AACR American Association for Cancer Research
ANNUAL MEETING
2024 • SAN DIEGO
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Ultra-sensitive ctDNA detection predicts response to immune checkpoint inhibition in advanced melanoma patients

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UKE HAMBURG
DKG KREBSGESELLSCHAFT Zertifiziertes Hautkrebszentrum
Fleur Hiege-Centrum für Hautkrebsforschung
UKE HAUT TUMOR ZENTRUM
Hubertus Wald Tumorzentrum
Hubertus Wald Tumorzentrum Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Disclosure Information

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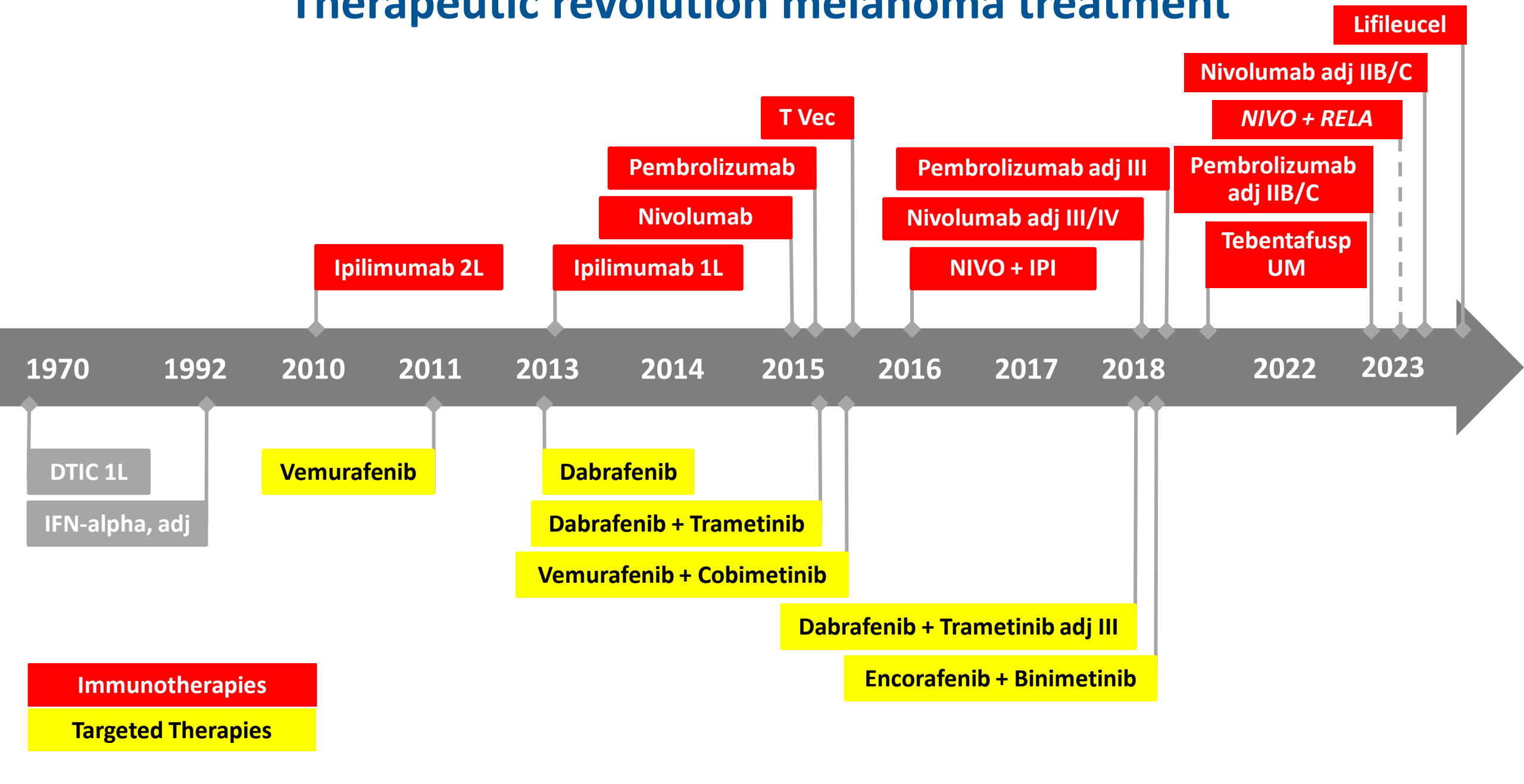
Prof. Dr. med. Christoffer Gebhardt

Advisory Roles for, and Honoraria as well as Travel Expenses by the following Companies:

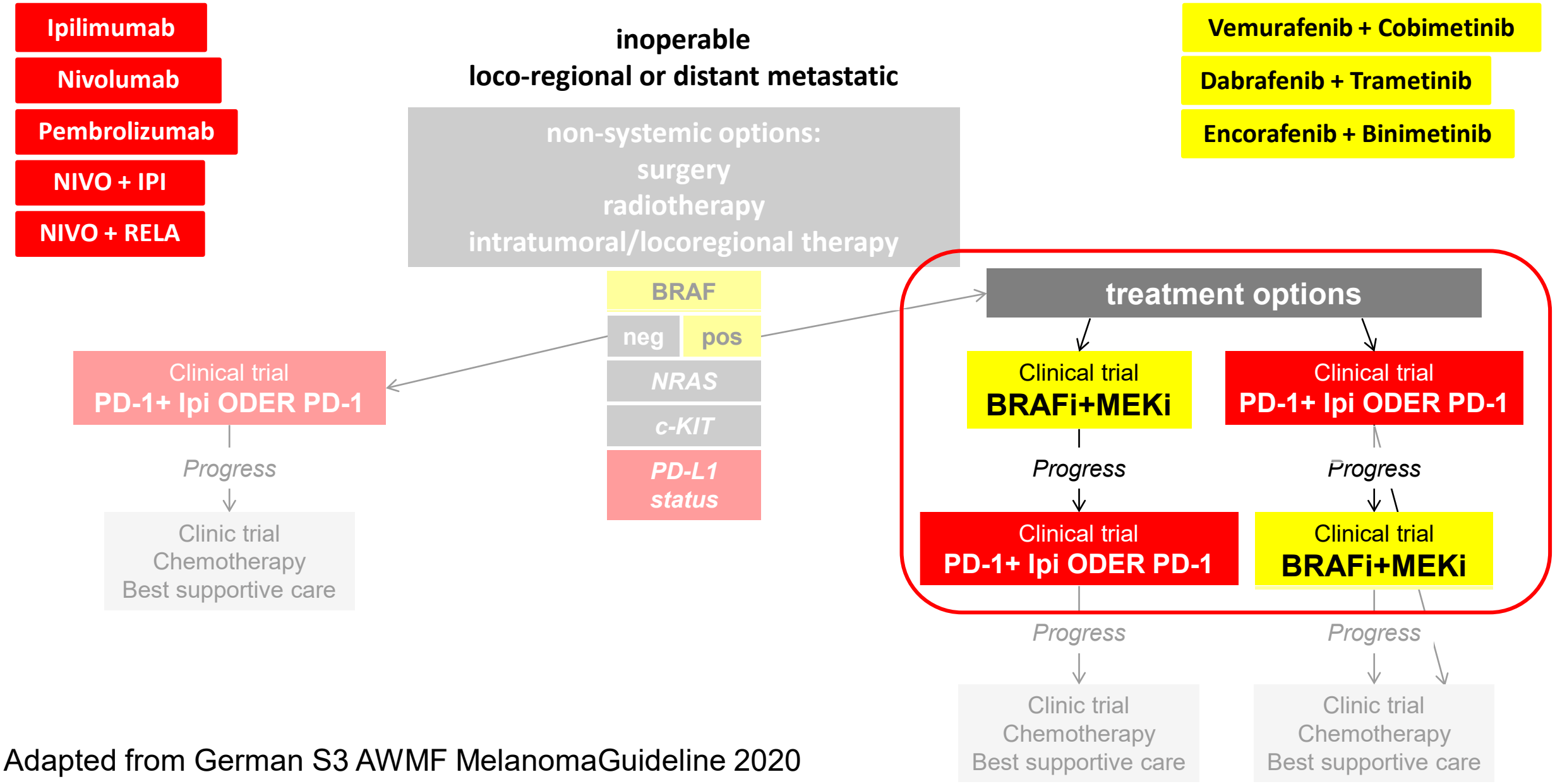
Almirall
Amgen
Beiersdorf
BioNTech
Bristol-Myers Squibb
Delcath
Immunocore
Janssen
MSD Sharp & Dohme
Novartis
Pierre-Fabre
Regeneron
Sanofi Genzyme
Sciomics
SUN Pharma
Sysmex/Inostix

Co-Founder of Dermagnostix and Dermagnostix R&D

Therapeutic revolution melanoma treatment



What is the best treatment sequence in metastatic BRAF mutant melanoma?



Adapted from German S3 AWMF MelanomaGuideline 2020

Biomarkers for therapy management in melanoma

Tissue-based (Tumor/Tumormicromilieu)

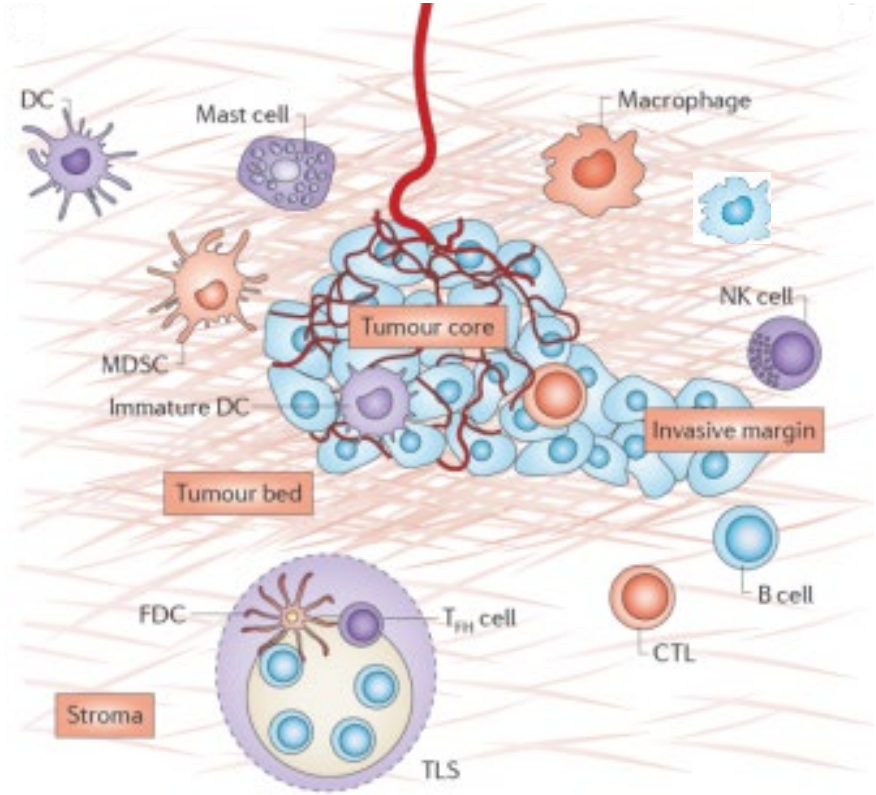
Immunoscore/
Immune-
profiling

PD-L1
Expression

Gene
Expression
Signatures

IFN-gamma
Signature

Tumor
mutation load
(TMB)



Fecal microbiome

Clinical Biomarker

Blood-based

S100B

LDH

ctDNA
(=cell-free Tumor-DNA)

CTCs

Chemokines/
Cytokines

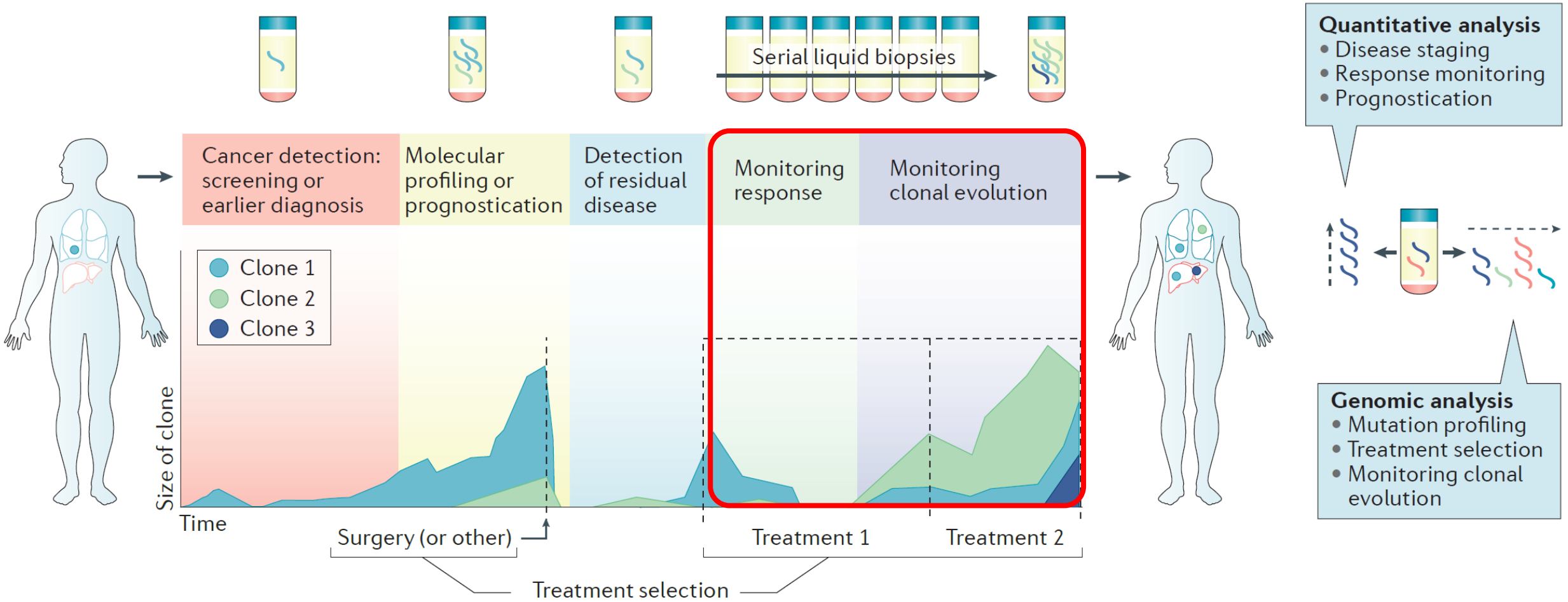
Exosomes

Immune cell-
subtypes

Metabolites

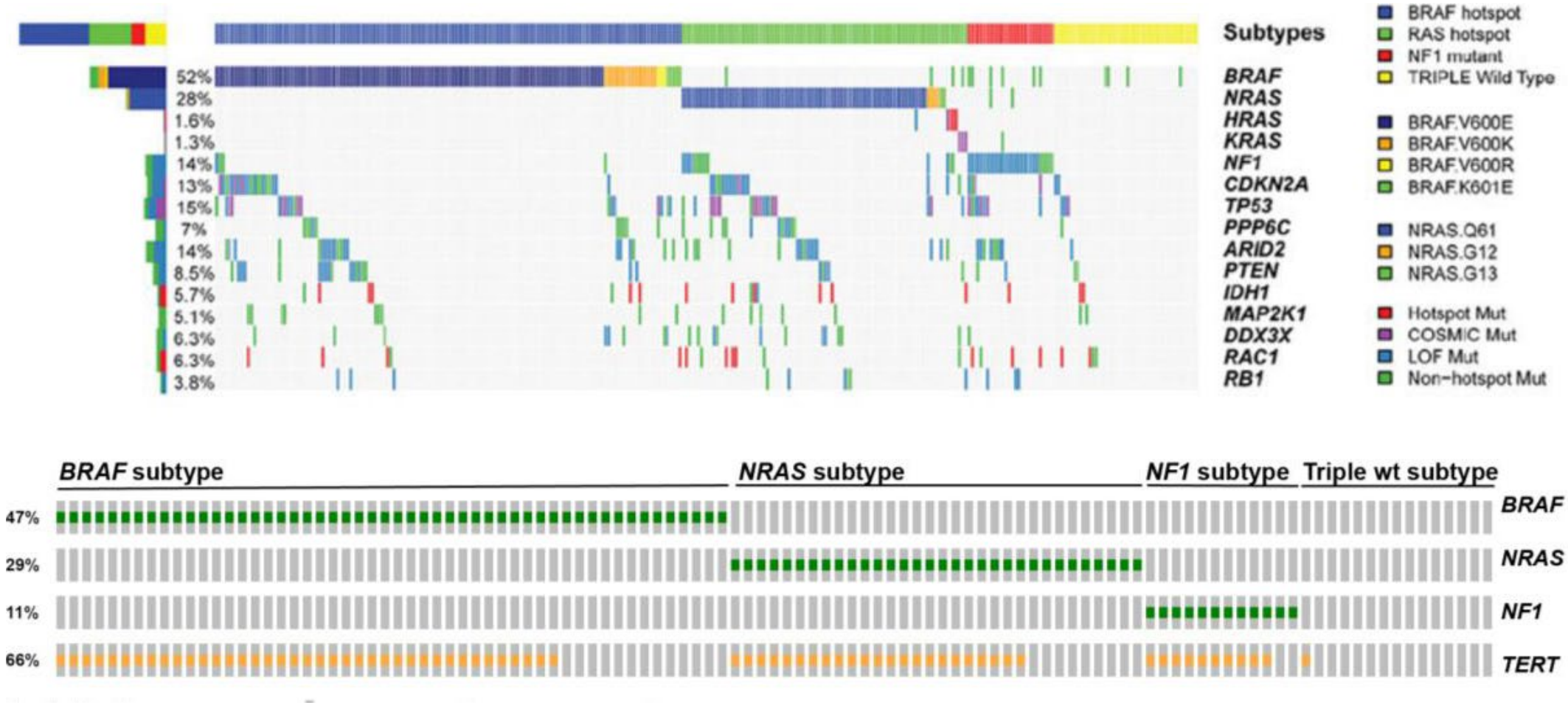
Fridman WH, et al. Nature Rev Cancer. 2012 Mar 15;12(4):298-306
Bardelli A & Pantel K. Cancer Cell. 2017 Feb 13;31(2):172-179

ctDNA diagnostics could guide sequencing of treatment



Wan et al., 2017 Nat Rev Cancer

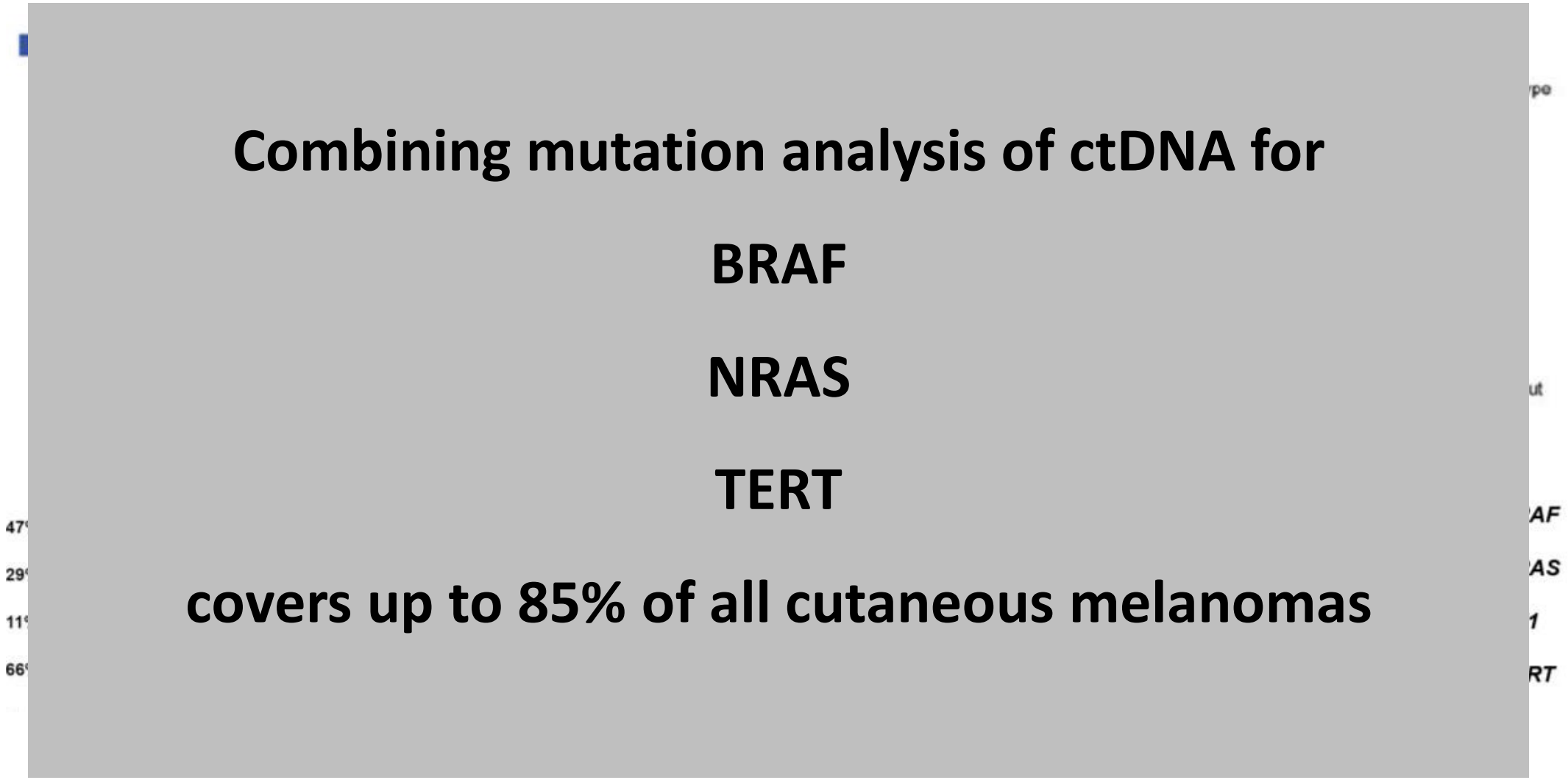
Driver Mutations in Melanoma: BRAF… and more



Cancer Genome Atlas Network TCGA. Genomic Classification of Cutaneous Melanoma, 2015, Cell

Varaljai et al., 2018, JCO Precision Oncology

Driver Mutations in Melanoma: BRAF… and more



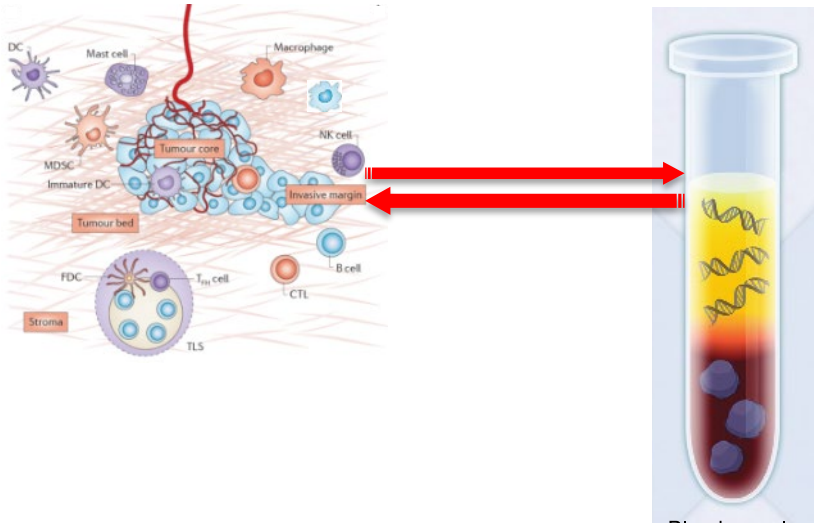
Cancer Genome Atlas Network TCGA. Genomic Classification of Cutaneous Melanoma, 2015, Cell

Varaljai et al., 2018, JCO Precision Oncology

Establishment of the LiquiMEL Biobank

Multicenter Biobank together with Buxtehude, UKSH Lübeck and Kiel (since 2018)

To date **>16,000 blood specimens of skin cancers patients receiving systemic treatment**



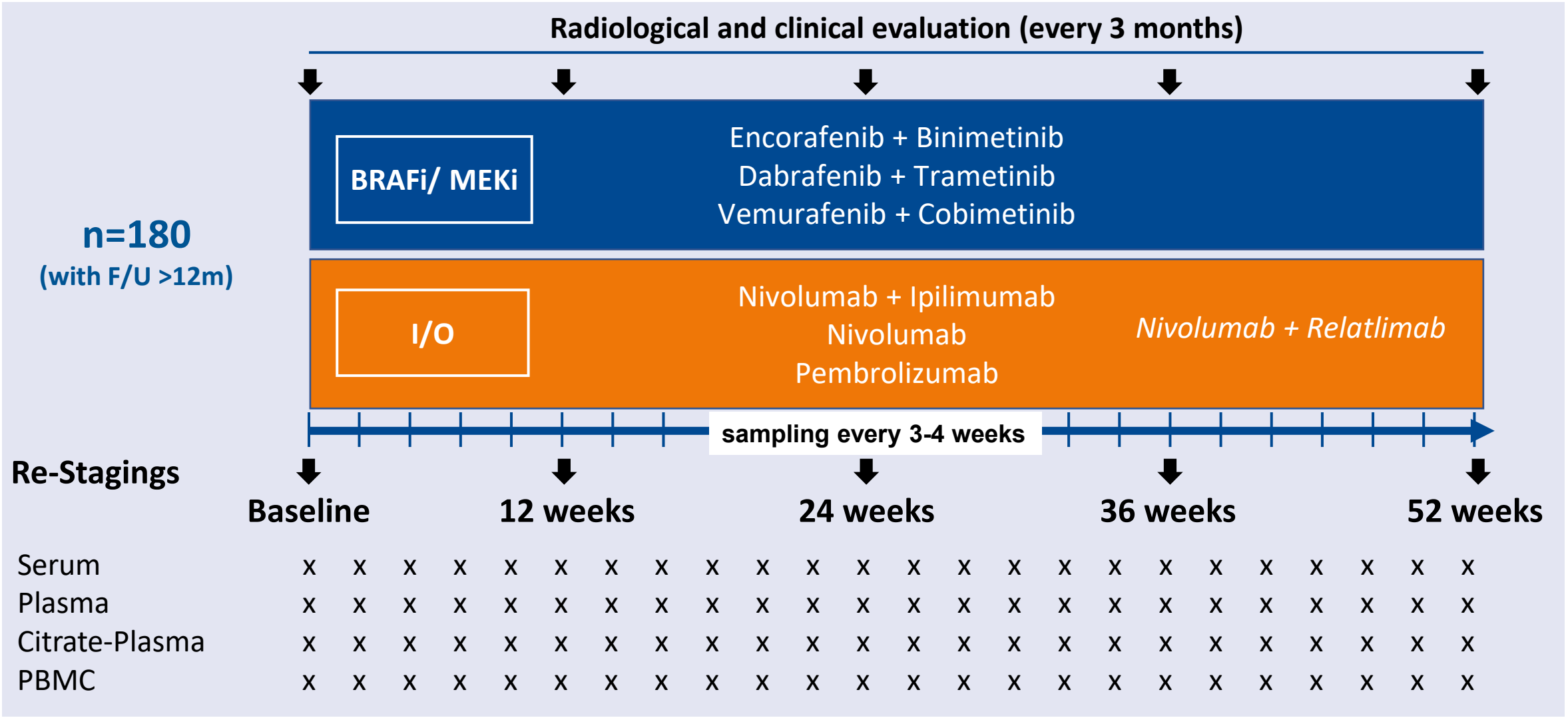
Collaborative Effort of Skin Cancer Center and Institute of Tumor Biology (Prof. Klaus Pantel)

Several collaborations **internally, nationally and internationally**

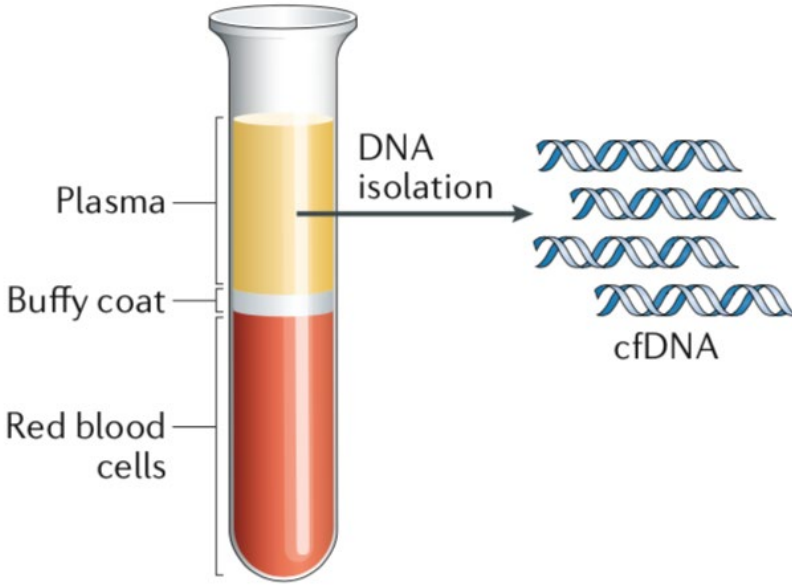
Fleur Hiege Center
for Skin Cancer Research

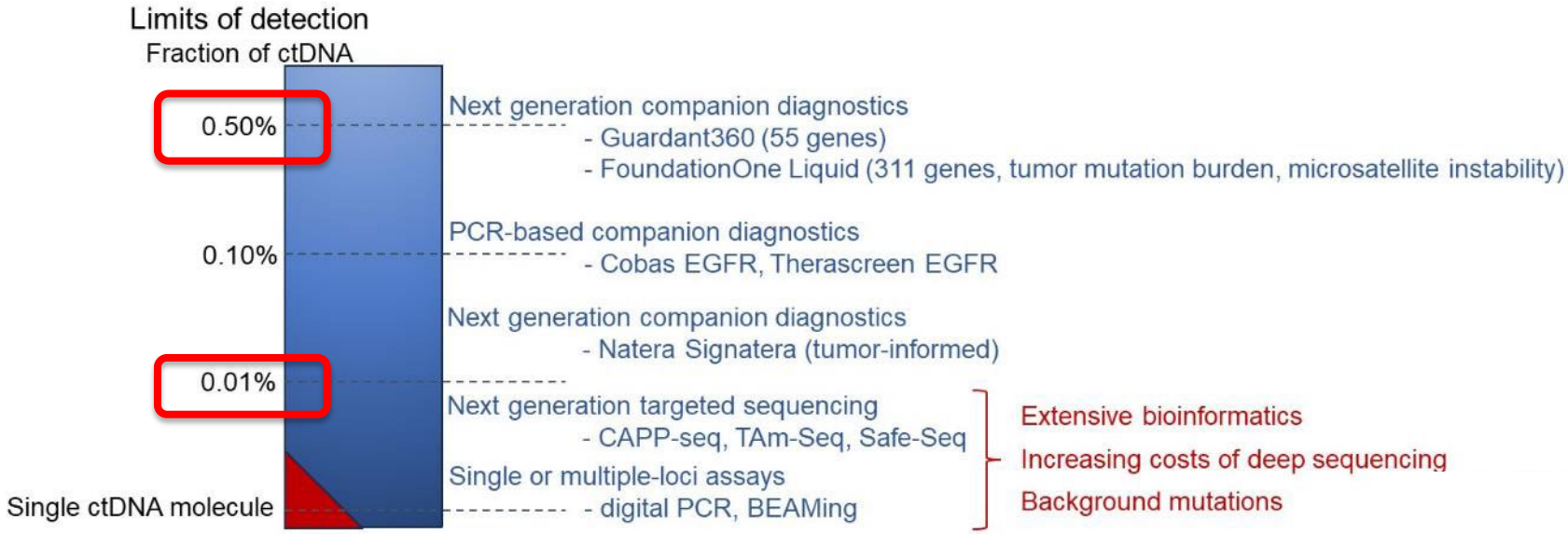
LiquiMEL Biobank

>230 non-resectable Stage III/IV Melanoma Patients (since 2018)



Methods of ctDNA Analysis and Limits of Detection

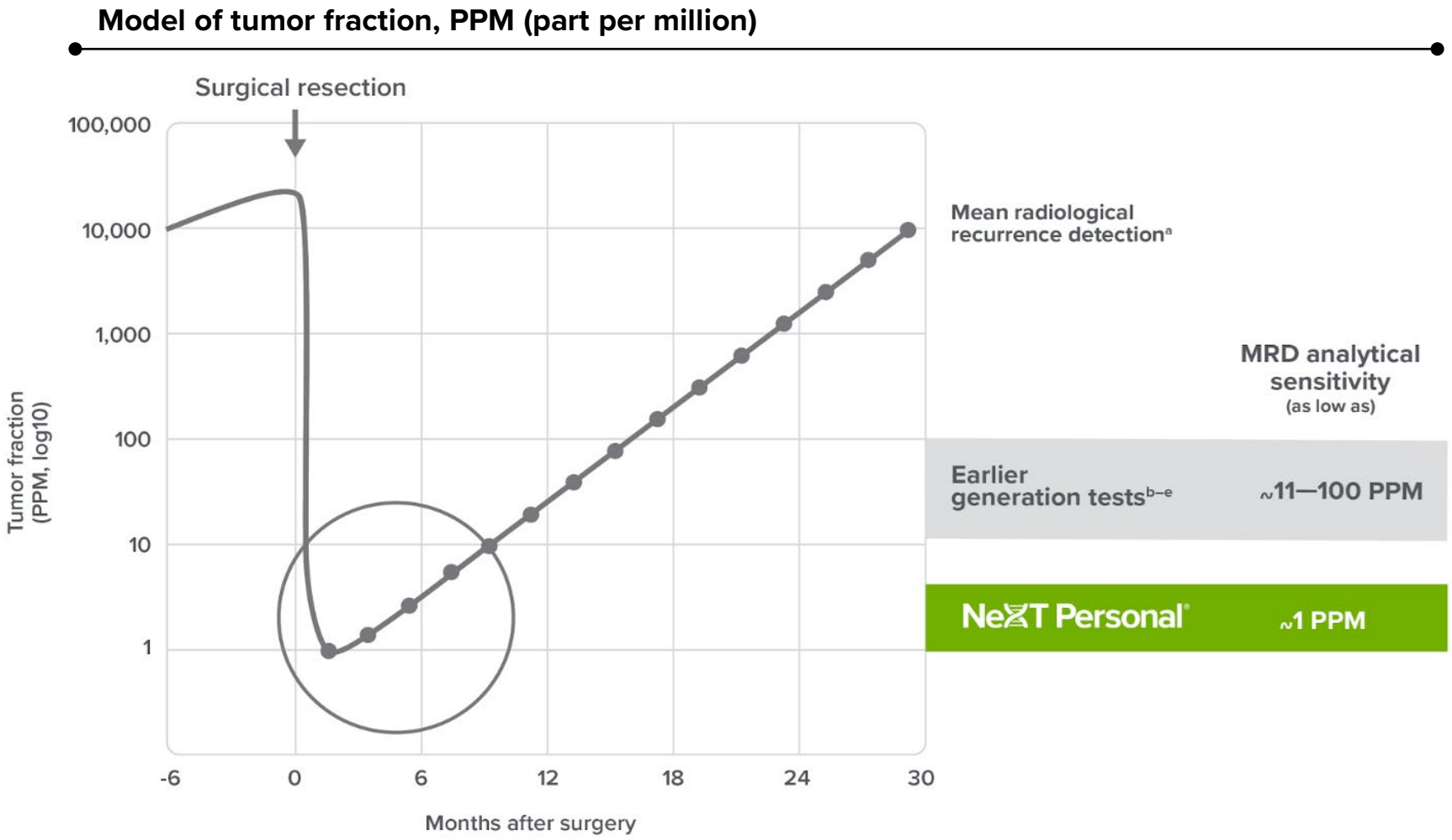




Standard ddPCR reaches sensitivity of up to 100 PPM

Pantel and Alix-Panabières, 2019, Nat Rev Cancer
Rizos, Educational, ASCO 2023

NeXT Personal is an ultra-sensitive and specific MRD test designed to see MRD earlier and more accurately

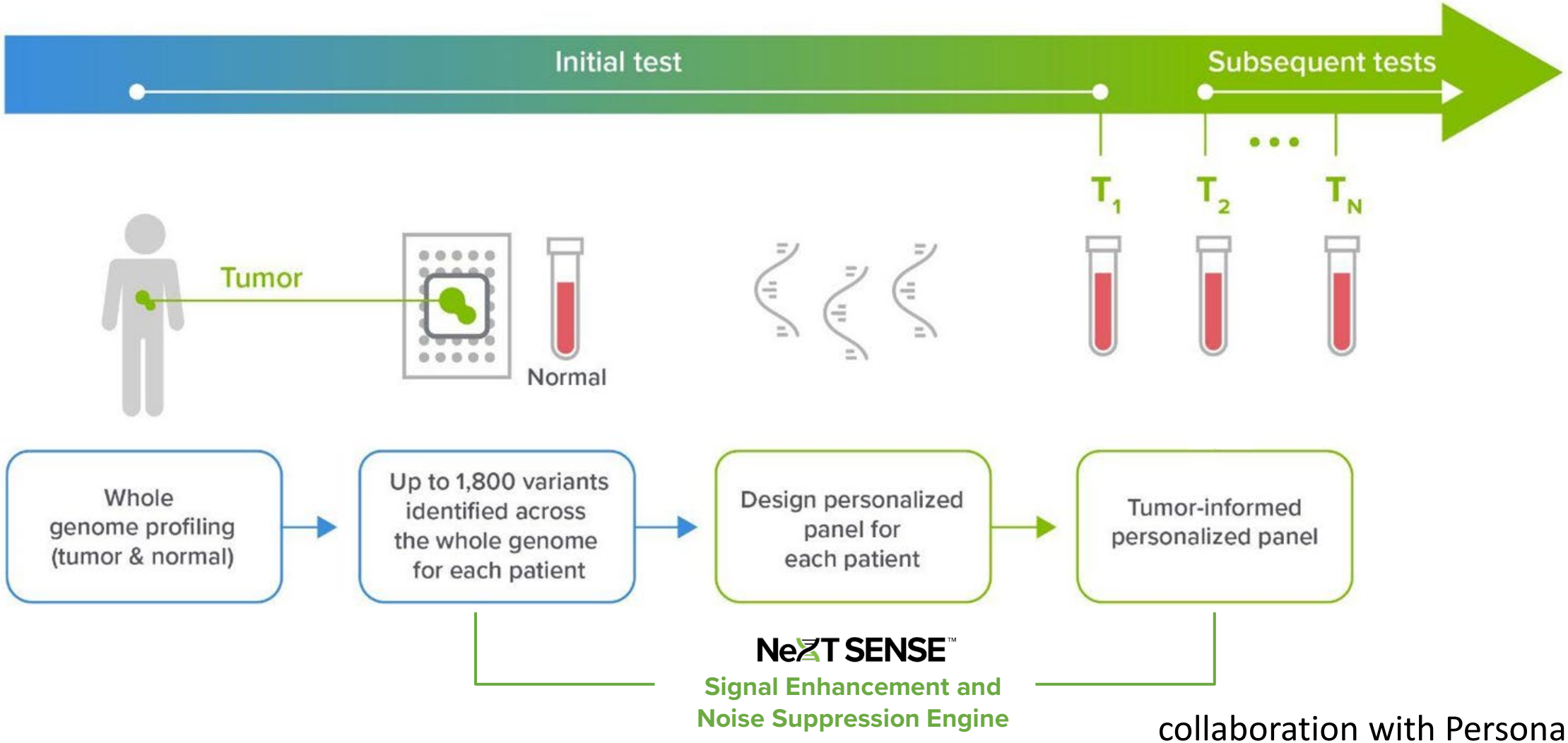


Post-surgical model assumptions: Median breast tumor size detected by mammography: 1.3cm, Median shedding per NSCLC TracerX study[e]; Residual tumor from surgery: 1%; Volume doubling time (actual VAF time): 2 months. Pre-surgical values are illustrative. PPM: Part Per Million

a. Adler et al., EJNMMI Physics, 2017 **b.** Sethi et al., AACR, 2018, Abstract 4542 **c.** Abbosh et al., Nature, 2023 **d.** Marsico et al., AACR 2020, Poster 309 **e.** Abbosh et al., Nature, 2017

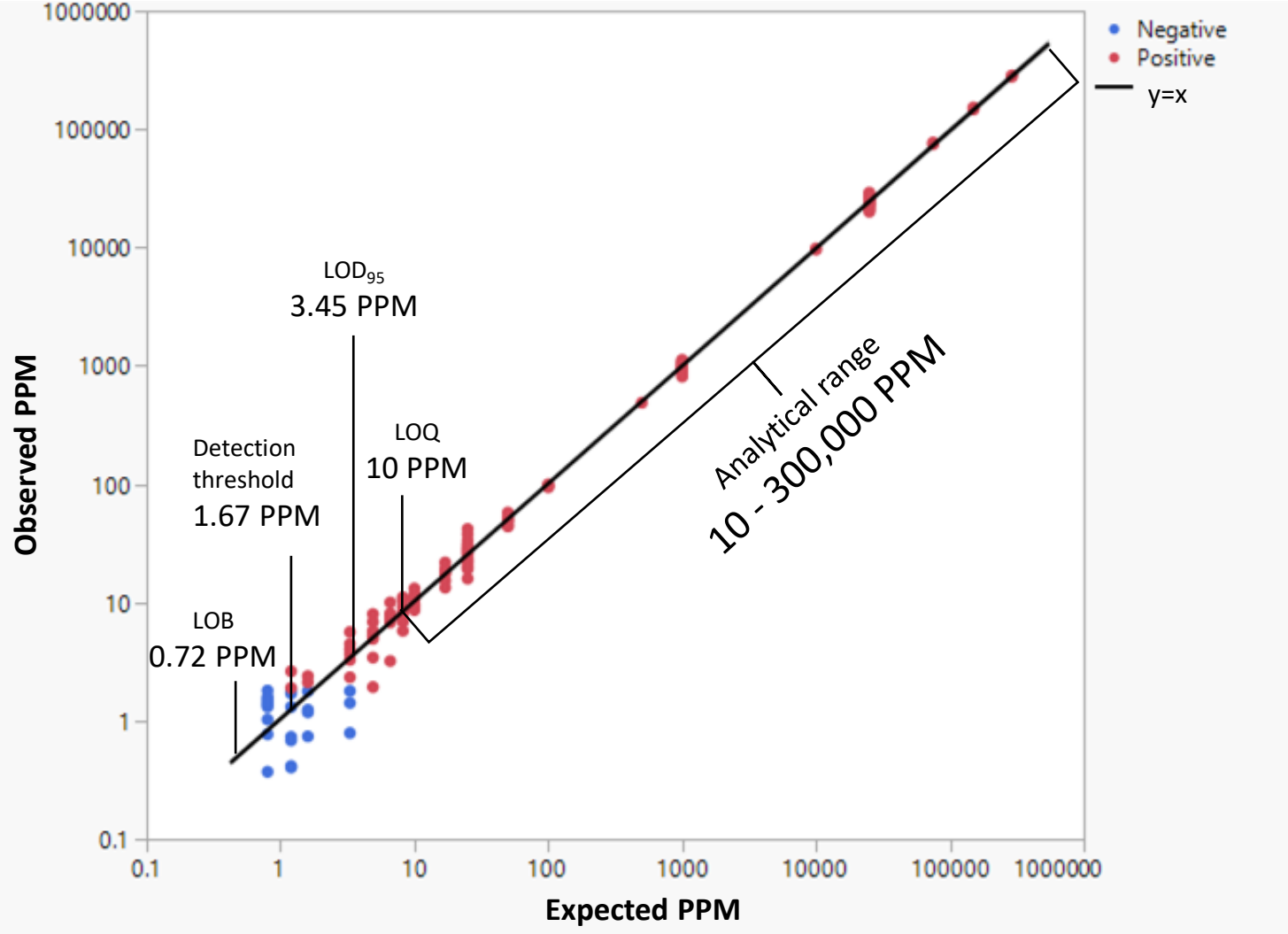
collaboration with Personalis Inc.

Tumor informed MRD approach powered by whole genome sequencing and advanced analytics



collaboration with Personalis Inc.

Analytical range of the NeXT Personal platform



Limit of blank (LOB): 0.72 PPM
The level of signal (noise) detected in instances where no tumor is present.

Detection threshold: 1.67 PPM in AV study
The lower limit at which a positive call can be made at the defined specificity; defines LOD_{50}.

95% Limit of detection (LOD_{95}): 3.45 PPM
The concentration at which 95% of reading would be positively detected.

Limit of quantification (LOQ): 10 PPM
The lower limit at which two measurements can be quantitatively distinguished.

Analytical range: 10 PPM - 300,000 PPM
The range over which which two measurements can be quantitatively distinguished.

Northcott J., Bartha G., Harris J., Li C., Navarro F. C.P., Pyke R. Marty, Hong M., Zhang Q., Ma S., Chen T. X., Lai J., Udar N., Saldivar J., et al Analytical validation of NeXT Personal®, an ultra-sensitive personalized circulating tumor DNA assay. Oncotarget. 2024; 15: 200-218.

collaboration with Personalis Inc.

Patient characteristics

Age at diagnosis	Median (SD)	55 (5.3)
Gender		
	F	8 (35)
	M	15 (65)

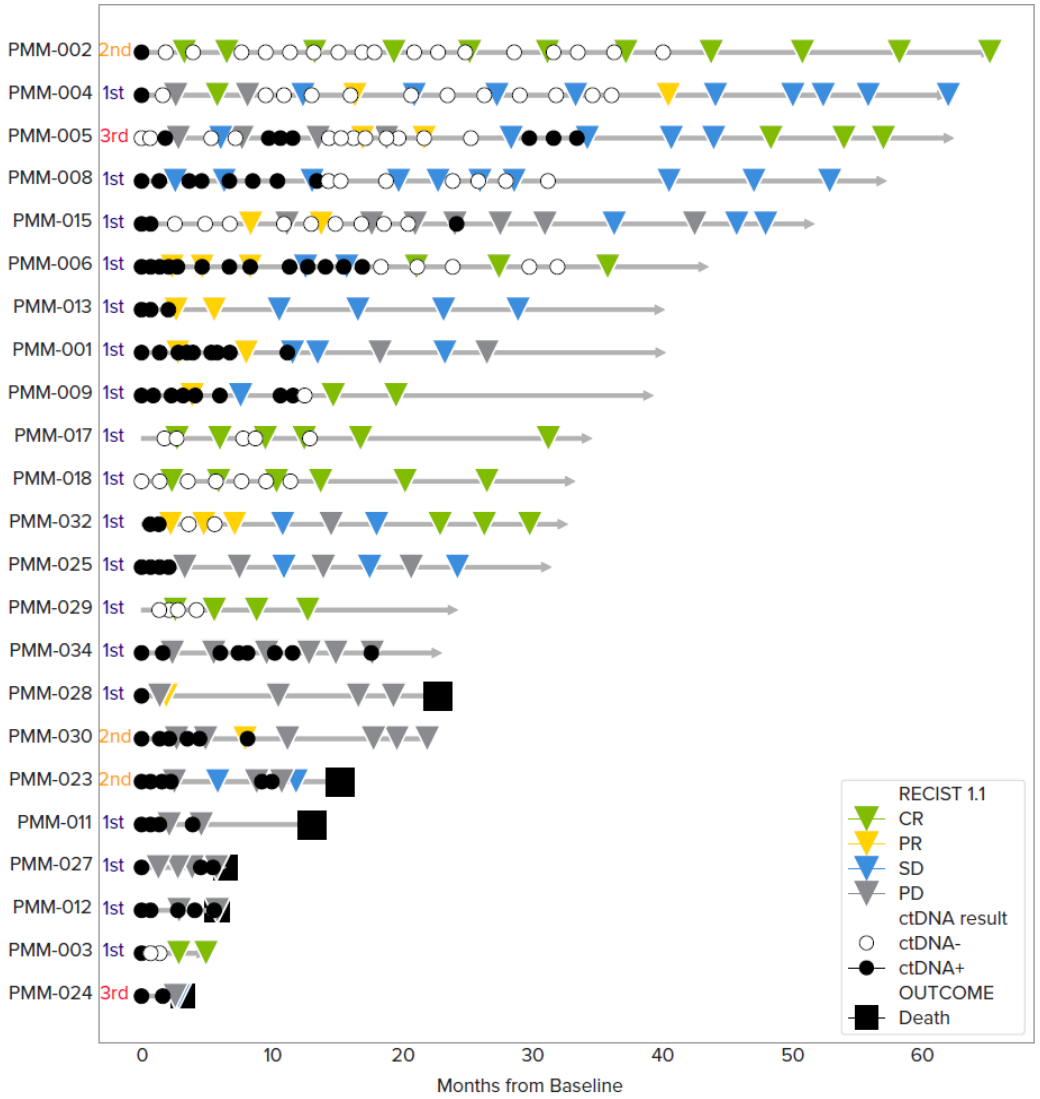
Melanoma subtype		
	Cutaneous	18 (78)
	Mucosal	3 (13)
	CUP	2 (9)

S100B		
	Elevated	12 (52)
	Normal	11(48)
LDH		
	Elevated	16 (70)
	Normal	7 (30)
BRAF		
	wt	11 (48)
	mut	12 (52)

Tumor stage (AJCC version 8)		
	III	2 (9)
	IV	21 (91)
ICI Treatment		
	Pembro	3 (13)
	Nivo	2 (9)
	Ipi+ Nivo	18 (78)
Therapy line		
	1st	18 (78)
	2nd	3 (13)
	3rd	2 (9)
Best overall response to ICI		
	Complete response	10 (43.5)
	Partial response	5 (21.7)
	Stable disease	4 (17.4)
	Progressive disease	4 (17.4)

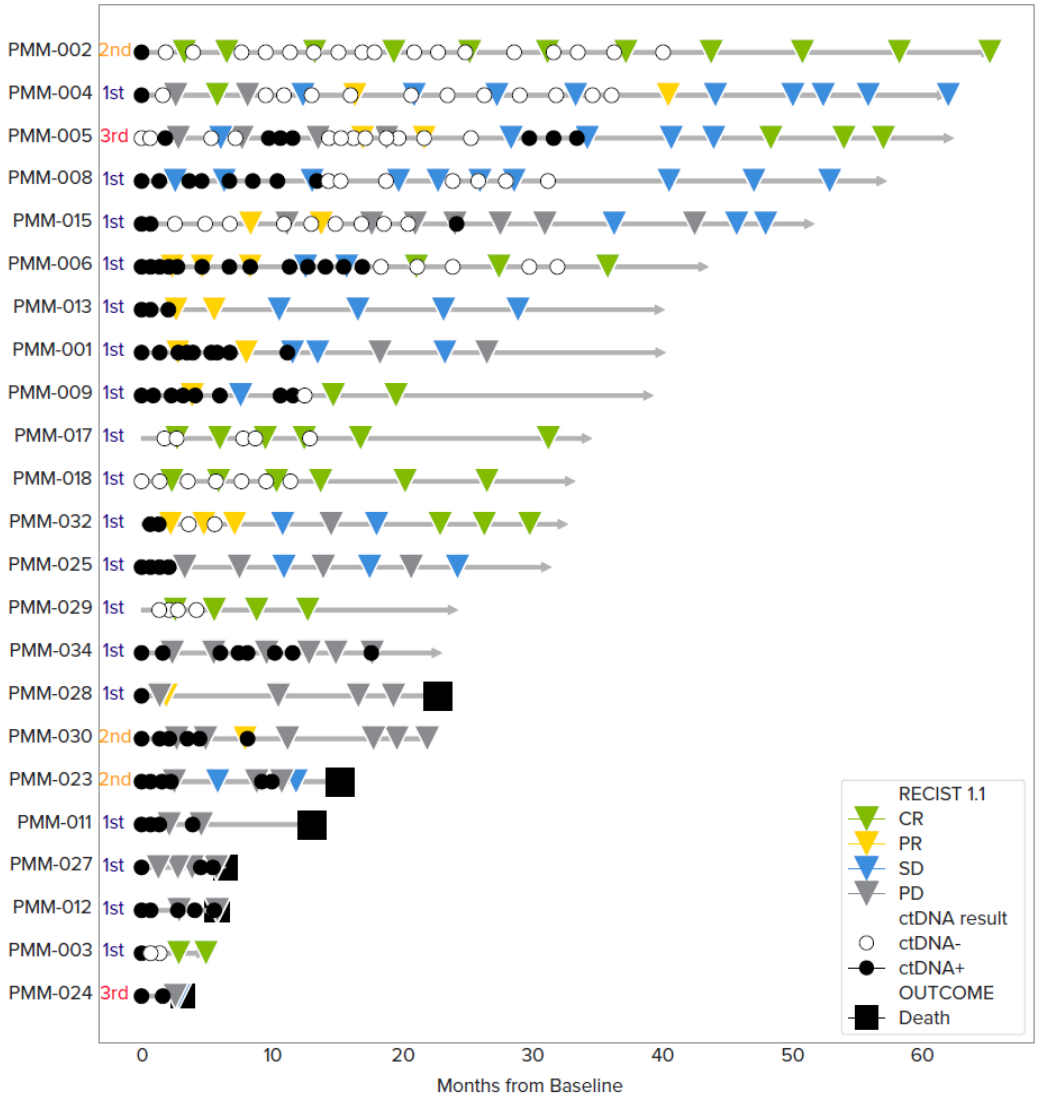
Brain metastasis (at treatment start)		
	None	17 (74)
	Present	7 (26)
Liver metastasis (at treatment start)		
	None	17 (74)
	Present	6 (26)
Lung metastasis (at treatment start)		
	None	8 (35)
	Present	15 (65)
Bone metastasis (at treatment start)		
	None	21 (91)
	Present	2 (9)

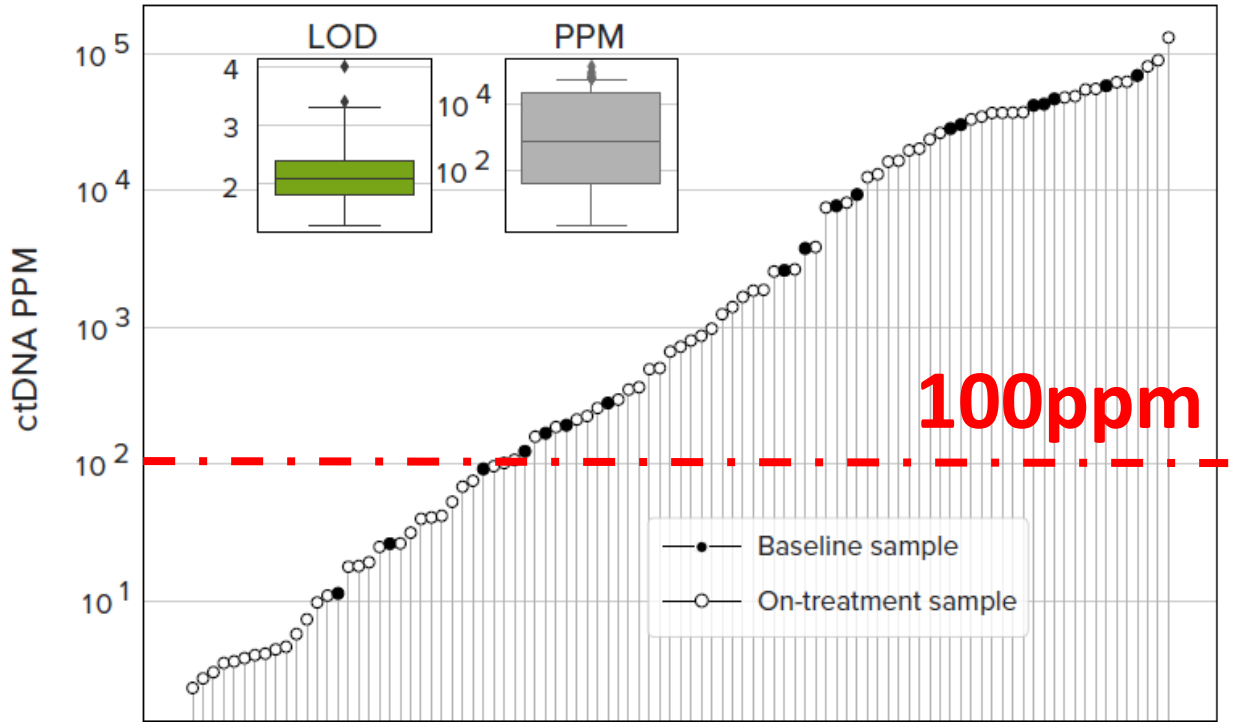
Majority of patient baseline samples detected using an ultra-sensitive ctDNA assay



188 plasma samples from 23 melanoma patients receiving ICI over several years

Majority of patient baseline samples detected using an ultra-sensitive ctDNA assay

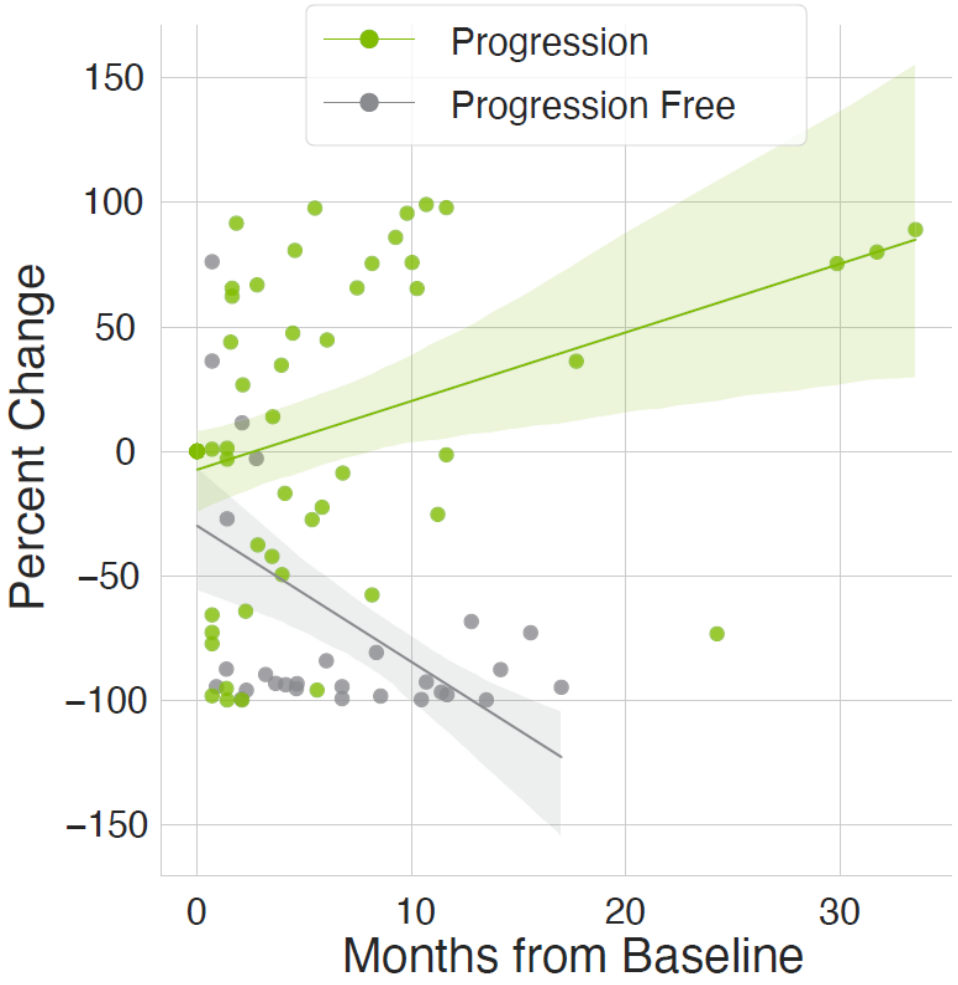


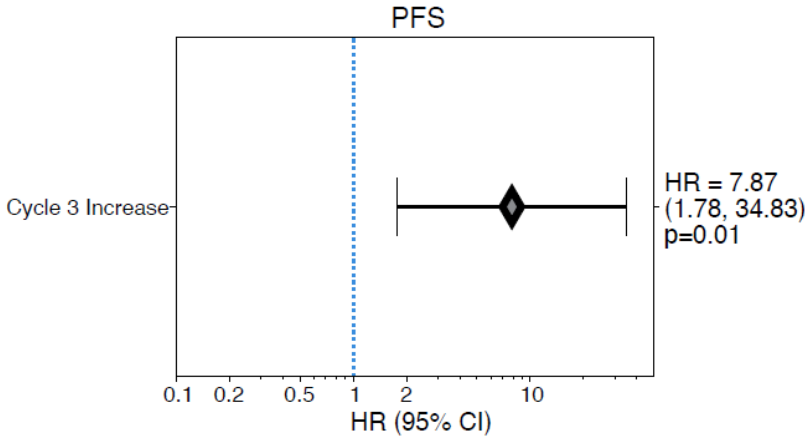


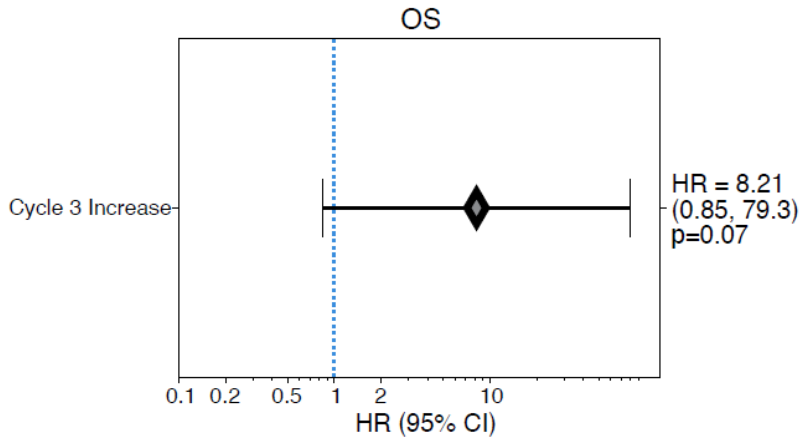
ctDNA was detected with a **sensitivity down to 2.3 PPM**
Up to 28.6% of all positive detections fall below 100 PPM

Standard ddPCR reaches sensitivity of up to 100 PPM

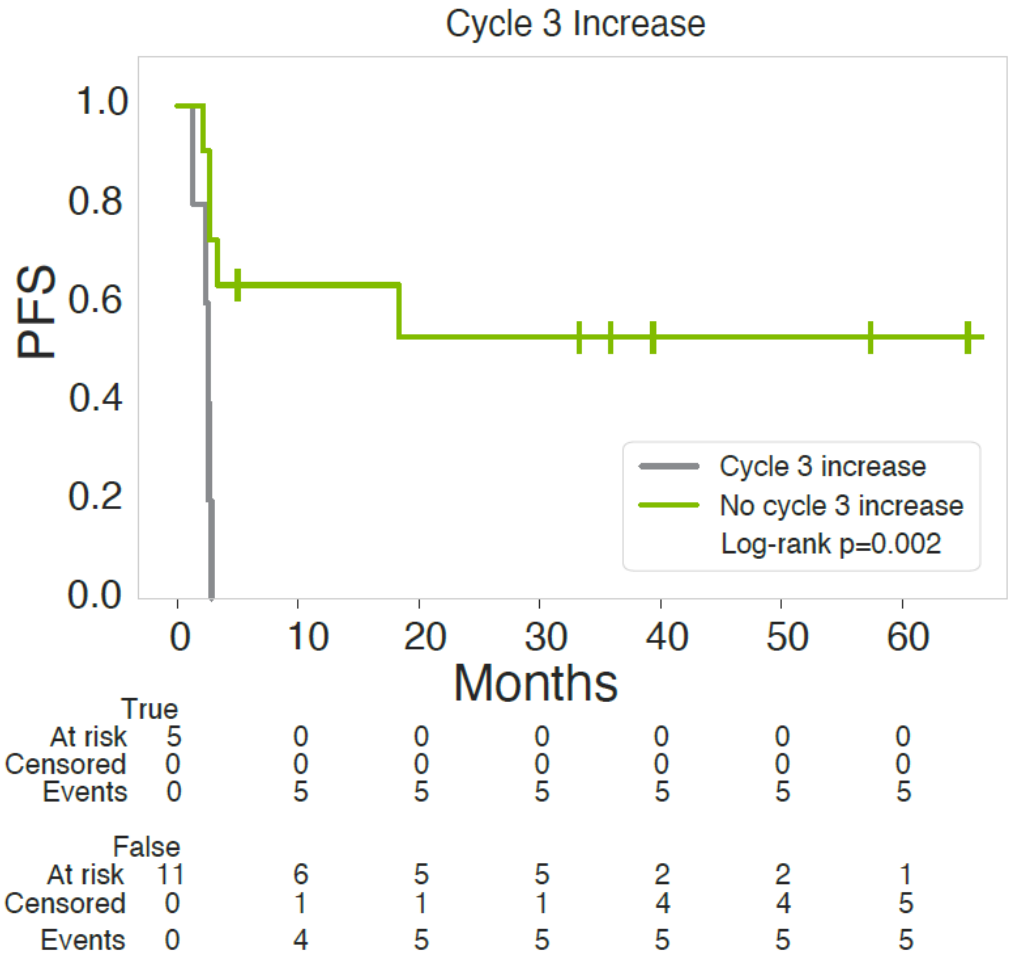
Early ctDNA increases from baseline are prognostic of progression-free survival

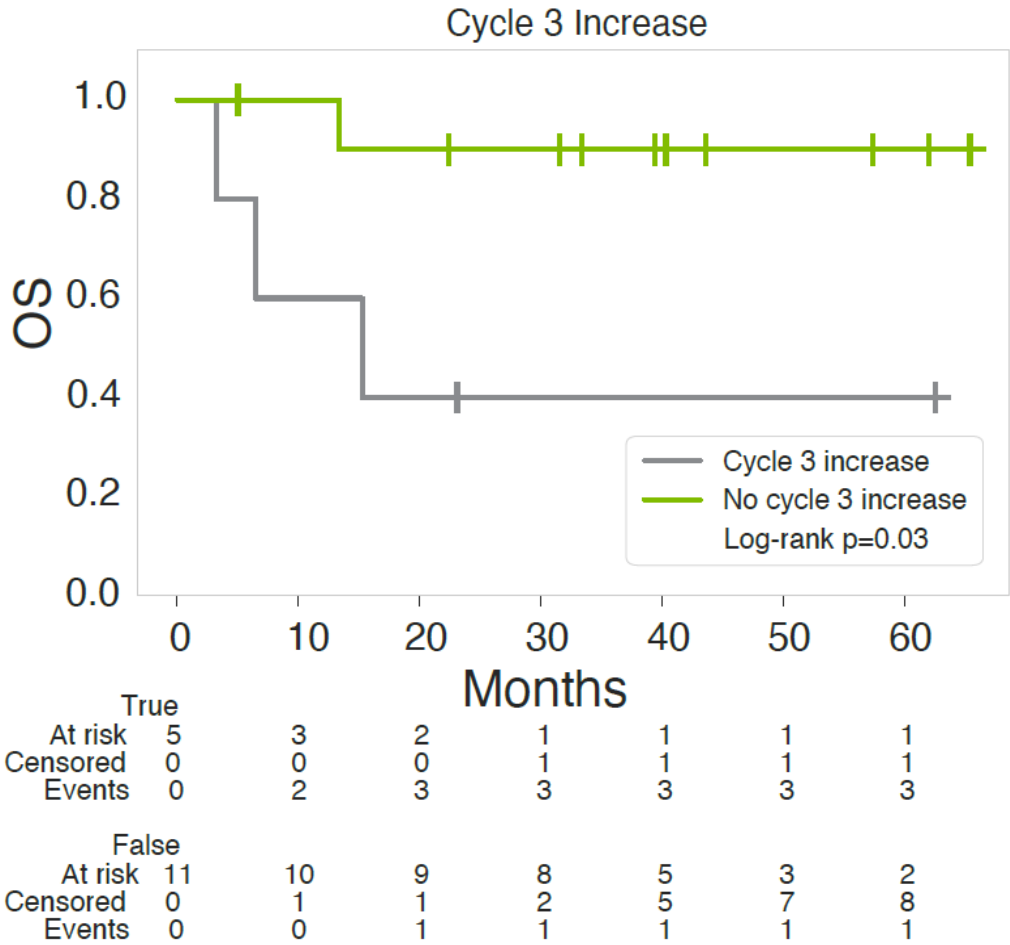




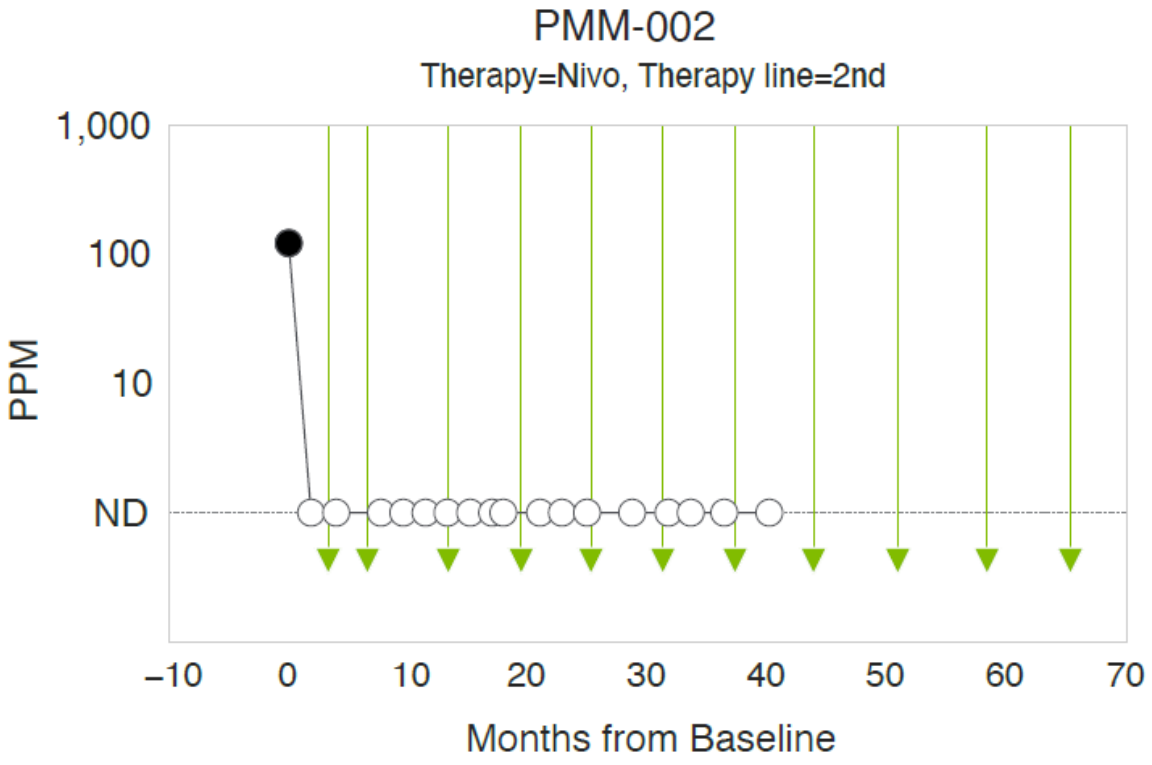


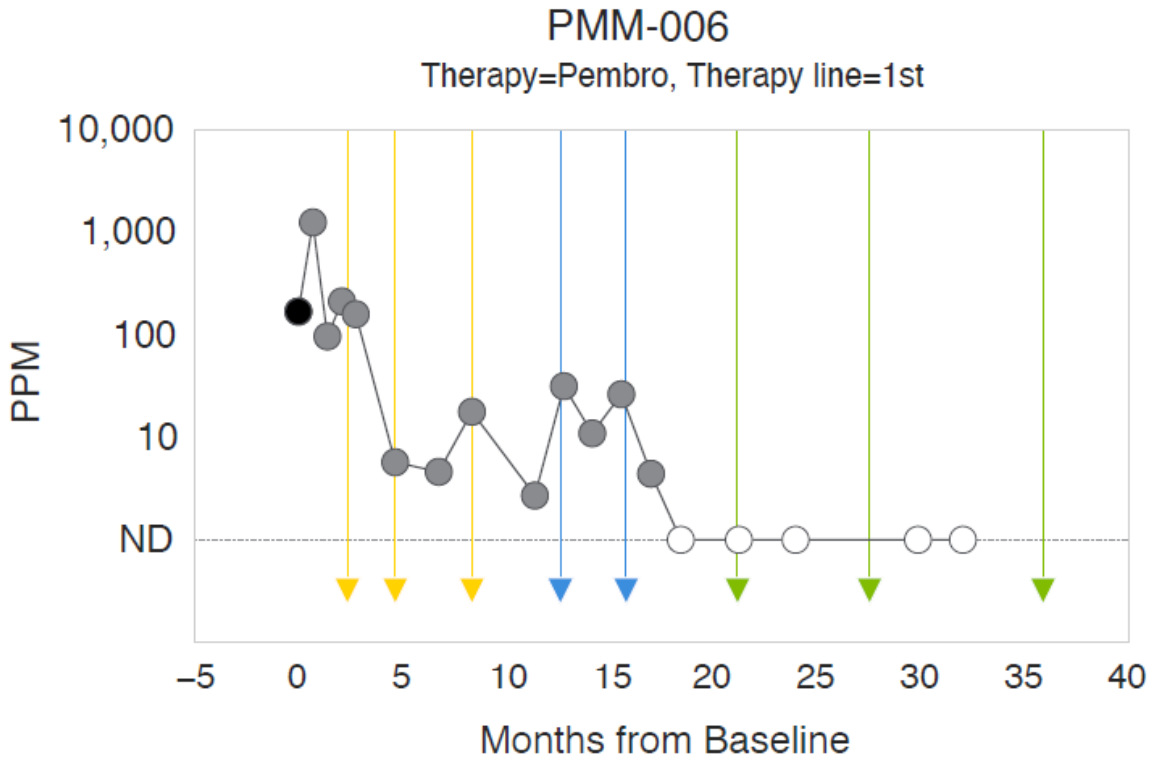
Early ctDNA increases from baseline are prognostic of progression-free survival





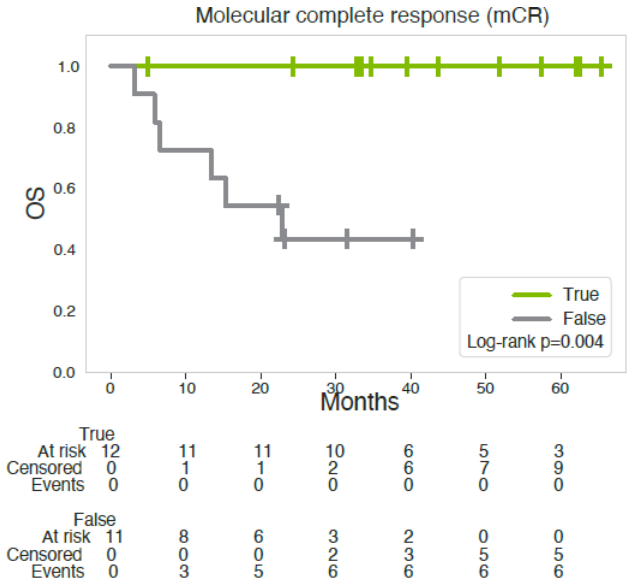
On-treatment ctDNA measures correlate with response and are prognostic of overall survival



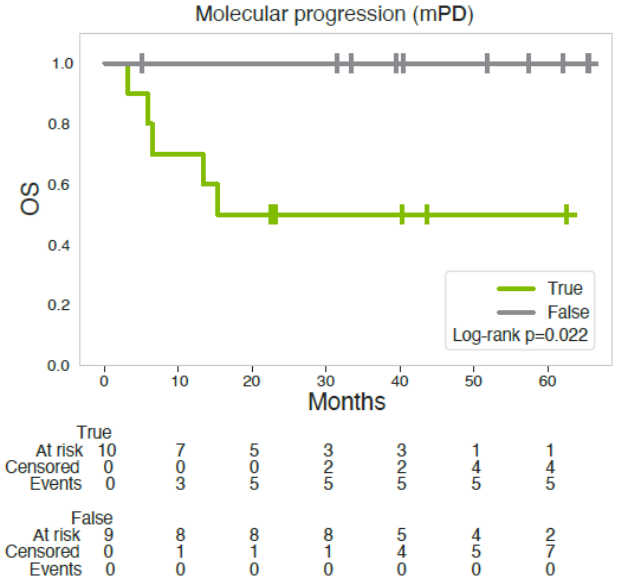


On-treatment ctDNA measures correlate with response and are prognostic of overall survival

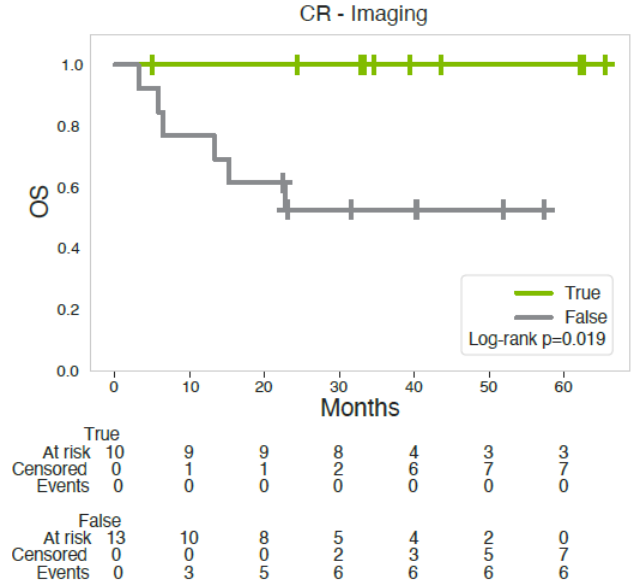
Molecular Complete Response (mCR)



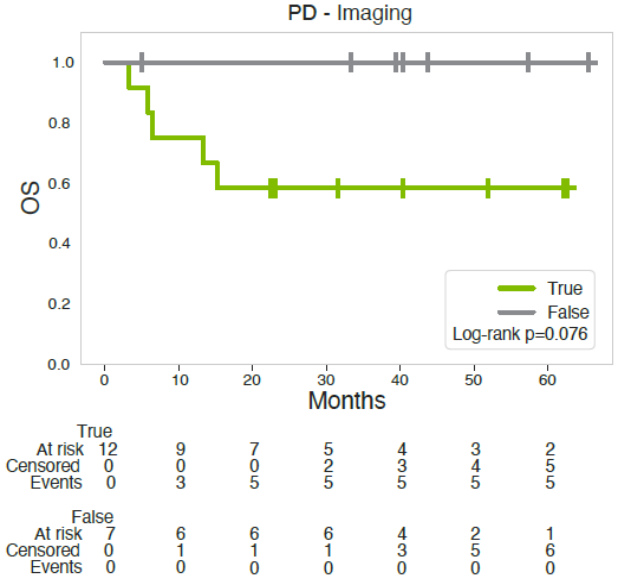
Molecular Progressive Disease (mPD)



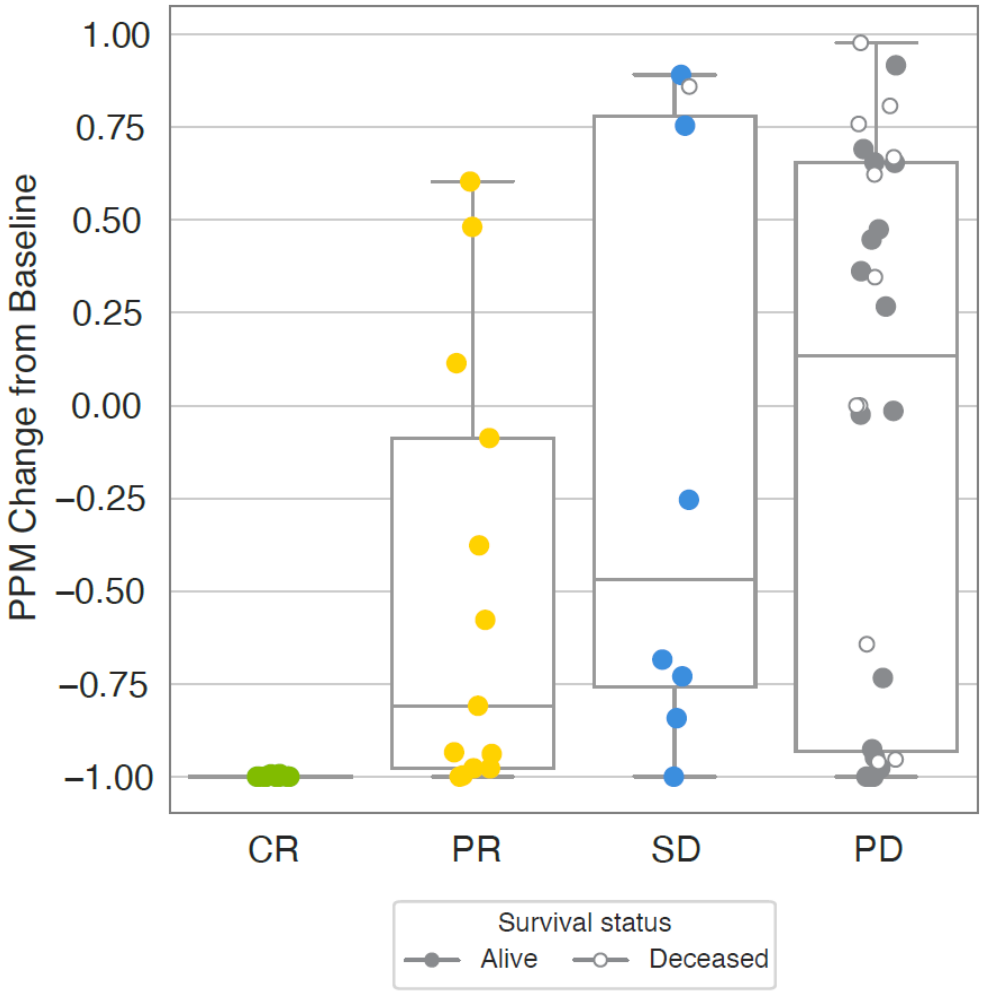
Radiological **Complete Response (CR)**

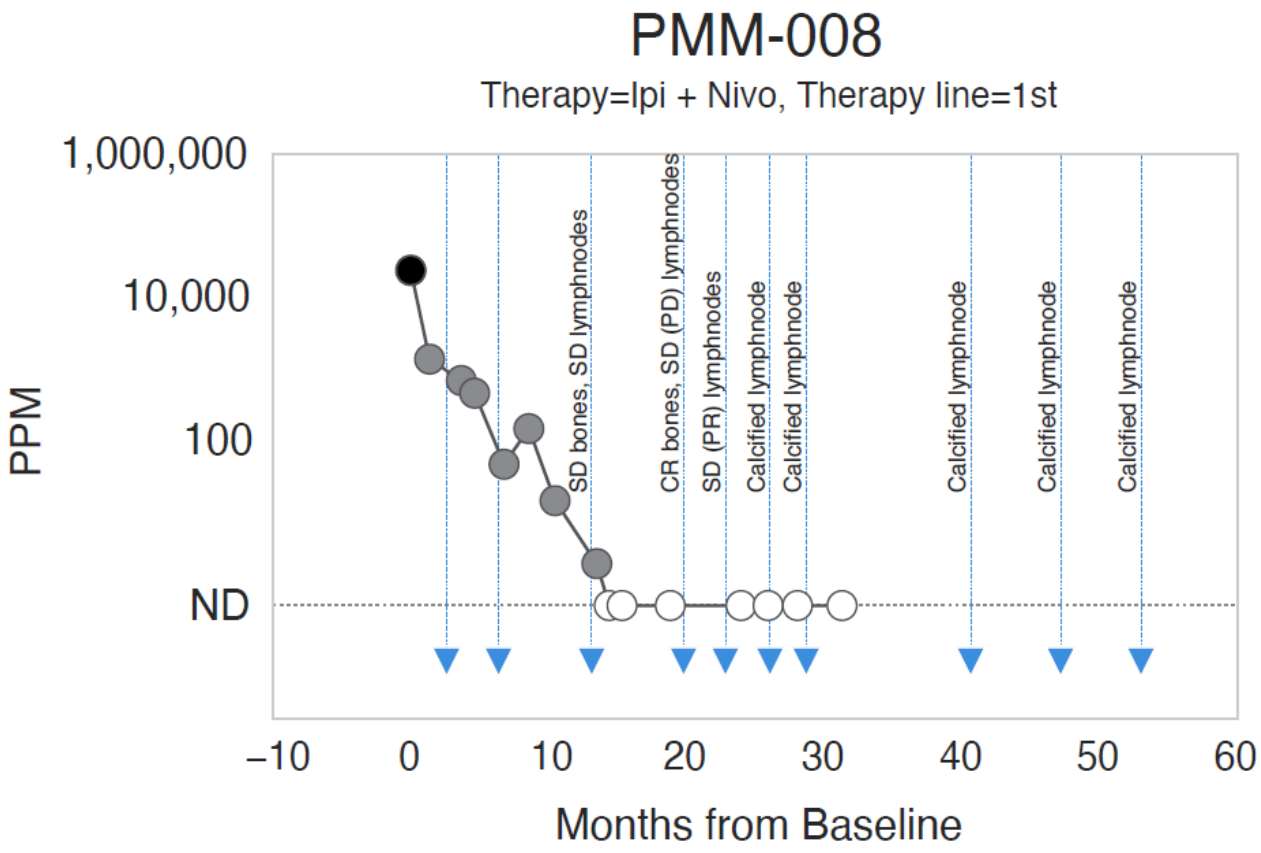


Radiological **Progressive Disease (PD)**

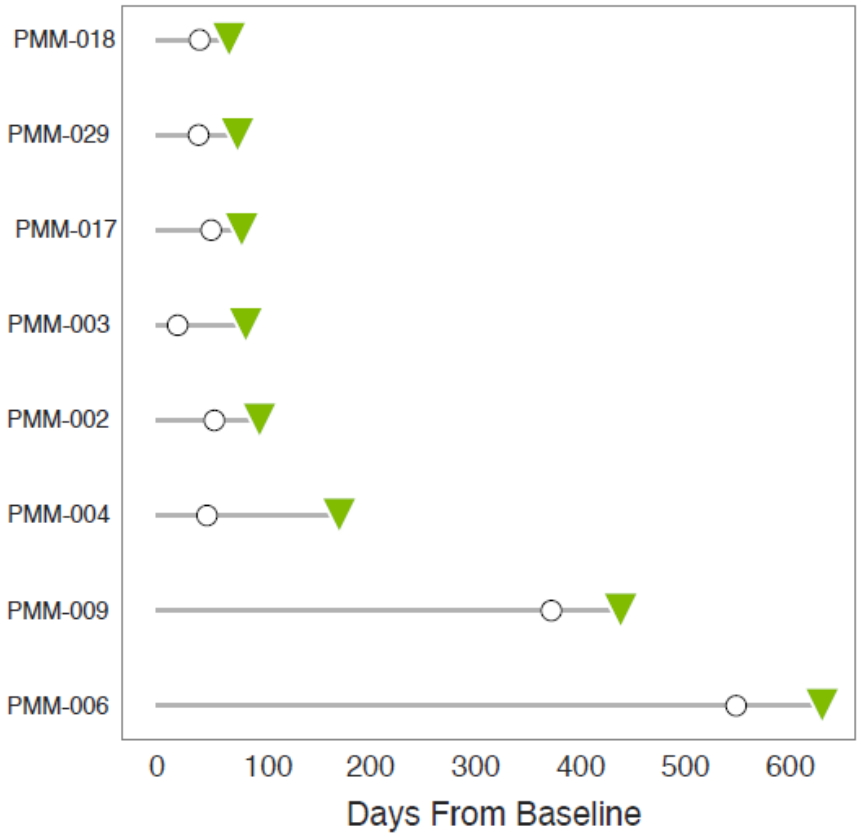


Pairing ctDNA and imaging-based response evaluation improves the accuracy of response classifications



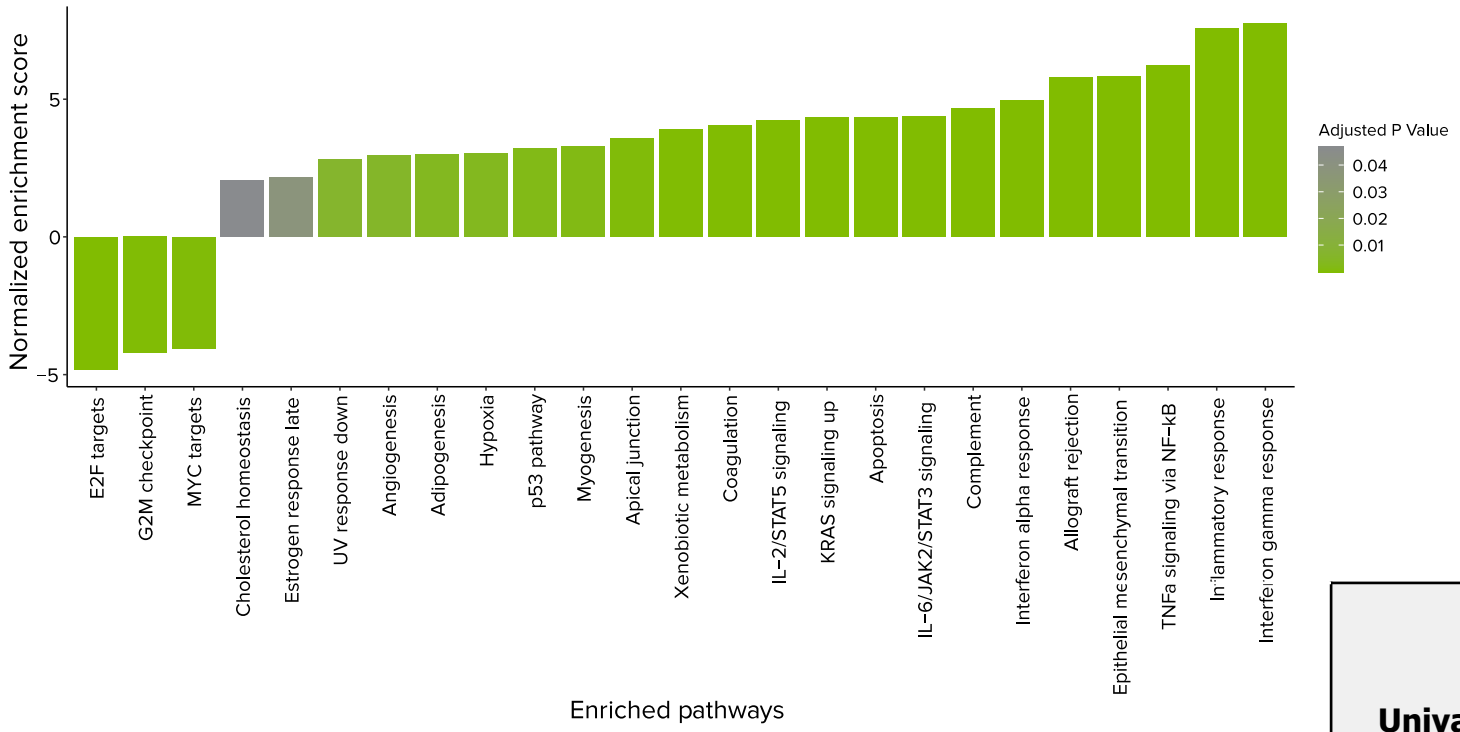


ctDNA status identifies response prior to imaging



Radiological CR was preceded by at least one on-treatment ctDNA negative determination in 100% (10/10) of CR patients,
with mCR occurring an average of 250 days prior to imaging based CR (median = 66 days)

Deep ctDNA monitoring and tumor immune profiling accurately predicts ICI resistance



NeXT Liquid Biopsy® (NeXT LB) platform

Multivariable Cox models of progression free survival that combine immune features with ctDNA measures compared to univariable assessment

	Univariable model			Multivariable model adjusted for ctDNA burden			Log-likelihood ratio test between models with and without ctDNA
	log-likelihood	p-value	HR	log-likelihood	p-value	HR	p-value
Myeloid DC's	4.0533	0.0441	0.163	6.6057	0.0368	0.25	0.024
Neoantigen Burden	9.6178	0.0019	0.17	11.6453	0.003	0.18	0.044
CD8 T cells	3.9206	0.0477	<0.01	6.4836	0.0391	<0.01	0.024

Wald; adjusted p<0.01), as measured by baseline RNA expression profiling

Abbott et al. AACR 2024, Poster #2415

Summary and Conclusions

- Despite remarkable progress in the treatment of melanoma by immune checkpoint inhibitors (ICI), a **large proportion of patients still do not respond or achieve durable clinical benefit from ICI**
- Circulating tumor DNA (ctDNA) monitoring in peripheral blood has shown promise for disease surveillance and prognostication of ICI response. Yet even in the metastatic context, **ctDNA signals can be missed, suggesting the need for increased assay sensitivity**
- We used a **tumor-informed ctDNA assay capable of detection down to 1 part-per-million (PPM)** ctDNA to profile **188 plasma samples from 23 melanoma patients receiving ICI** over several years
- Residual disease was detected in **ctDNA over a broad range, from 130,000 PPM down to 2.3 PPM**, with approximately a third below 100 PPM and a quarter of detections below 50 PPM
- Early on-treatment increases in ctDNA level, and both ctDNA-based molecular clearance (mCR) and molecular progression (mPD) were all prognostic of both OS and PFS
- Additionally, mCR consistently preceded radiographic imaging
- **Our results show the importance and utility of an ultra-sensitive ctDNA assay** in advanced melanoma treated by ICI with potential implications for other cancers

Contributors and Funding

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Dermatology, UKSH Lübeck
Patrick Terheyden

Fleur Hiege-Center for Skin Cancer Research

Fleur-Mareen Habig, née Hiege (1972-2005)

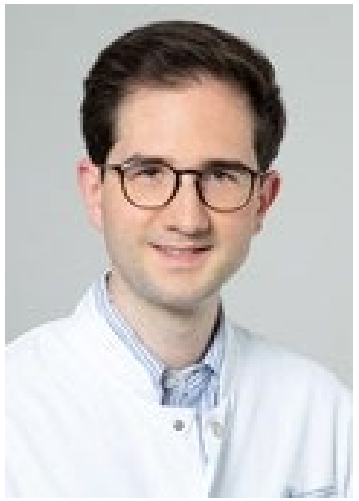
Ohne Forschung keine Zukunft

HIEGE-STIFTUNG

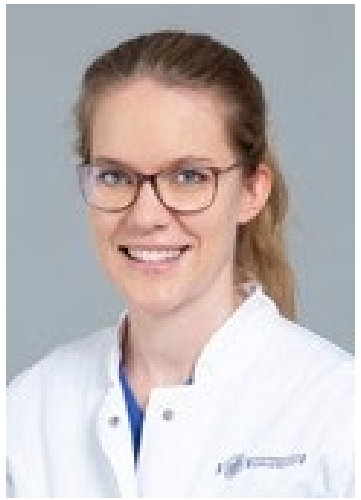
DIE DEUTSCHE HAUTKREBSSTIFTUNG

Collaborative research center of **University Skin Cancer Center**, Department of Dermatology and **Institute of Tumor Biology** at the University Medical Center Hamburg-Eppendorf (UKE)

Our Clinician Scientists in Skin Cancer Research:



Glenn Geidel



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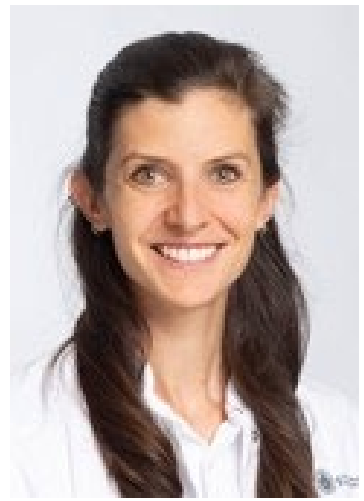
Julian Kött



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University Skin Cancer Center

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ANNUAL MEETING
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Thank you for your attention!

Fleur Hiege-Centrum für Hautkrebsforschung

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ERICH UND GERTRUD ROGGENBUCK-STIFTUNG

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