Erasmus MC
Universitair Medisch Centrum Rotterdam

Cancer Institute

New Advances in Organ Agnostic Therapeutic Approaches

Belgian Society of Medical Oncology – Bordet Meeting 2019

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Medical Oncologist

Erasmus MC Cancer Institute

Disclosures

- Grants for research (to Institute): JnJ/ Astellas/ MSD/ Sanofi
- Advisory role: Roche/ Bayer/ Amgen/ JnJ/ Sanofi/ Servier/ Pfizer/ Incyte

Why Invite a Dutch Scientist to Talk About This Subject?

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Back to basics: DNA is at the heart of every malignant disease

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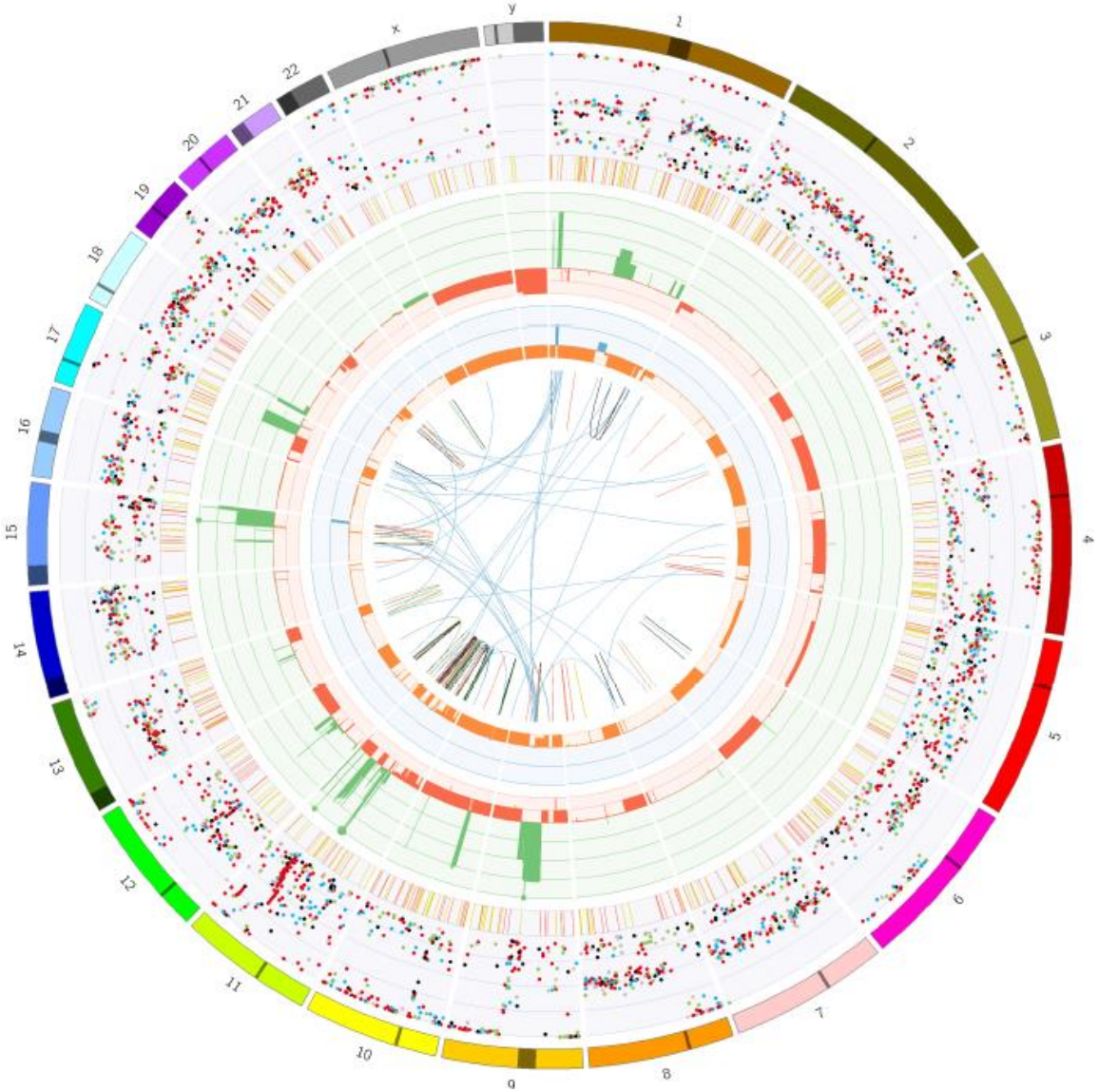

Priestley et al Nature 2019

The Genome of Metastatic Cancer

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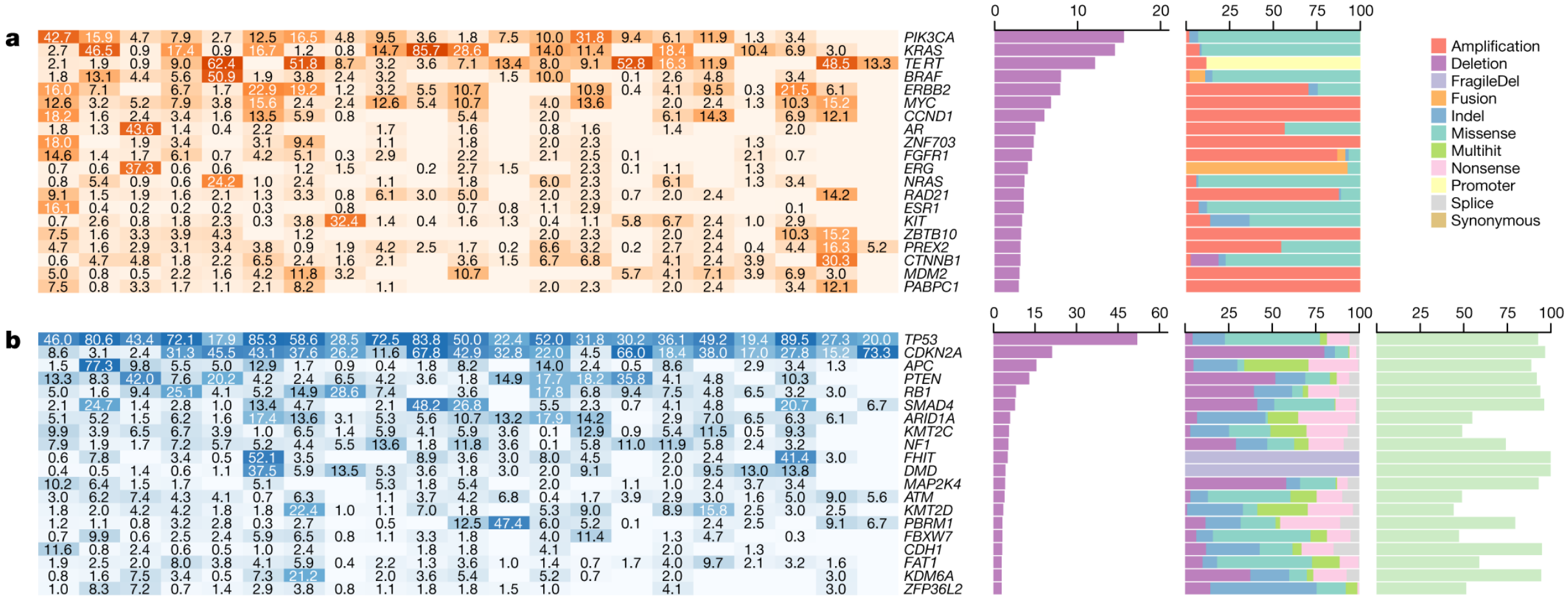
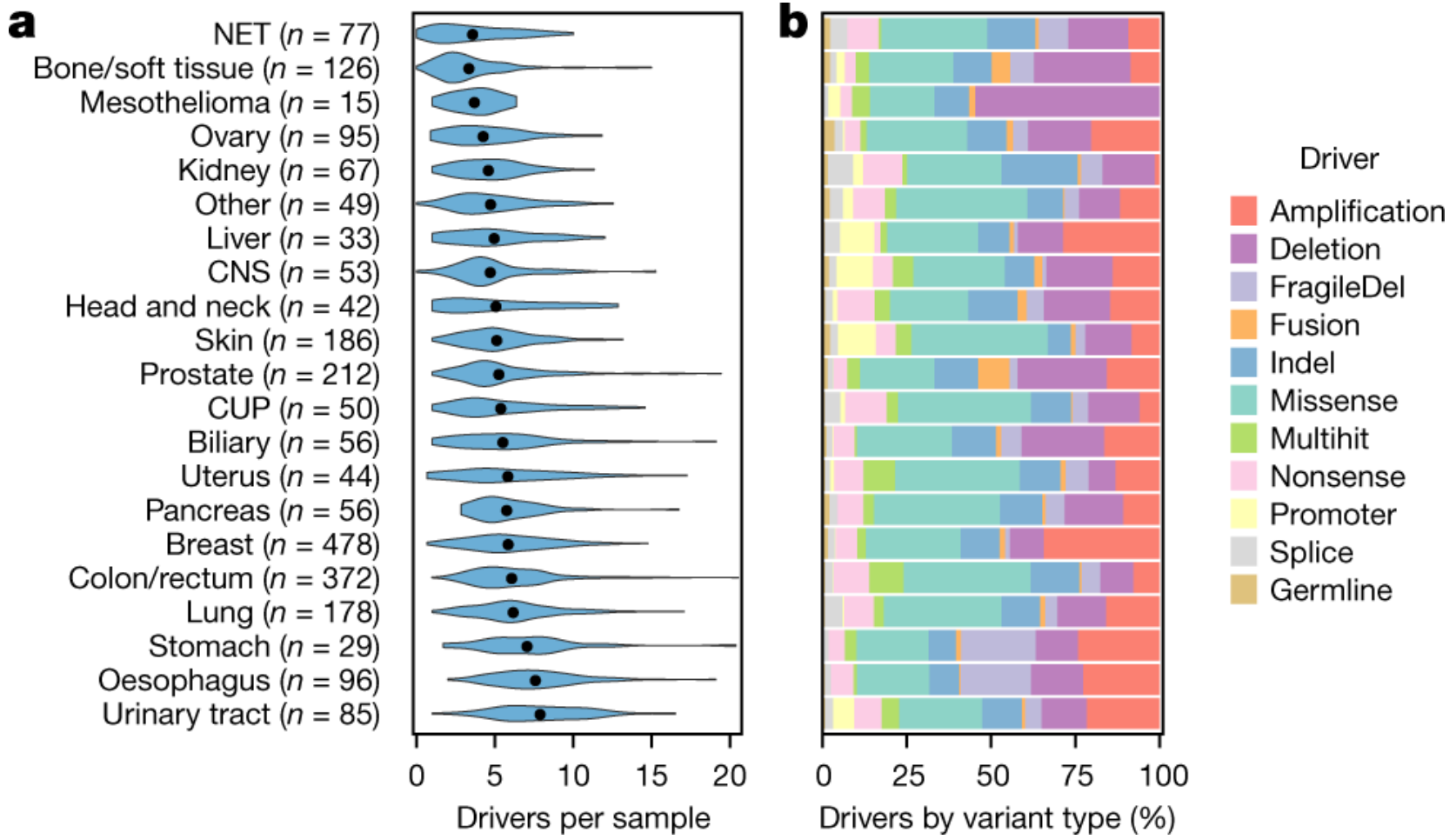


Priestley et al Nature 2019

Heterogeneity of Driver Gene Expression



Priestley et al Nature 2019

Large scale sequencing delivers….?

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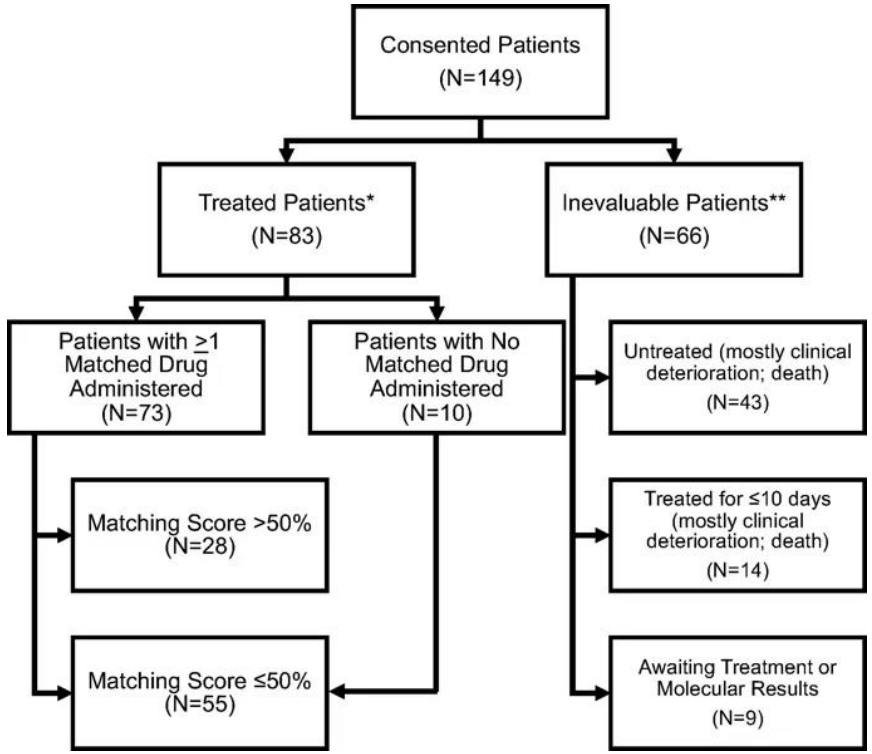
I-Predict/ Winther trial:

Patients without regular treatment option left with stage IV cancer (tumor type agnostic)

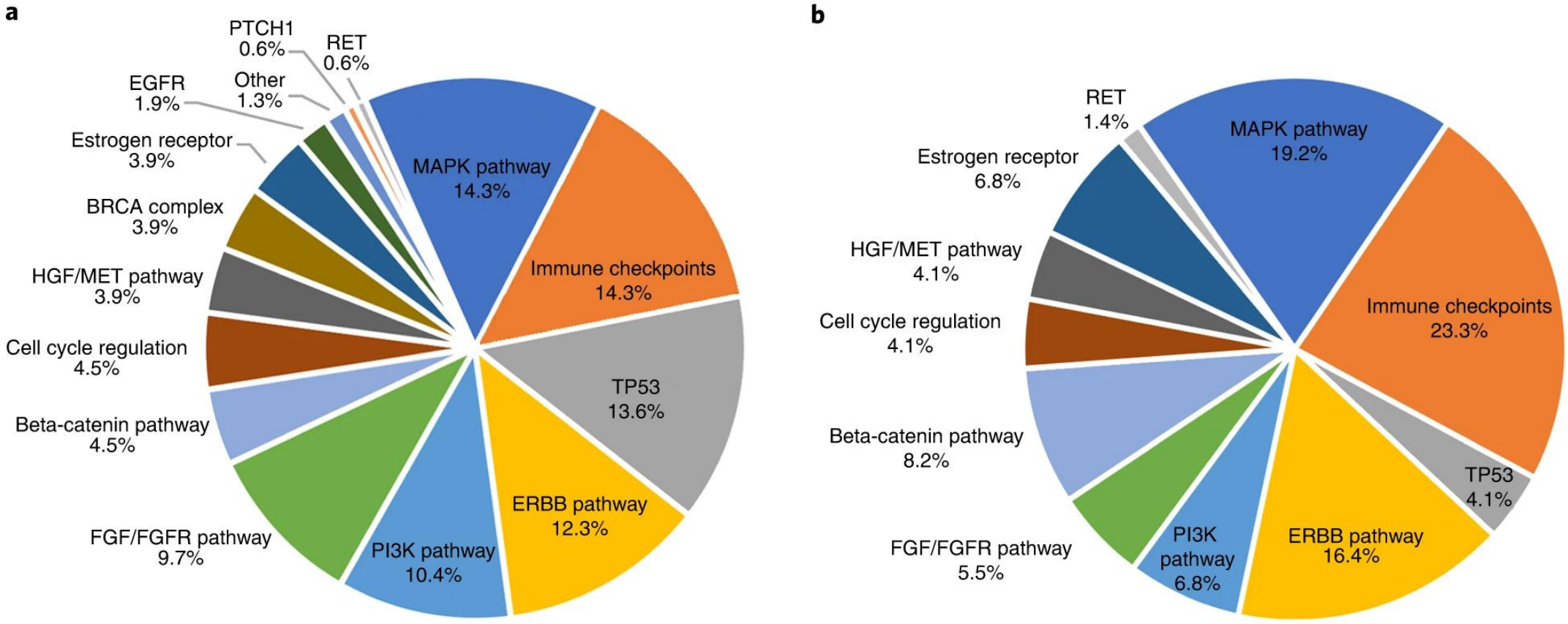
- Foundation One testing on archival tissue
- PDL1 IHC
- TMB/MSI
- ctDNA profiling
- Winther trial: addition of whole genome RNA sequencing



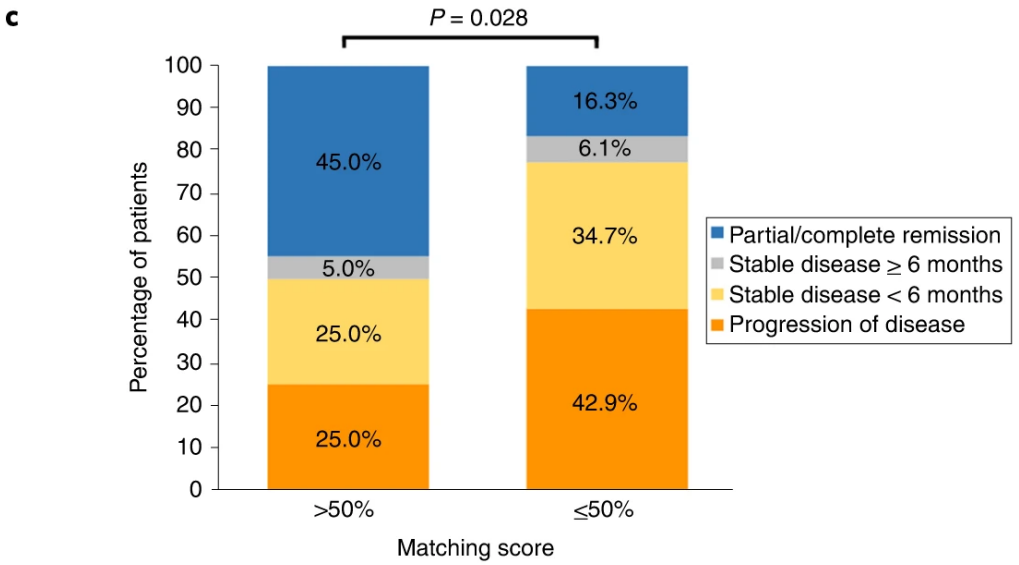
Sicklick et al. *Nature Medicine* ***volume 25****, pages744–750 (2019)*

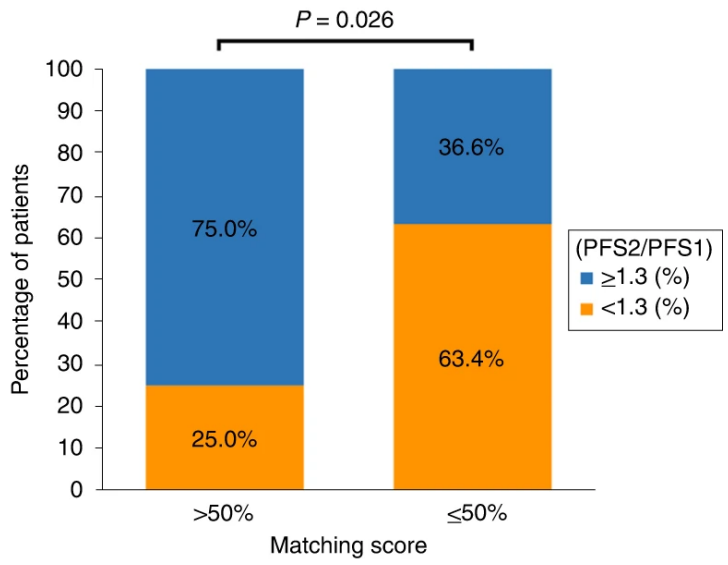
Rodon et al. *Nature Medicine* ***volume 25,*** *pages751-758 (2019)*

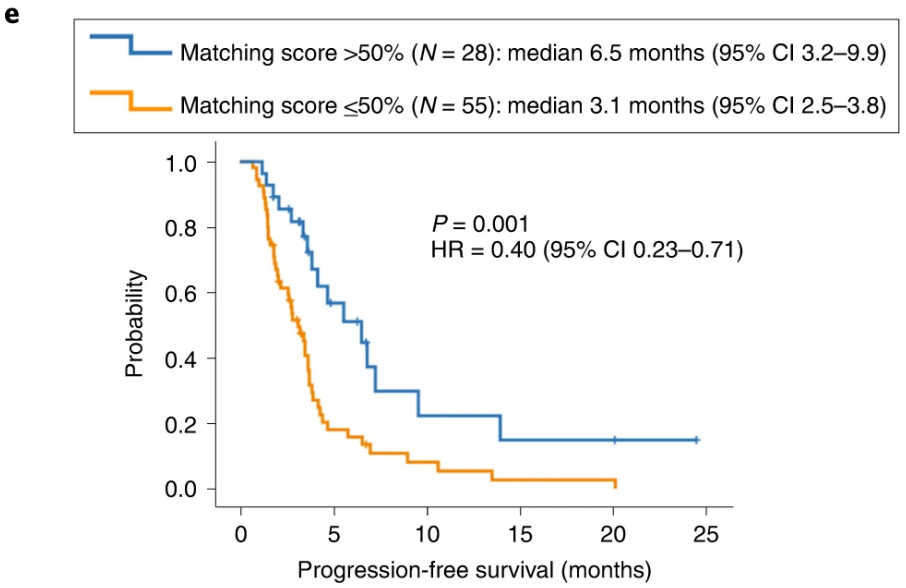
Outcomes I-Predict Trial

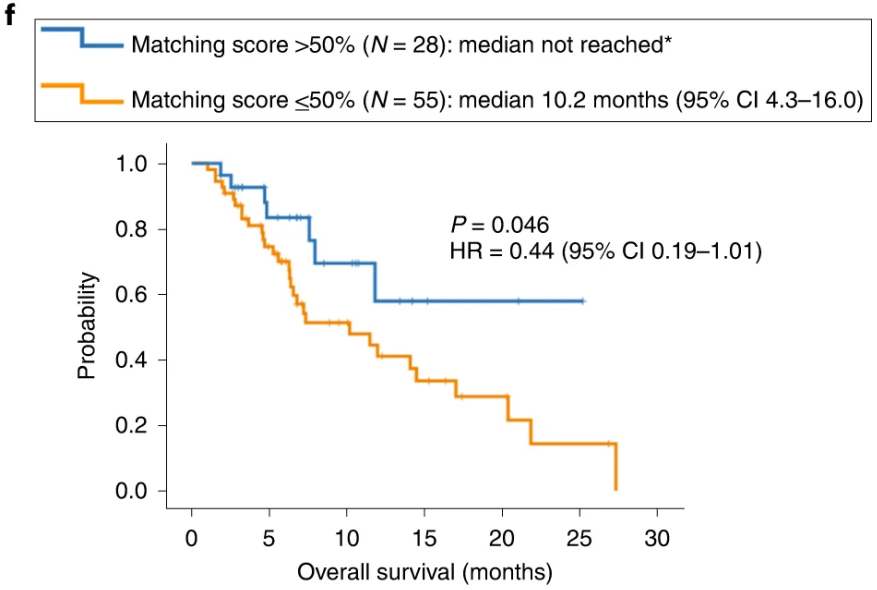


Clinical outcomes

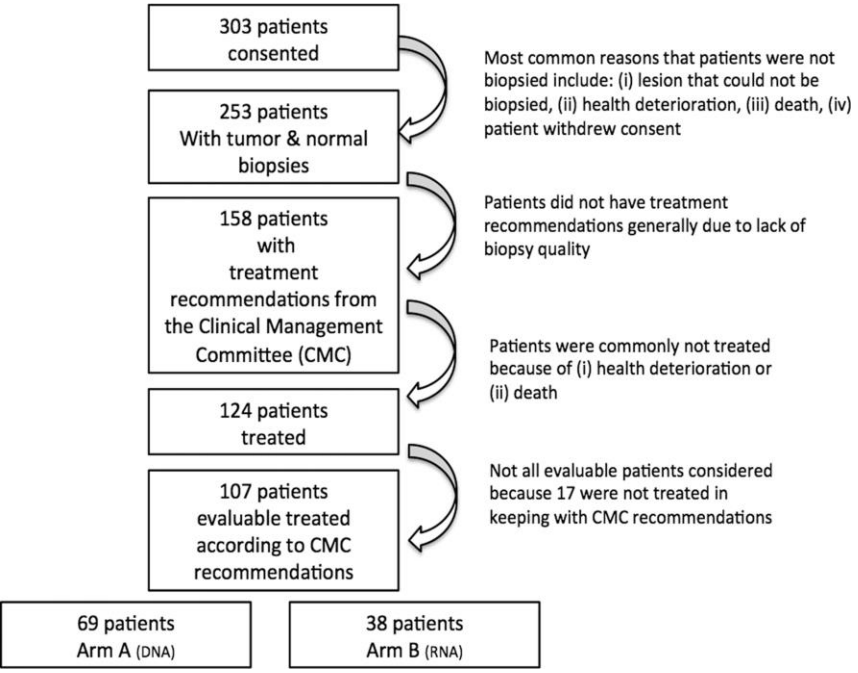


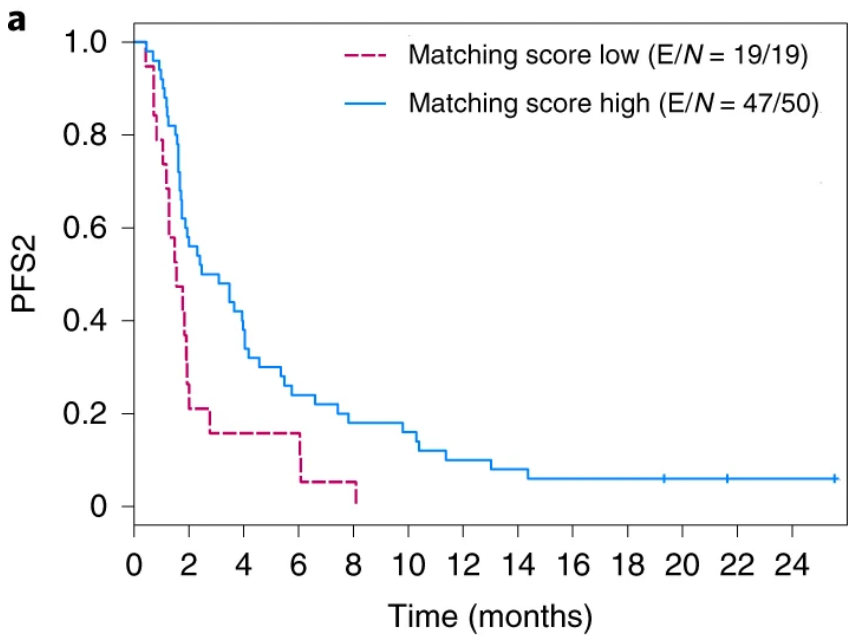


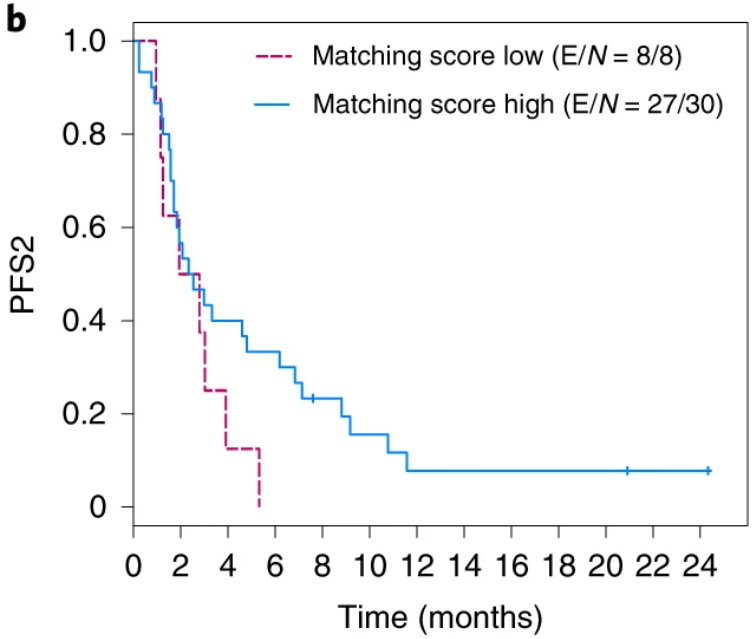




Winther Trial







Foundation One vs Whole Genome Sequencing

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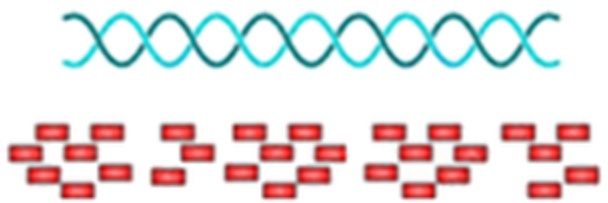
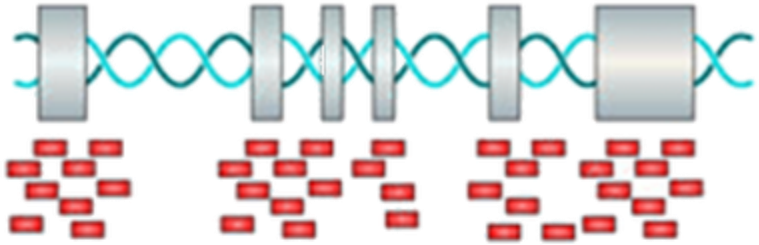
Whole genome sequencing



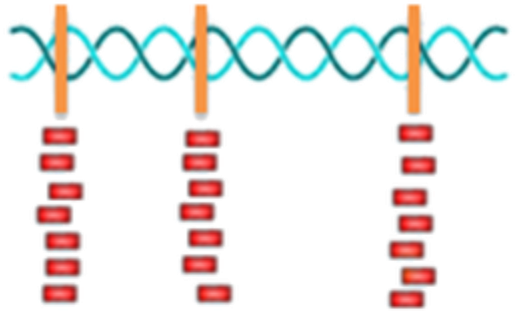
- Sequencing region : whole genome
- Sequencing Depth: >30X
- Covers everything – can identify all kinds of variants including SNPs, INDELs and SV.

Whole exome sequencing



- Sequencing region: whole exome
- Sequencing Depth : >50X ~ 100X
- Identify all kinds of variants including SNPs, INDELs and SV in coding region.
- Cost effective

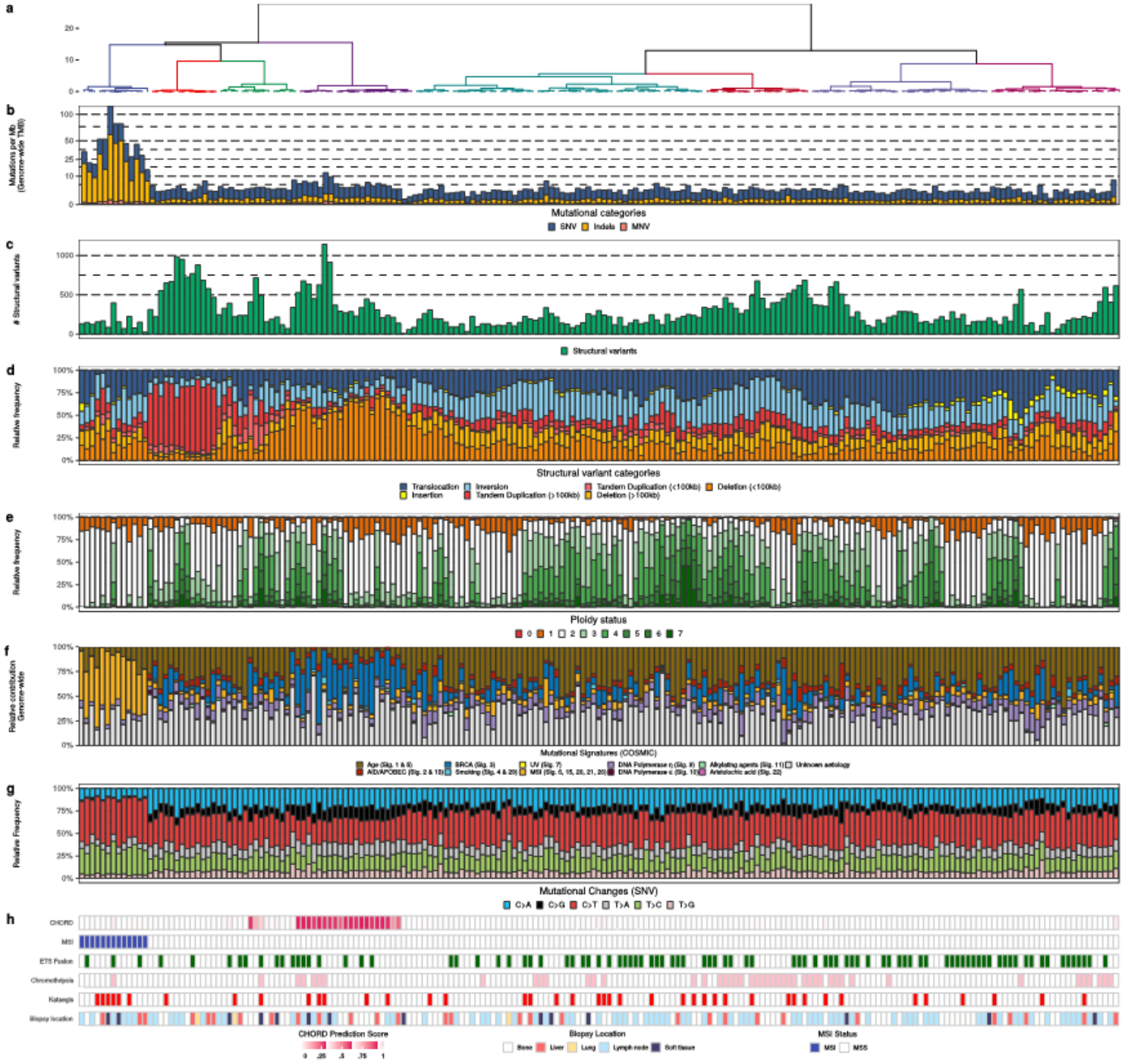
Targeted sequencing



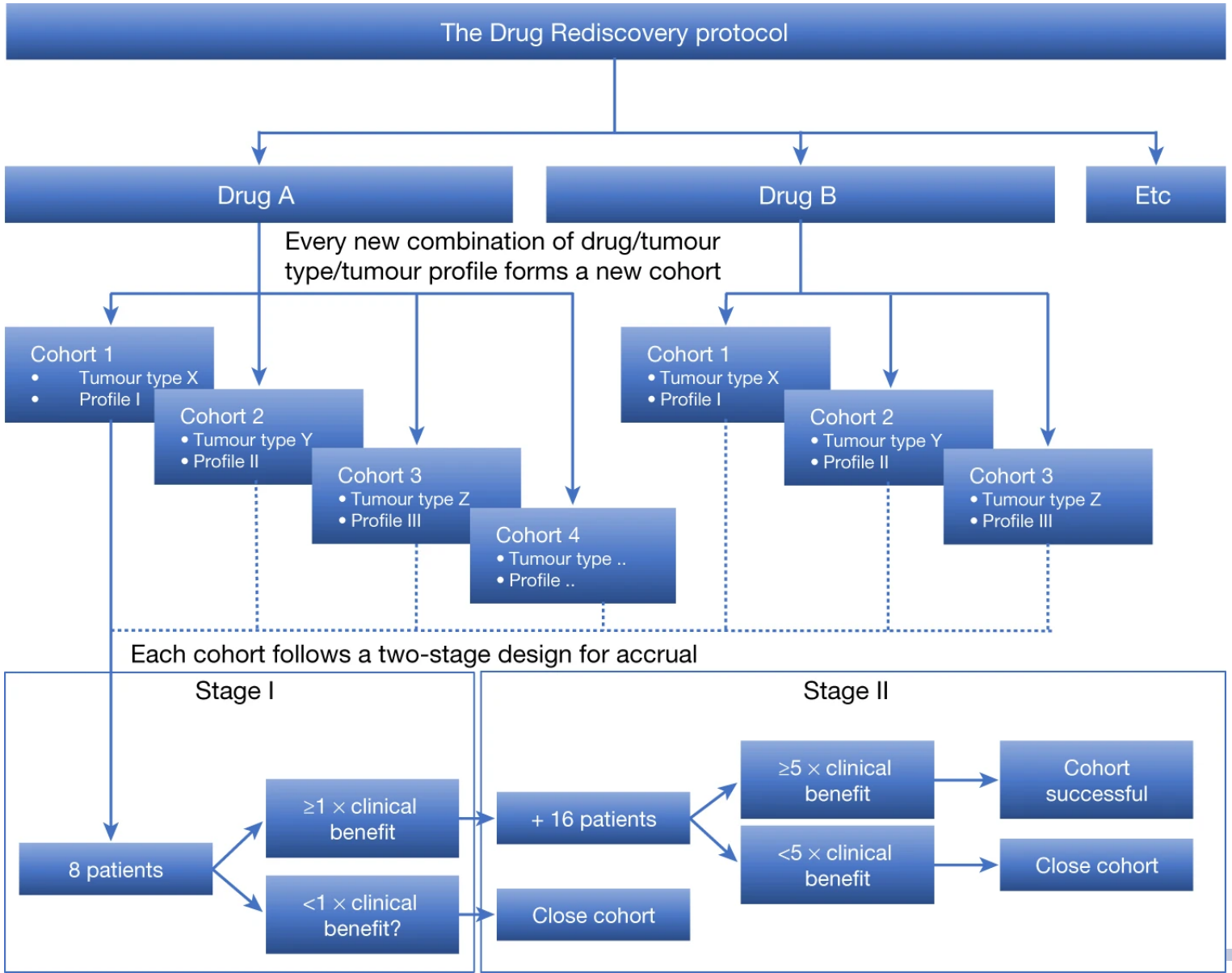
- Sequencing region: specific regions (could be customized)
- Sequencing Depth : >500X
- Identify all kinds of variants including SNPs, INDELs in specific regions
- Most Cost effective

What can we learn from those “in between”pieces of DNA?

Van Dessel et al Nature Communication in press



DRUP study



Van der Velden et al. Nature. 2019 Sep 30. doi: 10.1038/s41586-019-1600-x.

Rediscovery of Drugs: efficacy

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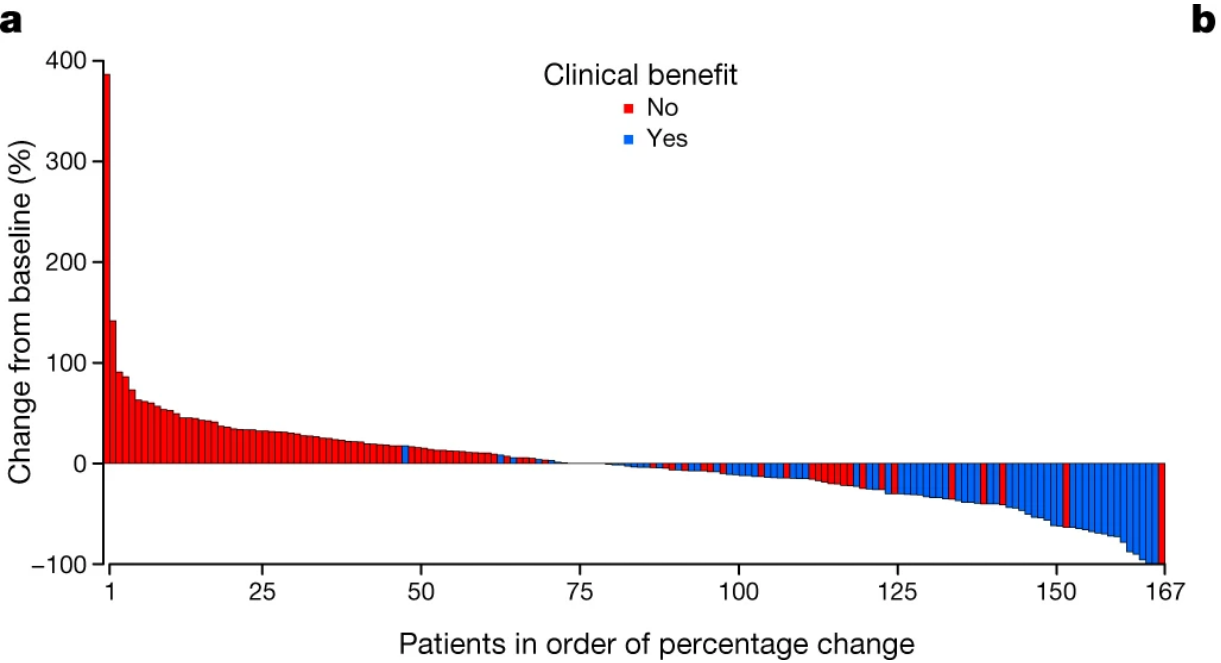

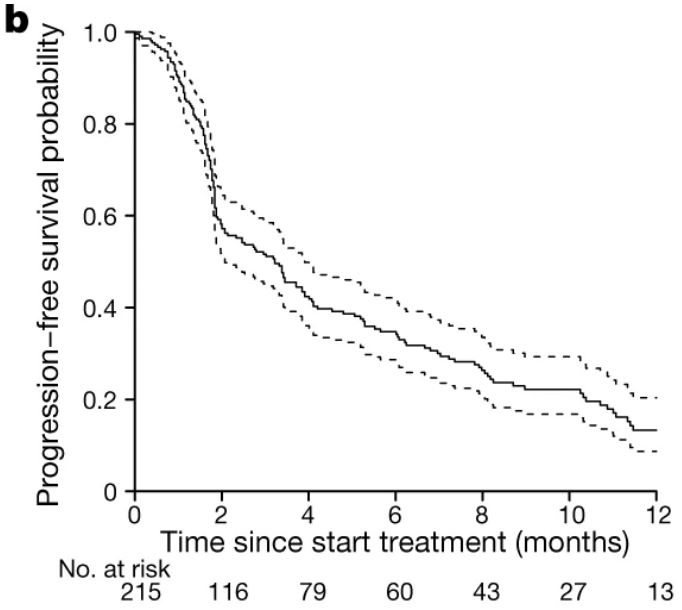

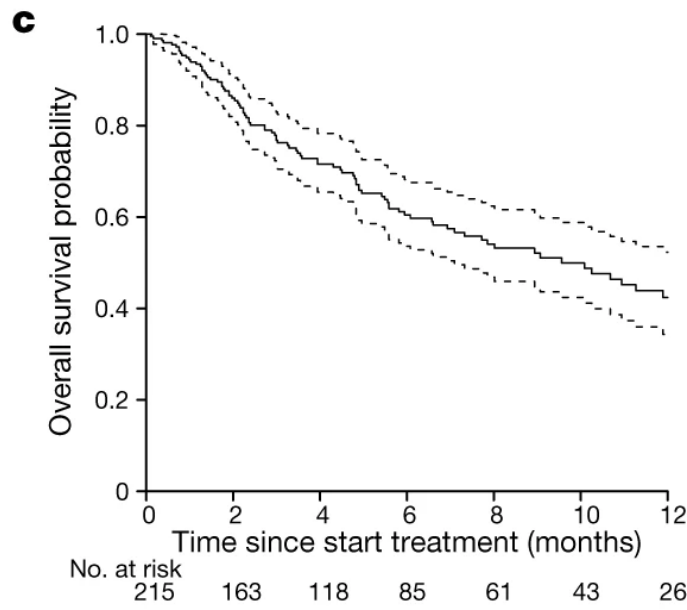

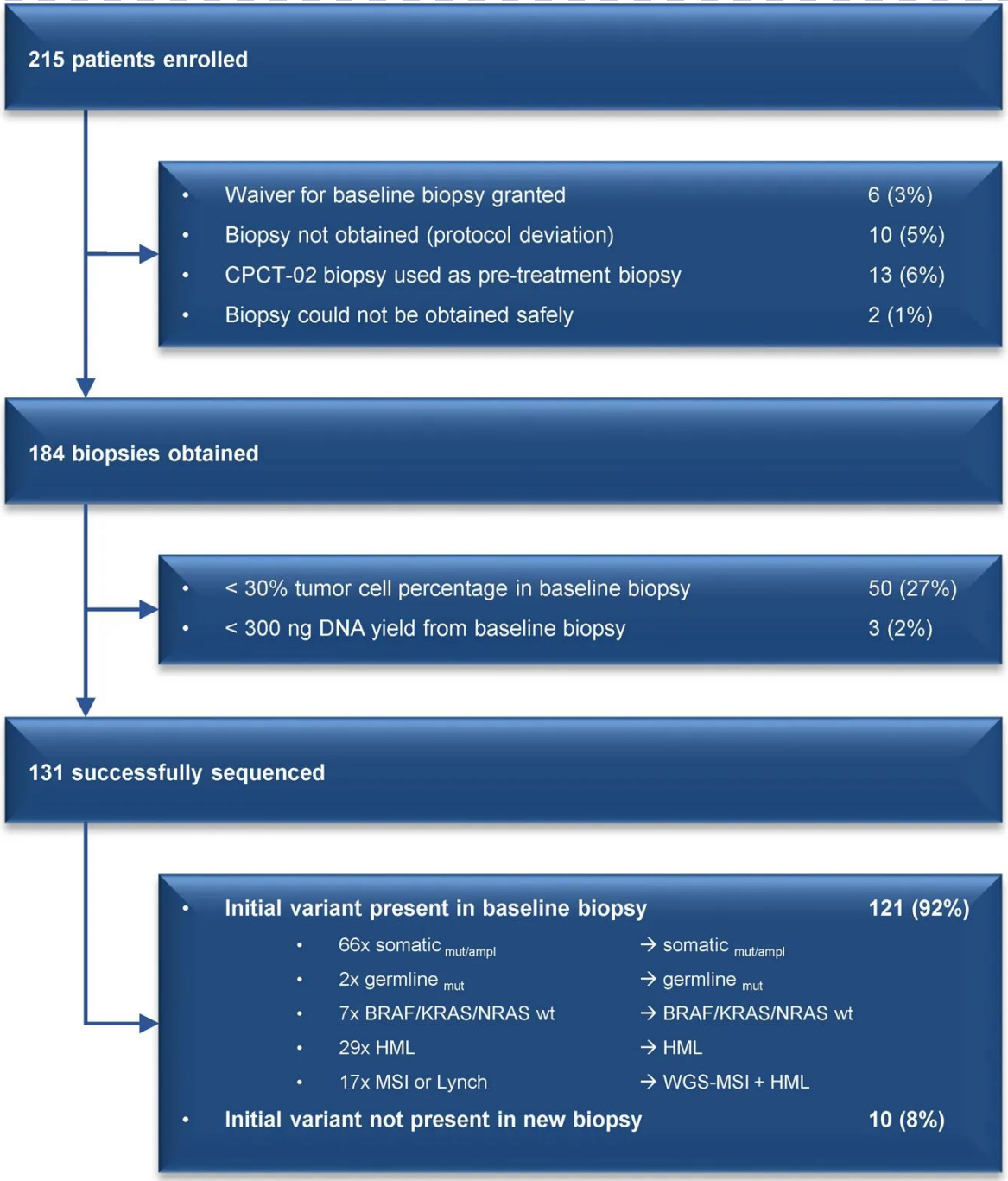

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Baseline biopsies in DRUP study: WGS as selection tool

Example: HER2 amplified Bladder Cancer Patient

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Gene	Position	Variant	Depth (VAF)	Predicted Effect	Cosmic	Ploidy (TAF)
PDGFRA *	4:55133538	C > T	16 / 89 (18%)	c.842C>T p.Thr281Met missense variant		AB (35%)
RET *	10:43613847	G > A	19 / 98 (19%)	c.2311G>A p.Asp771Asn missense variant		AAB (31%)
RB1	13:49037866	G > A	21 / 84 (25%)	c.2107-1G>A splice acceptor variant; intron variant	COSM2155323	A (69%)
TP53	17:7578190	T > C	44 / 84 (52%)	c.659A>G p.Tyr220Cys missense variant	COSM99719	AA (100%)

* Marked genes (*) are included in the DRUP study and indicate potential eligibility in DRUP. Please note that the marking is NOT based on the specific variant reported for this sample, but only on a gene-level.

Implied Tumor Purity: 52%

Tumor Mutational Load: 154 **

** Patients with a mutational load over 140 could be eligible for immunotherapy within DRUP.

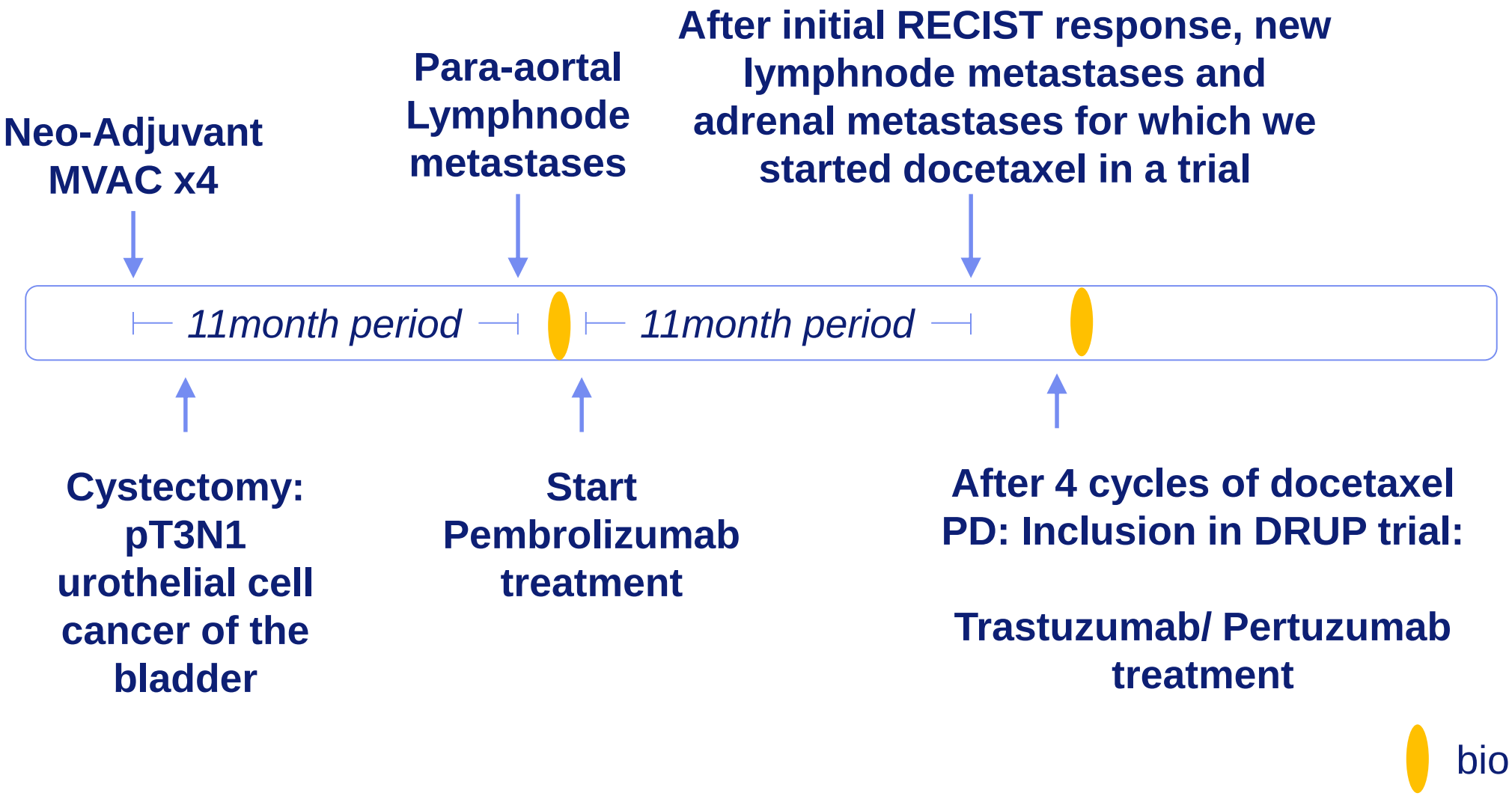
Somatic Copy Numbers

Chromosome	Band	Gene	Type	Copies
17	q12	CDK12	copy-gain	16
17	q12	ERBB2	copy-gain	16
19	q13.32	ERCC1	copy-gain	10
22	q12.1	CHEK2	copy-gain	8

23-10-2017

Clinical History

At diagnosis a 48 yo man



Response to treatment

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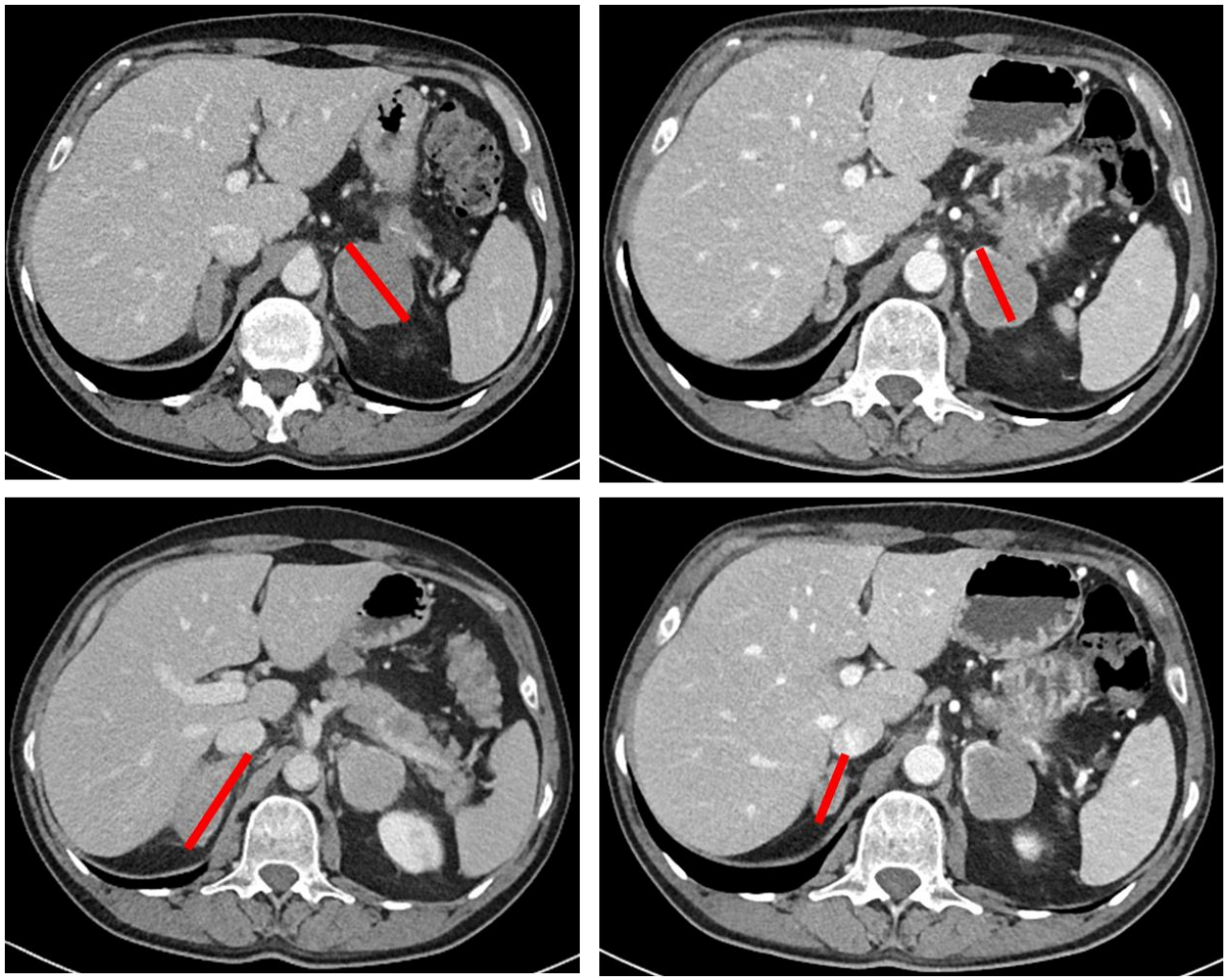
Start treatment

Nadir: 6 months later



WGS as selection tool for phase I studies in EMC

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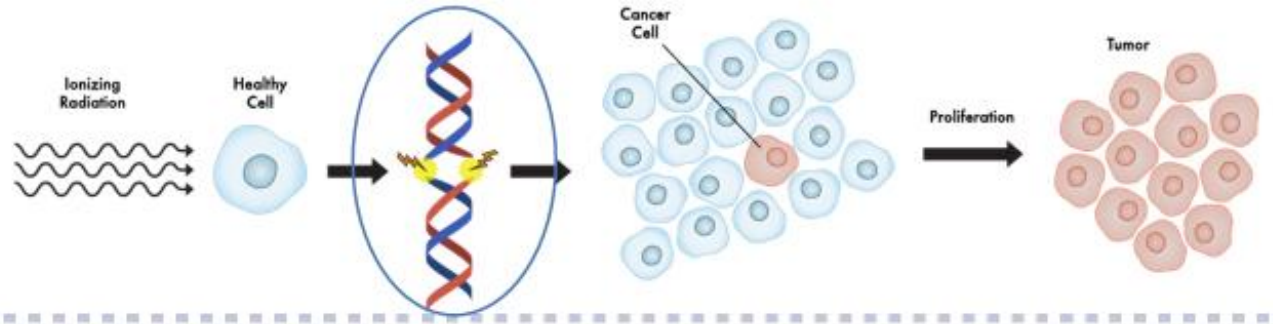
Hartwig Erasmus MC Last Resort Protocol (HELP)

Methods

- Referral to Phase I unit
- Whole Genome Sequencing by HMF (50-100 patients/year)
- Allocate patients based on alterations in DNA



Overall conclusions

- Patient selection based on genomic characterization improves selection for trial participation
- Whole Genome Sequencing is ready for prime time clinical application
- These new data show our ability to improve patient outcome by improving selection in a more or less tumor agnostic fashion

Thank you for your attention

CPCT: 44 Dutch Hospitals

Key people:

- Stefan Sleijfer
- Edwin Cuppen
- Hans Snellenberg
- Emile Voest
- ……..

Prostate Cancer Analysis:

- Lisanne van Dessel
- Job van Riet
- Niven Mehra
- ……

Twitter: @ErasmusOncology/ @MartijnLolkema