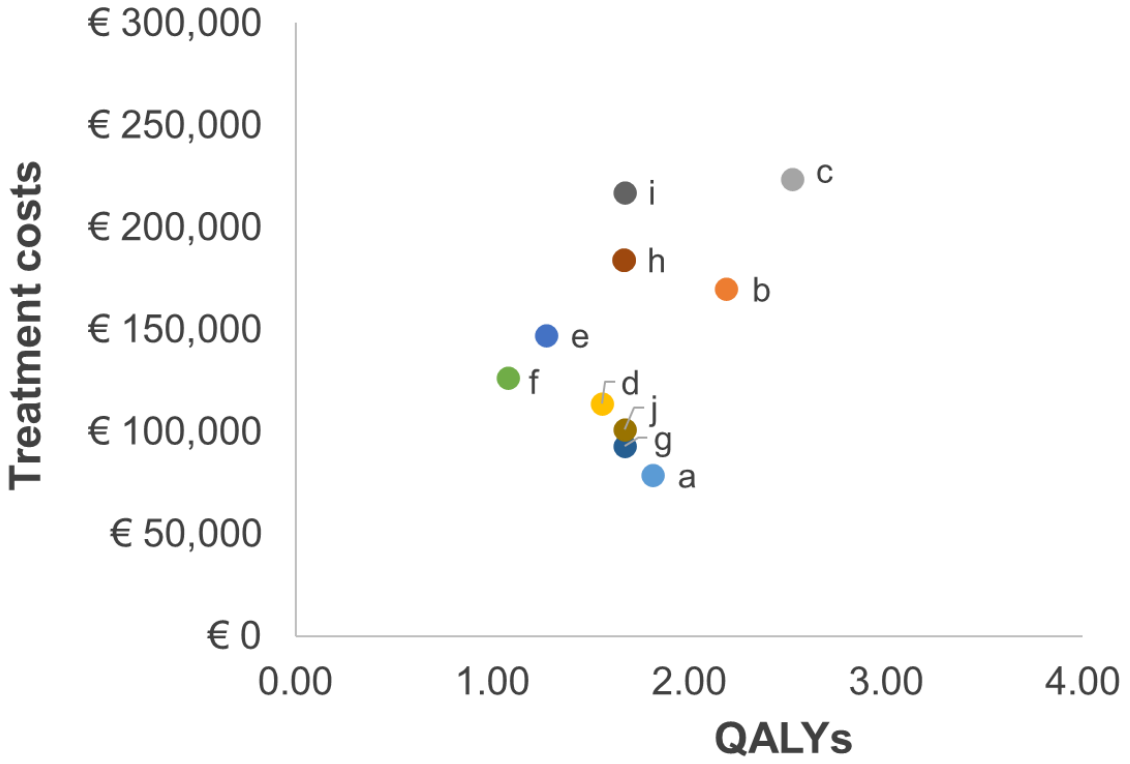
Cost-effectiveness analysis

Intermediate results
(treatment costs and QALYs of the treatment strategies)



- a. EGFR afatinib
- b. EGFR osimertinib
- c. ALK alectinib
- d. PD-L1 ≥50% pembrolizumab
- e. PD-L1 ≥50% pembrolizumab + PDCT
- f. PD-L1 unselected pembrolizumab + PDCT
- g. ROS1 crizotinib
- h. BRAF dabrafinib + trametinib
- i. NTRK larotrectinib
- j. Target X treatment X

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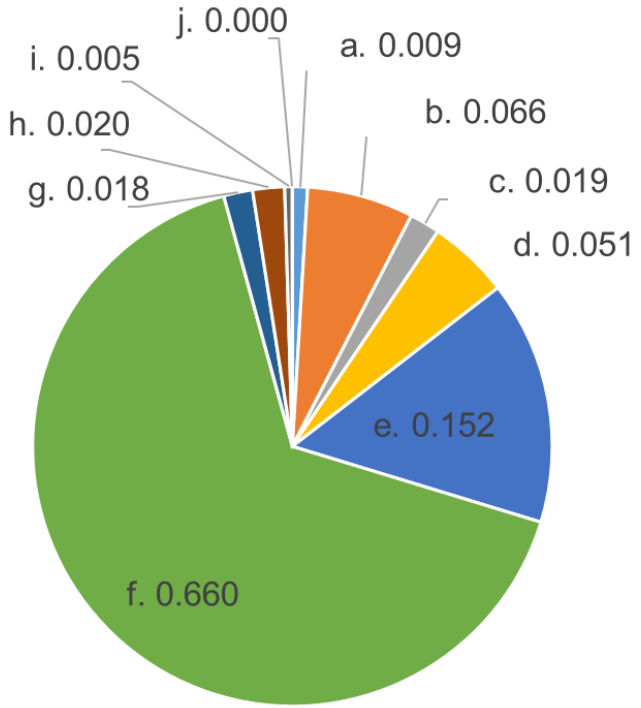
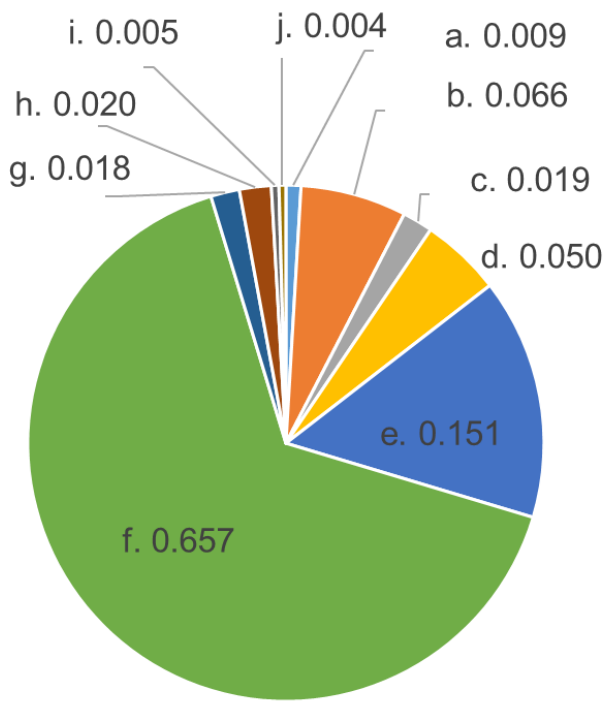
Cost-effectiveness analysis

Intermediate results

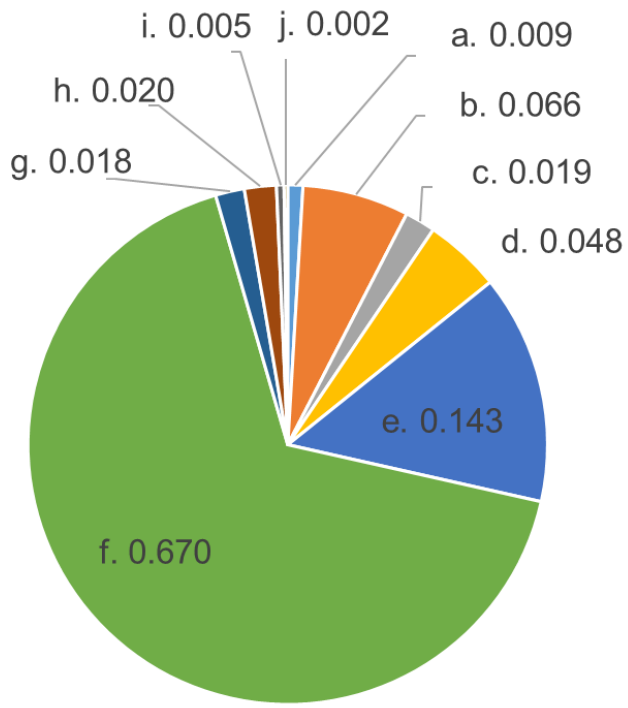
(Proportions of patients receiving the different treatment strategies)



Strategy A



Strategy B



Strategy C

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Cost-effectiveness analysis

Overall results per diagnostic strategy (sorted by costs)

Strategy	Life years (95% CI)	QALYs (95% CI)	Costs (95% CI)	Strategy comparison	Incremental life years (95% CI)	Incremental QALYs (95% CI)	Incremental costs (95% CI)	ICER[a]	iNMB[b]
A	1.878	1.235	€145,826	–	–	–	–	–	–
C	1.876	1.233	€147,891	versus A	-0.002	-0.002	€2,065	Inferior	-€2,202
B	1.882	1.237	€149,186	versus A	0.004	0.002	€3,360	€1,436,007	-€3,173

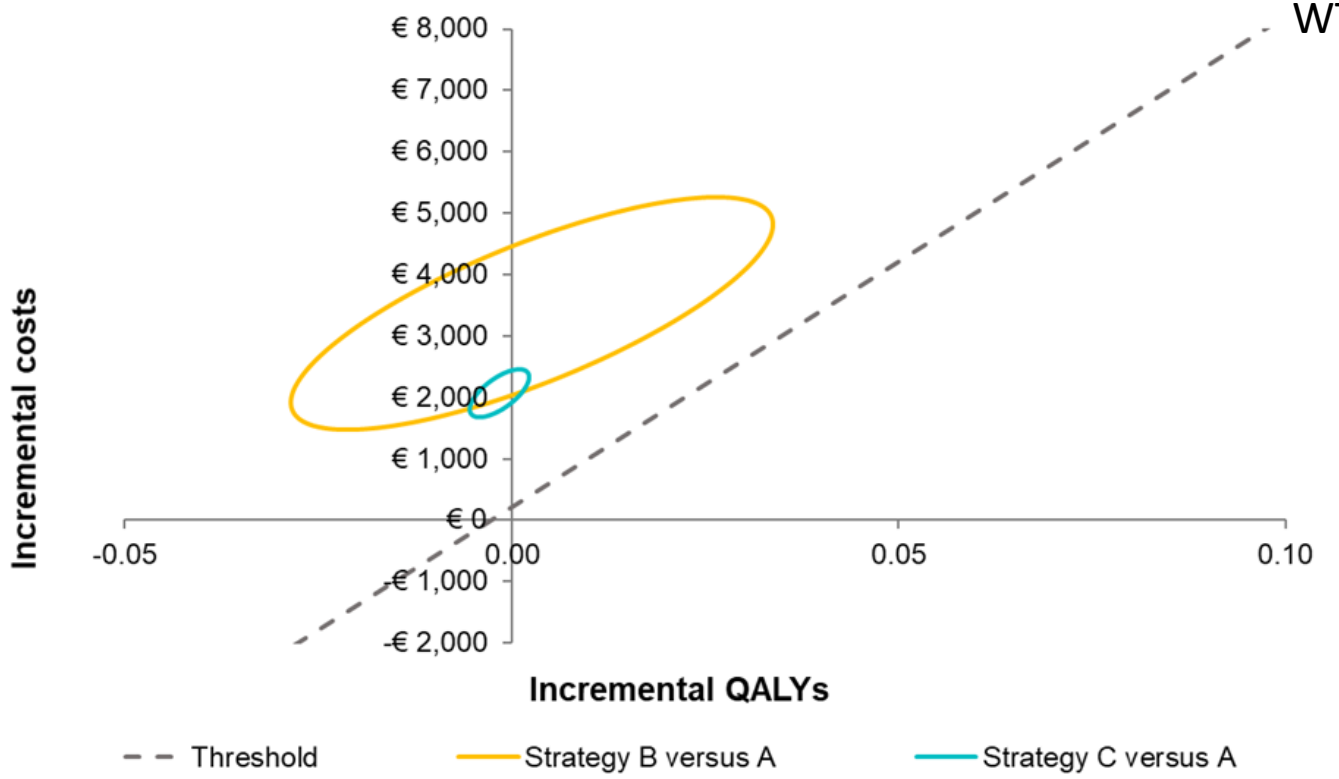
[a], A diagnostic strategy was inferior compared to another diagnostic strategy if the ICER was below zero. A diagnostic strategy is considered cost-effective compared to strategy A if the ICER is a positive value equal or below €80,000.

[b], A diagnostic strategy is considered cost-effective compared to strategy A if the iNMB is equal or above 0, with a willingness to pay threshold of 80,000 per QALY.

Strategy A: SoC; Strategy B: WGS; Strategy C: SoC + WGS. CI, confidence interval; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio; iNMB, incremental net monetary benefit;

Cost-effectiveness analysis

Results: cost-effectiveness plane



WTP threshold €80,000 / QALY

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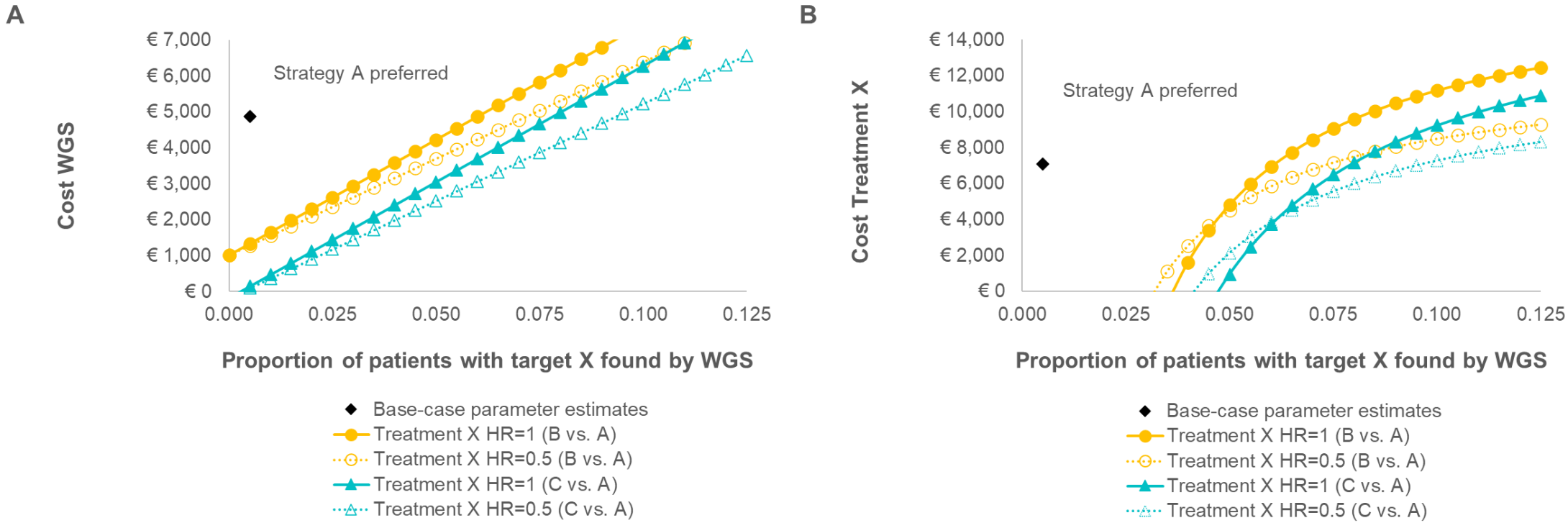
Cost-effectiveness analysis

Results of the threshold analyses



Cost-effectiveness WGS

- Lower cost WGS ↑
- Higher detection rate target X ↑
- Better treatment effect treatment X ↓

- Lower cost treatment X ↑
- Higher detection rate target X ↑
- Better treatment effect treatment X ↓ ↑

Cost-effectiveness analysis
Conclusion

- Based on currently available literature, the use of WGS as a clinical diagnostic is not cost-effective compared to optimised SoC.
- While in practice costs are further decreasing and more actionable targets become available, our analyses show that by these developments WGS could rapidly become cost-effective.

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Cost-effectiveness analysis
Discussion

- Model was based on currently available literature, while developments are very fast in this field
- WGS was compared with a most optimal SoC testing strategy which resulted in lower diagnostic costs for SoC
- No costs included for keeping tests up to date and for delays due to technical adaptations
- Finding additional targets with WGS would most likely result in off-label treatment or in clinical trial setting
- Model assumptions were made due to limited data
    - Most notably about the treatment effect and cost of treatment X

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Main goal WP4

Next steps

Plans for modelling the future scenarios (next paper)

- Model scenarios from scenario drafting paper with highest impact on the ICER
- Also perform three-way threshold analyses
- Likelihood of the resulting ICERs = likelihood future scenarios

Wider benefits of WGS paper

- Costs and benefits of storing WGS data for future patients

Quality of life of personalized treatment paper

- QoL data gathered
- Clinical data requested
- Data analysis plan

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Modelling the organization of care for WGS

WP5 leader: Maarten IJzerman

Members: Erik Koffijberg, Valesca Retèl, Wim van Harten, Michiel van de Ven

UNIVERSITY OF TWENTE. | Health Technology & Services Research

WP5 recap

- Overall research question of WP5:
  - What difficulties in the process of the implementation of WGS need to be overcome to achieve the optimal cost-effective implementation in the Netherlands?

- Milestones:
  - Real-world evidence related to NSCLC
  - Scenario drafting
  - Model building

Current status

Milestones	Articles	Status
Real-world evidence NSCLC	1. Variation in the time to treatment for stage III and IV non-small cell lung cancer patients for hospitals in the Netherlands	Published in *Lung Cancer*
	2. Real-world utilization of biomarker testing for patients with advanced non-small cell lung cancer in a tertiary referral center and referring hospitals	Submitted to *Molecular Diagnostics*
Scenario drafting	3. Whole Genome Sequencing in oncology: Using scenario drafting to explore future developments	Will be submitted to *Implementation Science*
Model building	4. Using Dynamic Simulation Modeling to support the implementation of Whole Genome Sequencing in lung cancer	Ongoing
	5. Do we even need to increase the capacity of Whole Genome Sequencing for cancer patients?	Ongoing

Model building

- Research questions and model requirements
- Outcomes of interest
- Model structure
- Model components to be added

Research question and model requirements

- Research question: What changes in the organization of care are required to realize the potential value of WGS?
  - *Should the capacity to conduct WGS be increased or decreased? When?*
  - *What is the impact of organizing MTB's differently, for example, by including a fast track?*

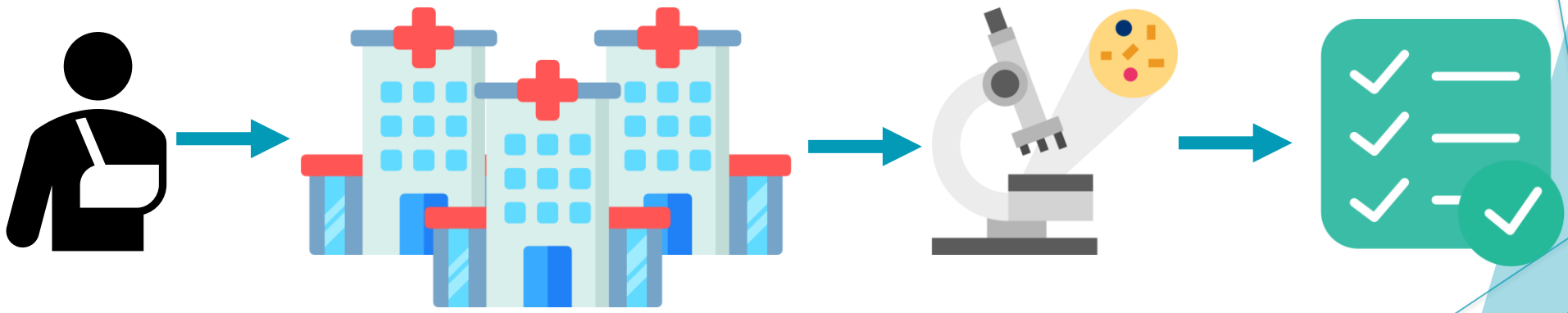
- Primarily, the model needs to be able to:
  - Include biomarker test strategies
  - Reflect patient heterogeneity
  - Reflect hospital heterogeneity
  - Include a spatial context

Outcomes of interest

- Final outcomes:
  - The number of patients deceased during the diagnostic pathway
  - Cost per patient of biomarker testing
- Intermediate outcomes:
  - Duration of the diagnostic pathway
  - Guideline-based treatment decisions
  - Access to WGS
  - The required capacity for WGS

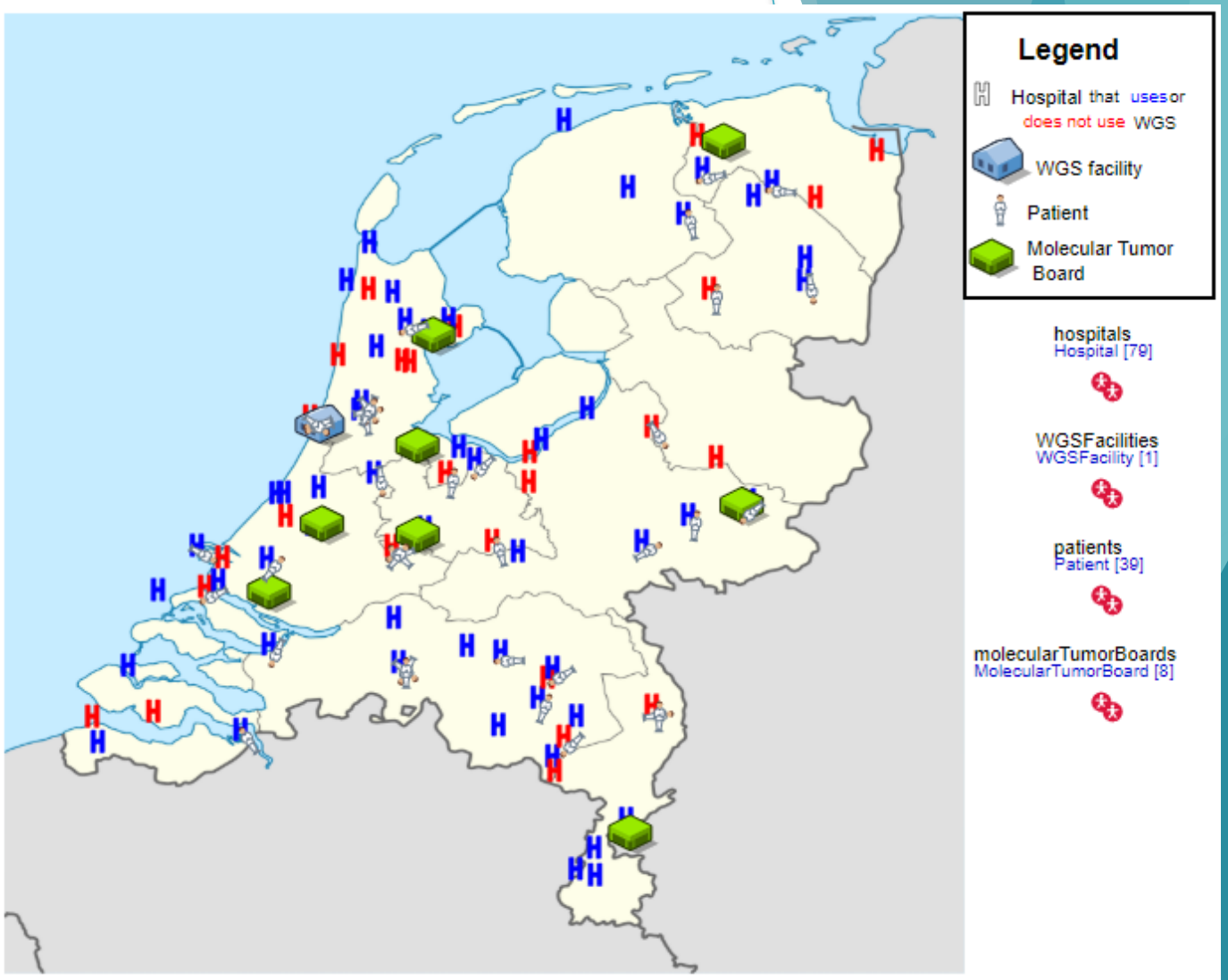
Model structure

- The model structure includes workflows of hospitals, genomic services, and molecular tumor boards.
- Implemented as a dynamic simulation model in AnyLogic

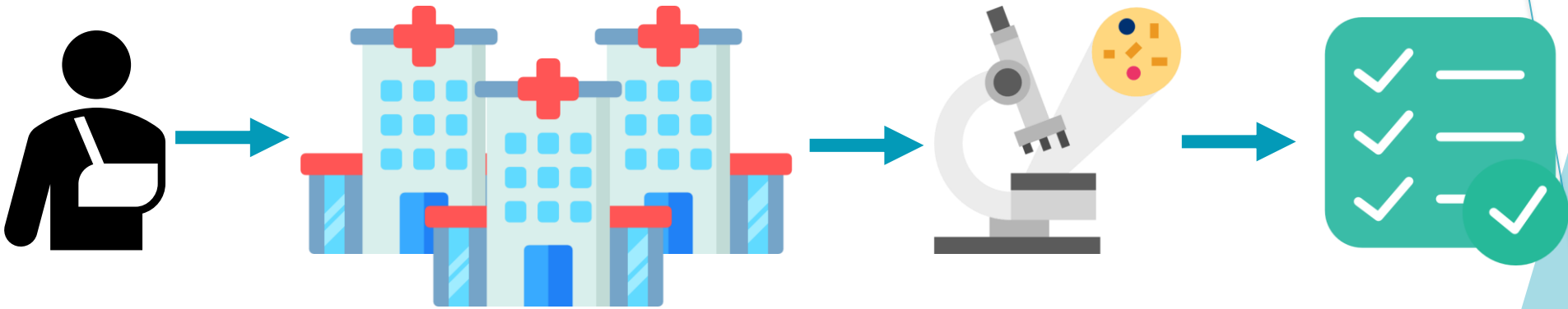


Model structure

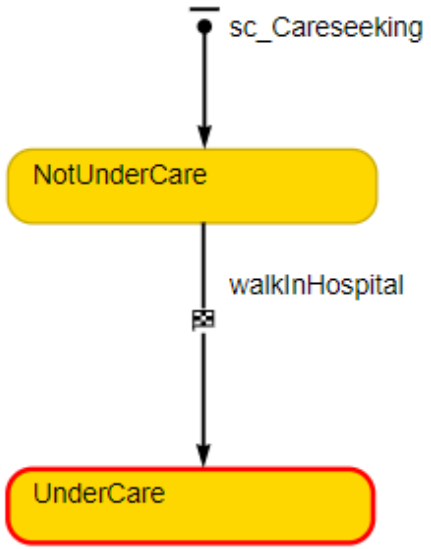
- Patients are generated somewhere on the map
- Patients select the most nearby hospital to receive diagnostics
- Blue hospitals have implemented WGS, red hospitals have not

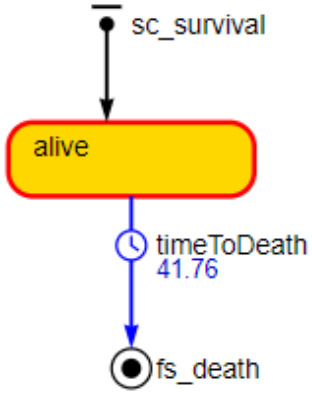


Model structure



Patient heterogeneity





Received diagnostics

1st p_Dx1_1 WGS

2nd p_Dx1_2 StandardDiagnostics

3rd p_Dx1_3 null

p_Dx1TurnaroundTime 25.349

p_timeArrivedDx1 0.203

p_timeCompletedDx1 25.552

If WGS

p_wgsSuccess false

p_sufficientQualityBiopsy Insufficient

If SoC

p_standardDiagnosticsSuccess true

Patient characteristics

p_age 73.588

p_sex Male

p_PS PS01

p_morphology NOS

p_patientId 3

p_myHospital root.hospitals[75]

Test results

p_Dx1KRAS Mutated

p_Dx1EGFR NotMutated

p_Dx1PDL1 Low

p_Dx1ALK NotMutated

p_Dx1ROS1 NotMutated

p_Dx1BRAF NotMutated

p_Dx1HER2 UnknownStatus

p_Dx1MET UnknownStatus

p_Dx1NTRK UnknownStatus

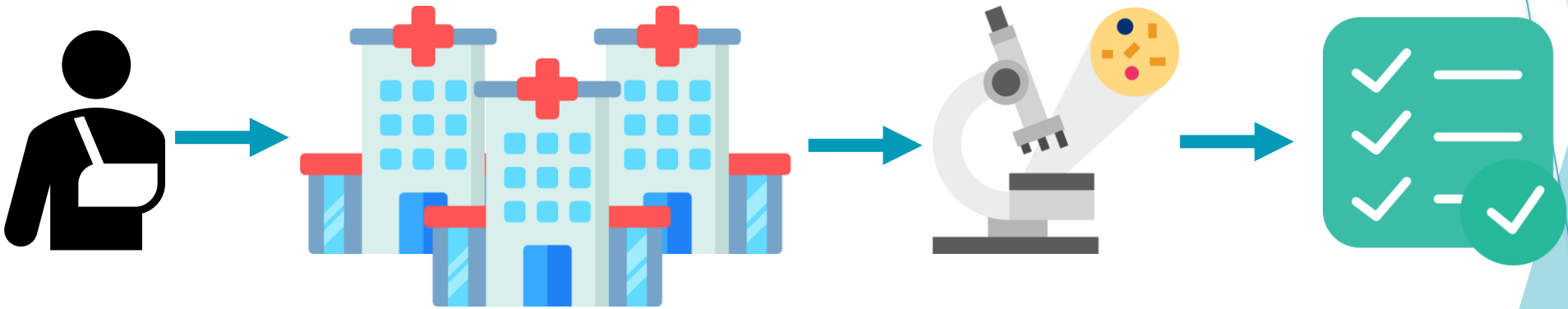
p_Dx1RET UnknownStatus

p_Dx1TMB UnknownBurden

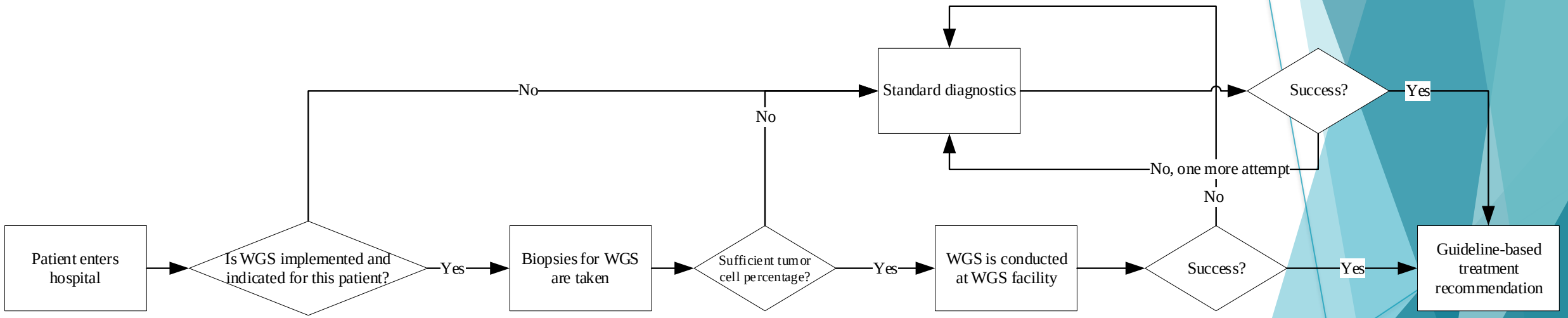
Guideline-based treatment recommendation

p_Tx1 Chemotherapy

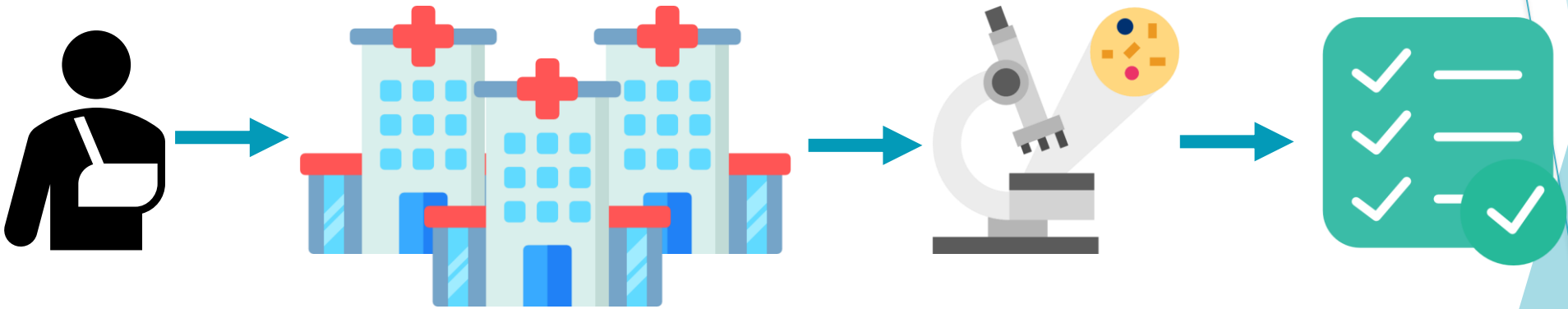
Model structure



Diagnostic pathway in hospitals

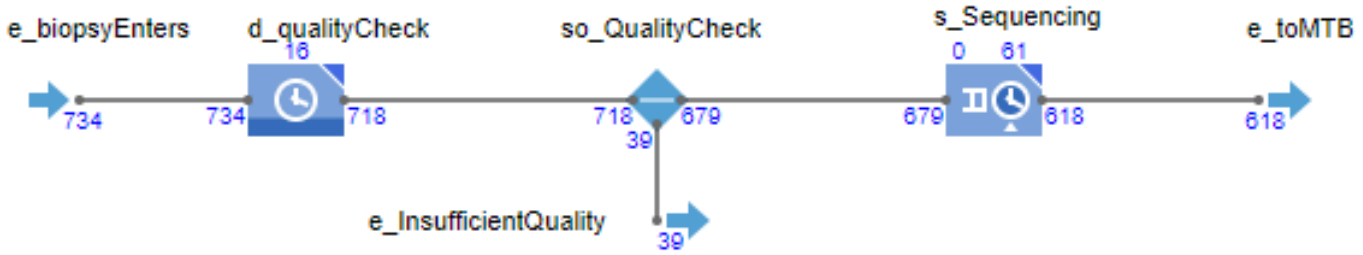


Model structure

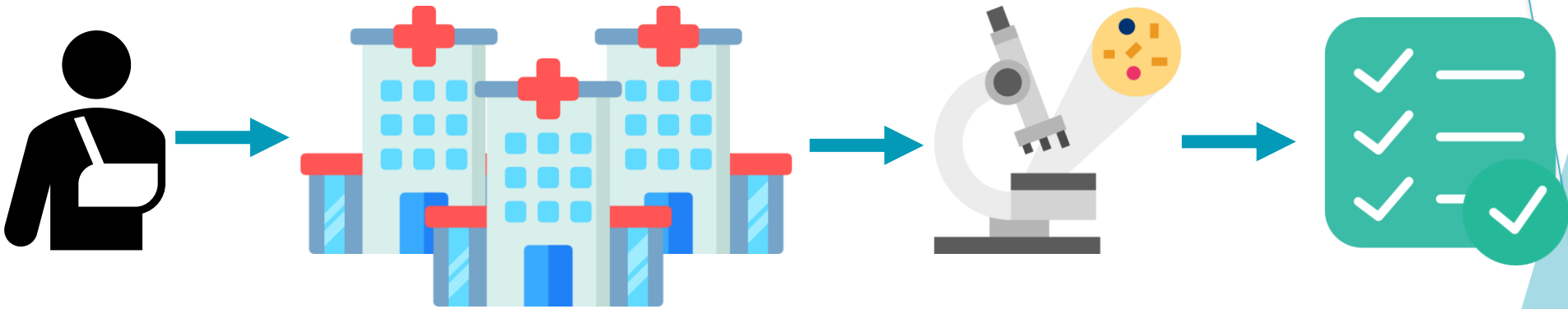


Conducting WGS

- Hospitals send biopsies to the WGS facility
- Patients linked to unsuitable biopsies will receive SoC in the hospital
- Total turnaround time is split between shallow sequencing and full WGS
- Shallow sequencing incurs 25% of the costs of full WGS

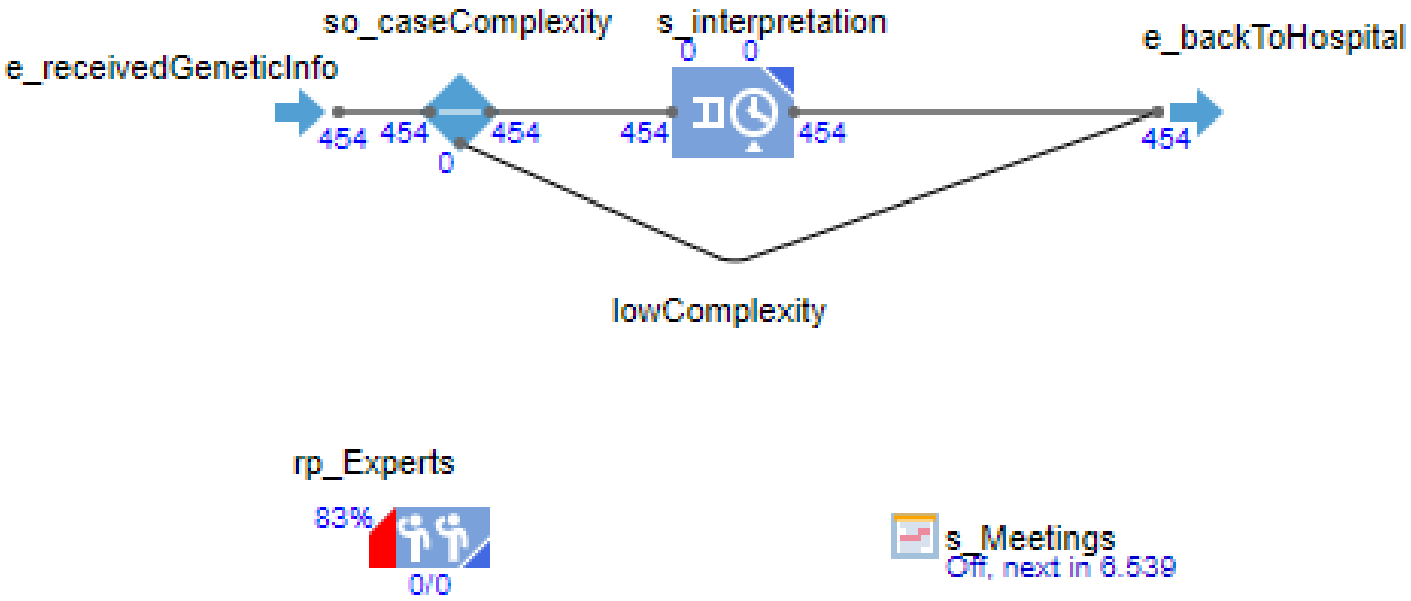


Model structure

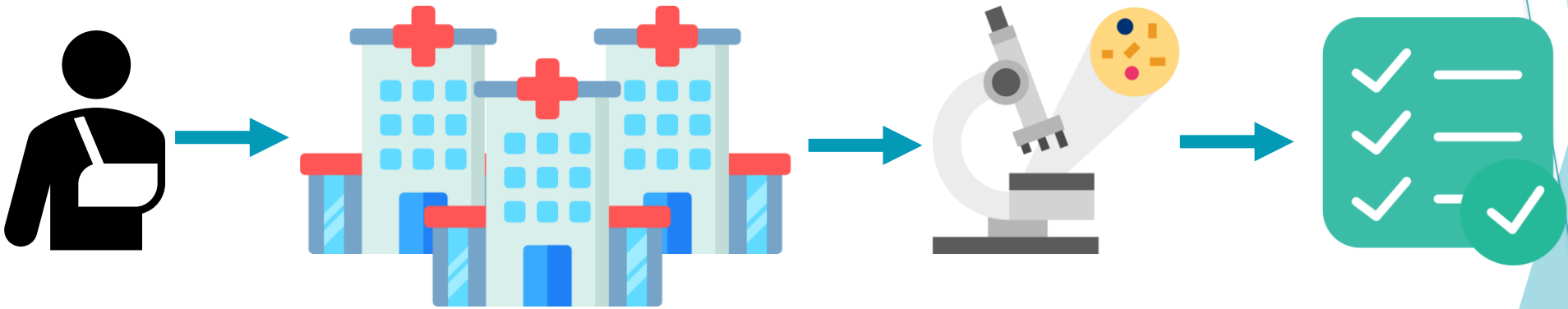


Molecular tumor boards

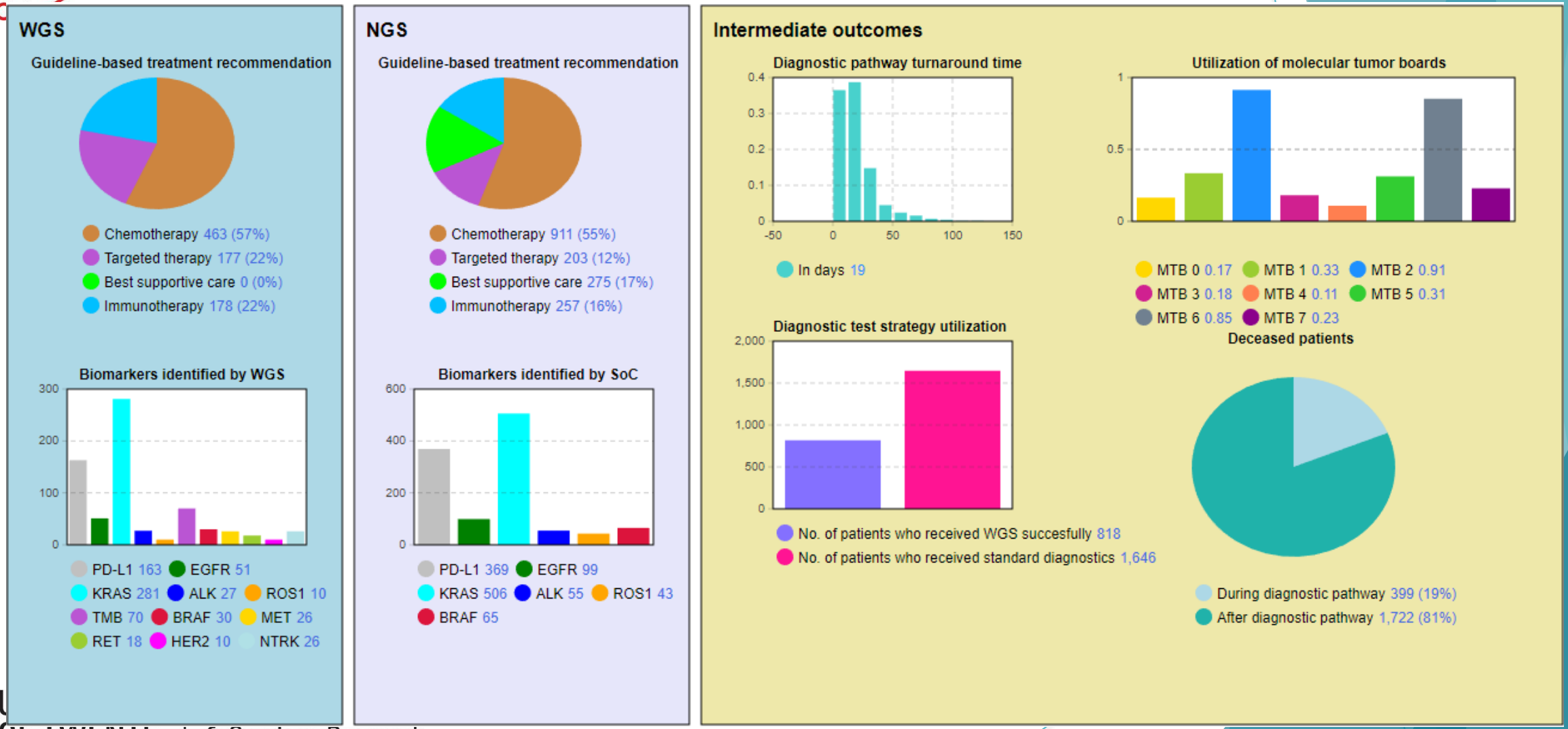
- WGS reports will be discussed in MTB meetings
- Meetings occur according to a schedule (once or twice a week)
- After the discussion, the report is sent to the hospital



Model structure



Visualizing model outcomes during runtime



Model components to be added

- Make a distinction between three hospital types (academic, teaching, general) that have varying degrees of testing capabilities

- Include referrals between hospitals:
  - If testing in a general hospital found no actionable target, refer patient to nearest teaching hospital
  - If testing in a teaching hospital found no actionable target, refer patient to nearest academic hospital

Modelling
the organization of care for WGS

WP5 leader: Maarten Ijzerman

Members: Erik Koffijberg, Valesca Retèl, Wim van Harten, Michiel van de Ven

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WP6: Ethical part

Genetics in oncology: a focus group study on recontact

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Background (1)

- Genetics en genomics in oncology
  - WGS to develop targeted treatment
  - Genetic trait breast cancer
  - …

- Ethical issues
  - Informing family members
  - Unsolicited findings in NGS
  - Returning individual research results

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Background (2)

New (genetic) information relevant for health or reproduction can become available

(1) New treatment possibility or screening recommendation
(2) New technique or new genetic test available
(3) New gene identified relevant in relation to the disease of the patient
(4) Reclassification of variant

Ploem et al. 2018

Background (3)

- Strong arguments to support a prima facie moral duty to recontact, such as beneficence and respect for autonomy

- The strenthg of the duty context-specific

- Six contextual factors
  1. Informational aspects
  2. Costs and efforts involved
  3. Personal preference, if known
  4. Patient or family member
  5. Clinical or research setting
  6. Time

Giesbertz et al. 2019

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Aim

- Explore views and intuitions of oncology patients and professionals on contextual factors and recontact in oncology

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Methods (1)

- Three focus groups: 1 group with (former) oncology patients/relatives 2 groups with healthcare professionals
- Total 25 participant

Table 1. respondents patient group

Respondents	**n=12**
Sex	
Male	7
Female	5
Age	48-71 yrs.
Patient / relative	
Patient	11
Patient relative	1

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Methods (2)

Table 2. respondents professionals

Respondents	**n=13**
Sex	
Male	3
Female	10
Age	39-59 yrs.
Professional background	
(Plastic) surgeon	3
Oncologist/pulmonologist	2
Clinical geneticist	2
Nurse practitioner breast cancer care	2
Pathologist	1
Laboratory specialist clinical genetics	1
Ethicist	1
Social worker	1

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Methods (3)

- 60-90 minutes

- Outline

(1) short introduction on recontact in genetics

(2) general thoughts of the participants on recontact

(3) contextual factors that could influence a duty to recontact

- Recorded, transcribed verbatim, and stored coded

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Results

I find it a difficult subject, because you could think of so many different situations. It is almost incomprehensible.

professional

- Almost incomprehensible topic
- Important topic

- Support to contact patients with certain (genetic) oncological information
- Context differed, scale very restrictive – more unreserved

- No additional contextual factors
- Six factors further explored

Results: factor 1 information

- Patients:
  - Everyone wants to hear information with preventative/treatment options for themselves or relatives
  - Not all patients want to hear information without these options
  - Their choice

- Professionals:
  - Relevance linked to probability and possibility to act
  - Scale – certain threshold?
  - In line with initial testing

what would be the minimal expected health benefit before you contact a patient?

professional

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Results: factor 2 costs and efforts

- Patients
  - Realistic to weigh the costs and efforts
  - Certain costs and efforts are justifiable to benefit individuals
  - Society benefits as well
  - Decrease costs/efforts with technology

"… a database, that is regularly updated with information on your condition, which you could always check… Than you would not have to approach everyone"

patient

- Professionals
  - Balance with benefits
  - Decrease costs/efforts with technology

Results: factor 3 personal preferences

- Patients
  - Personal preferences important
  - Ideally taken into account: inform people or preferably ask consent
  - Exception for information relevant for family members?

- Professionals
  - Personal preferences important
  - Concerns with consent
    - Consent or indication of people attitudes?
    - Risk too high to harm people, to contact them against their wishes

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Results: factor 4 patient or family member

- Patients
  - Great importance (even against their own wishes?)

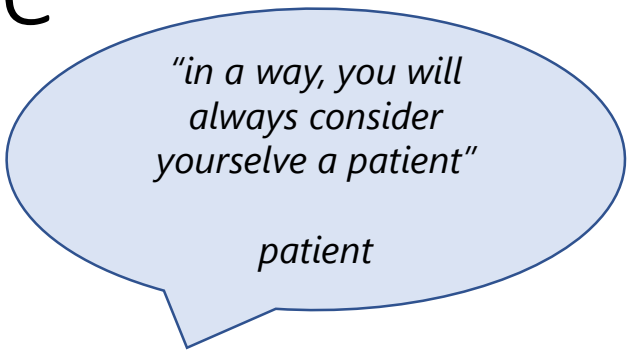
- Professionals
  - Hesitant to contact family members: no consent
  - At the same time, sometimes goal of genetic testing: particular information of great importance such as BRCA mutation

Results: factor 5 clinic or research setting

- Patients
  - Irrelevant

- Professionals
  - Difference between duties (care relationship)
  - Blurring boundaries?

Results: factor 6 time



- Patients
  - Irrelevant
- Professionals
  - More discussion
  - Plays at least a role in the value of consent

Conclusions (1) – work in progress

- Comparable considerations in our paper
- Basic principle: if the information is important and the patient wants to receive updates, it should be communicated
- Comparable with other empirical studies – further study (oncology context?)

Giesbertz et al. 2019

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Conclusions (2)- work in progress

- Patients:
  - Actionable information is more important, but also information without treatment or preventative options should be offered
  - Emphasize importance of personal choice
  - Possibly exceptional position for information relevant to family members: overriding?
  - Factors time and research vs. clinical setting not relevant

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Conclusions (3) - work in progress

- Professionals:
  - Relevance of information – threshold?
  - Costs and efforts
  - Concerns with consent and contacting people against their wishes
  - More discussion on the factors clinic/research and contacting family members

Technology Assessment of Next Generation Sequencing in Personalized Oncology

Conclusions (4) - work in progress

- ICT developments for informational updates and consent
- Reflection: shift from *question driven care* towards *information driven care*

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