Dr. Angus has no relevant financial relationships with commercial interests to disclose.

THE GENOMIC LANDSCAPE OF METASTATIC BREAST CANCER

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Disclosures

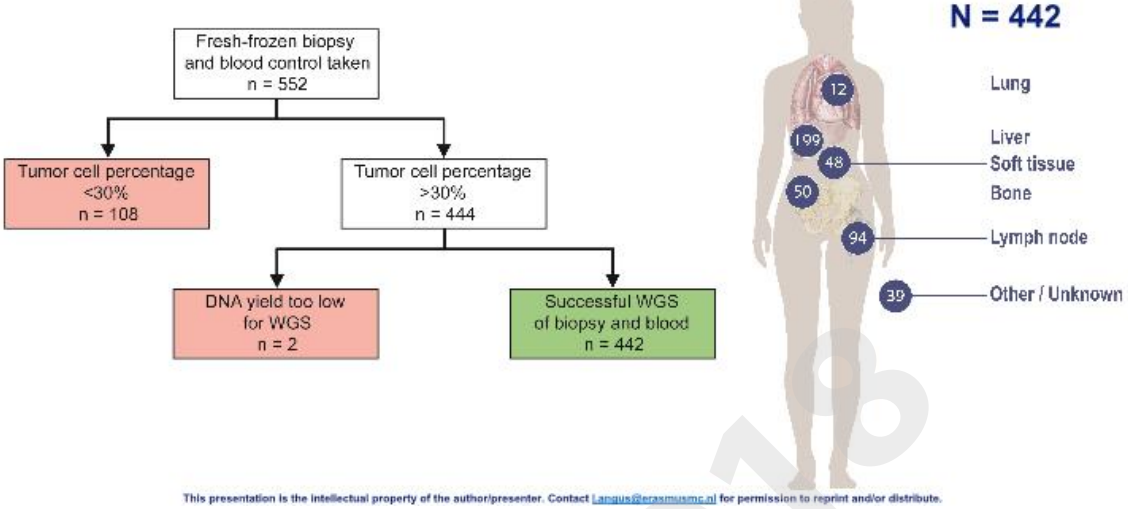
I have no financial relationship(s) with commercial interests to disclose.

Background

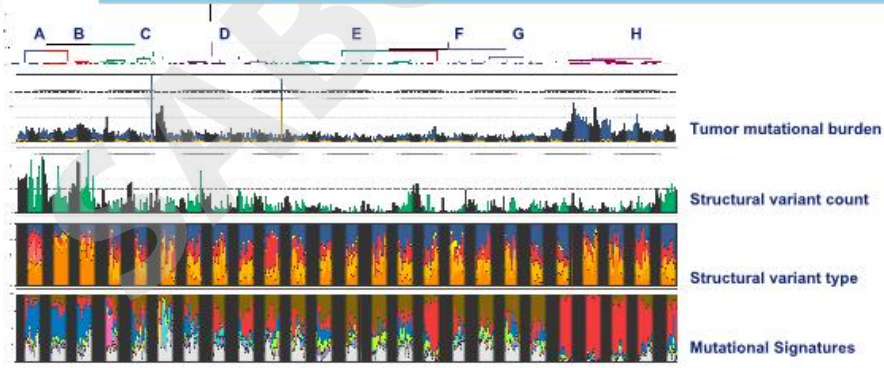
- **Primary breast cancer has been extensively characterized[1-3]**
- Problem
  - Patients die from metastatic disease
  - Molecular characteristics can substantially differ
- Solution
  - Whole genome sequencing (WGS) of metastatic breast cancer lesions
- Aims
  - To reveal the genomic landscape of metastatic breast cancer
  - To compare metastatic breast cancer with primary breast cancer
  - To distinguish patients with targetable mutational signatures and/or genomic alterations

[1]Nik-Zainal et al. Nature. 2016;534(7605):47-54.
[2]Cancer Genome Atlas Network, Nature. 2012; 4;490(7418):61-70.
[3]Ciriello et al. Cell. 2015; 8;163(2):506-19.

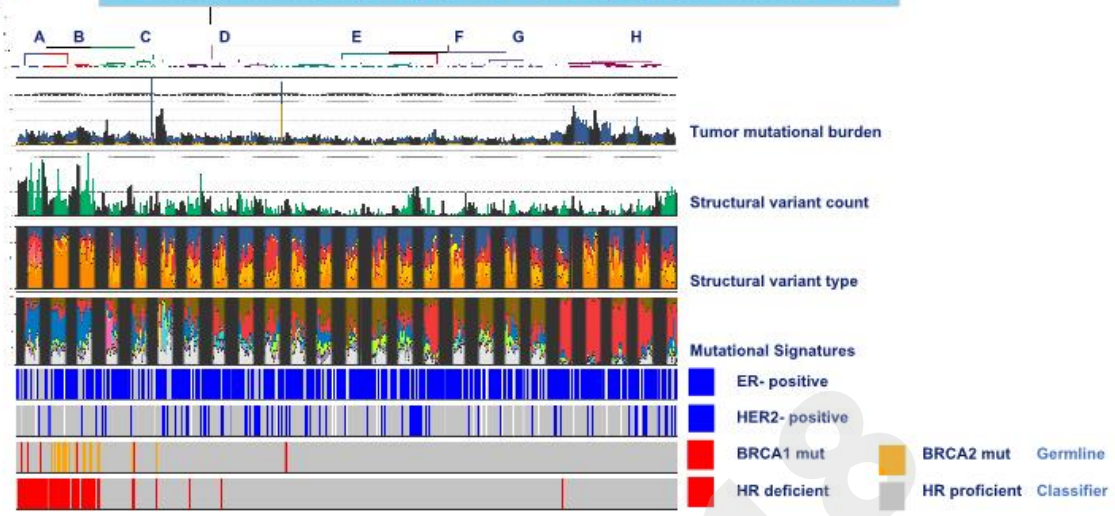
Study Design – CPCT-02



Genomic landscape of mBC – unsupervised clustering



Genomic landscape of mBC – unsupervised clustering



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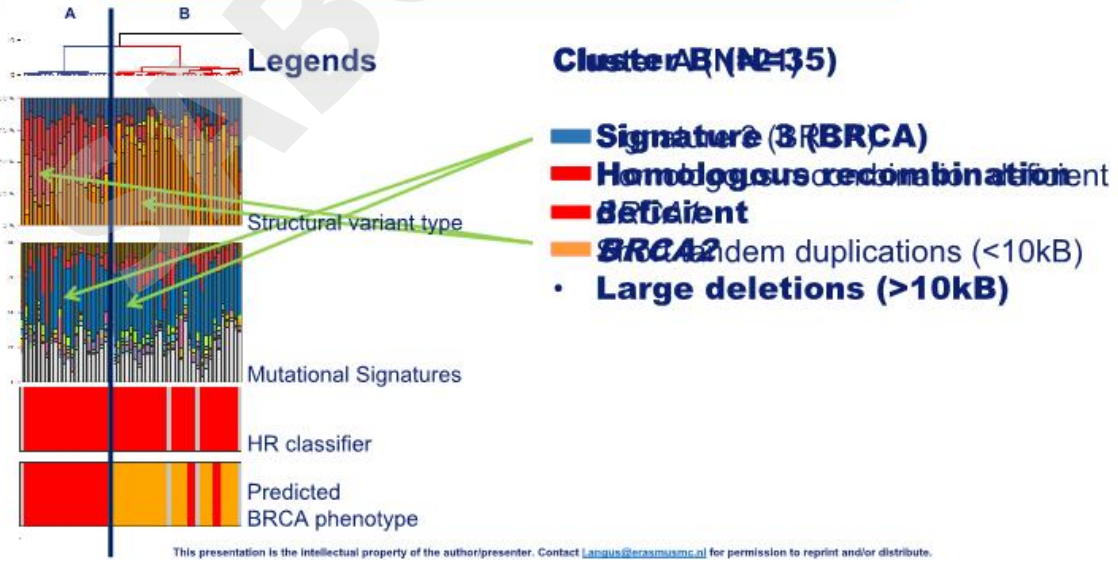
Cluster A and B – BRCA related



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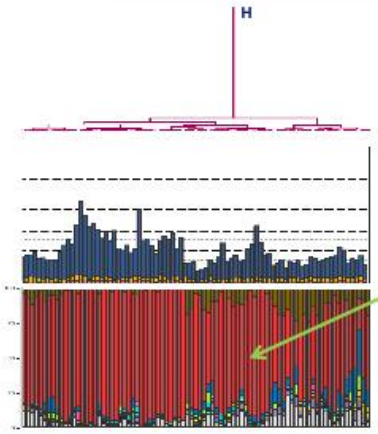
Cluster H - APOBEC



Legends

Cluster H (N=83)

- Signature 2 and 13
  - APOBEC
  - High TMB

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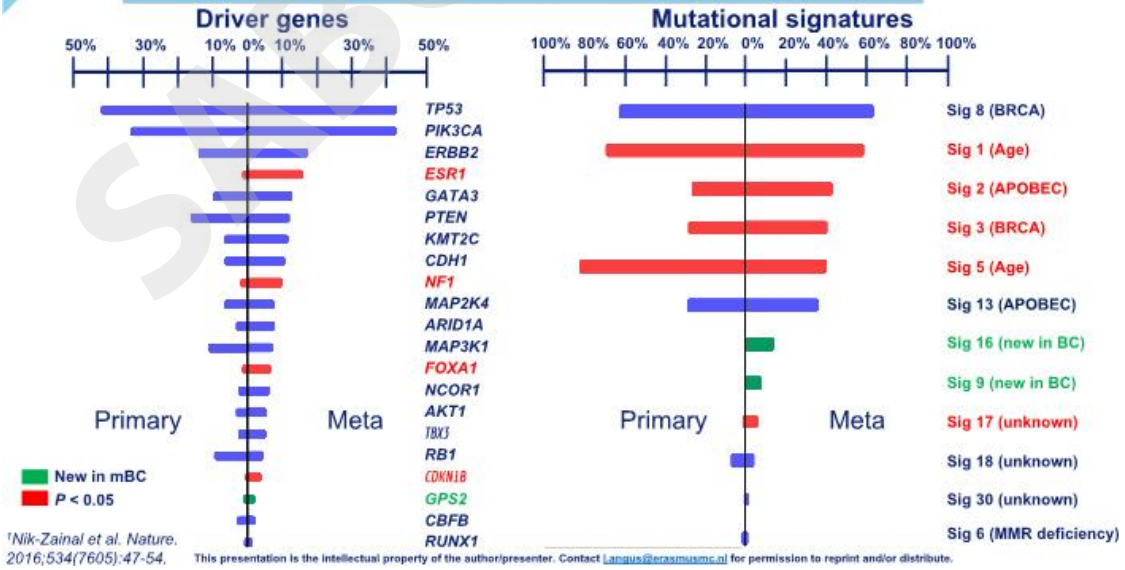
Primary[1] versus metastatic BC



[1]Nik-Zainal et al. Nature. 2016;534(7605):47-54.

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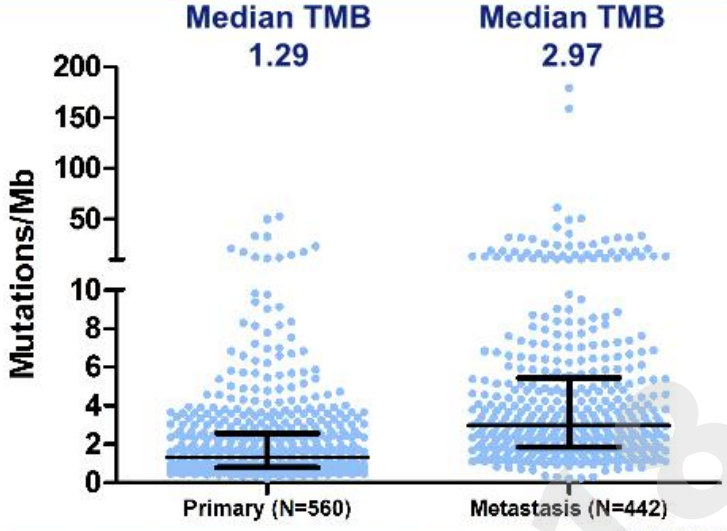
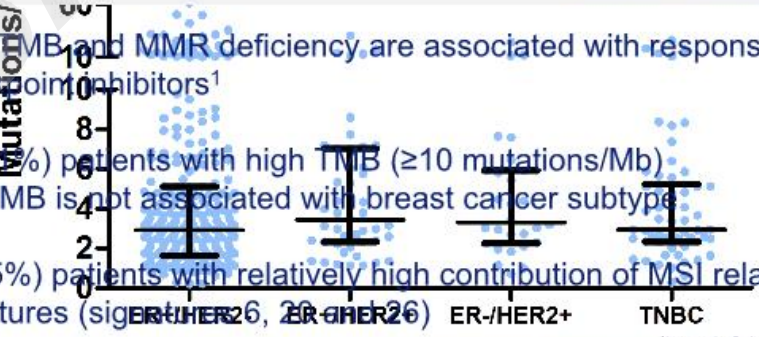
Primary[1] versus metastatic BC



[1]Nik-Zainal et al. Nature. 2016;534(7605):47-54.

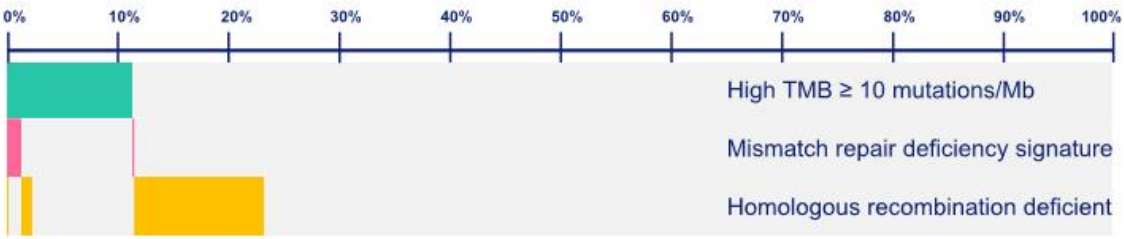
Clinical relevance - TMB

- High TMB and MMR deficiency are associated with response to checkpoint inhibitors[1]
- 50 (11%) patients with high TMB (≥10 mutations/Mb)
  - TMB is not associated with breast cancer subtype
- 7 (1.5%) patients with relatively high contribution of MSI related signatures (signature 6, 20 and 26)



[1]Le et al., Science 2017; 357(6349):409-13.

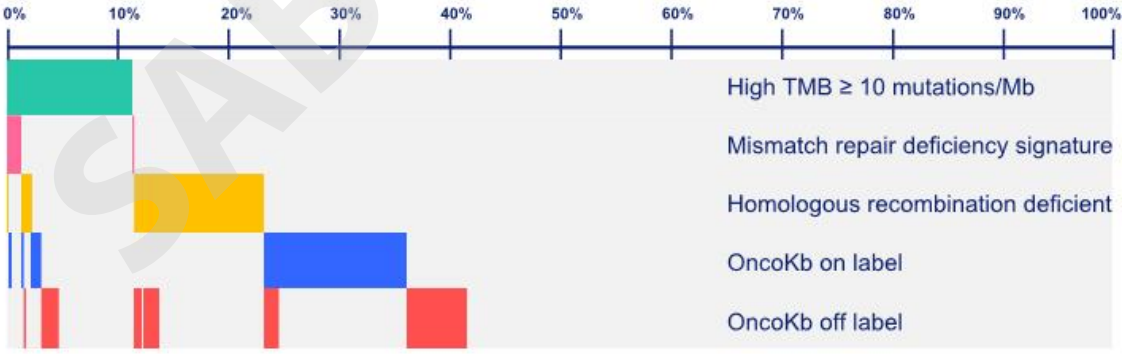
Clinical relevance - HRD



- Homologous recombination deficient (HRD) patients could benefit from PARP-inhibitors and platinum based chemotherapy[1]
- 57 (13%) patients classified as HRD by our classifier (CHORD)
  - 23 patients with biallelic loss of *BRCA1* or *BRCA2*
  - 34 additional patients classified as HRD

[1]*Davies et al. Nat Med. 2017;23(4):517-25.*

Clinical relevance - OncoKb



FDA approved drugs for breast cancer (on label)
FDA approved drugs for other cancer types (off label)

Clinical relevance - OncoKb[1]

- Patients with specific genomic alterations might benefit from drugs registered for these alterations:
  - Even if registered for an another indication
- 105 (24%) of patients have an alteration for which an FDA approved drug is available

[1] Chakravarty et al., JCO Precis Oncol 2017

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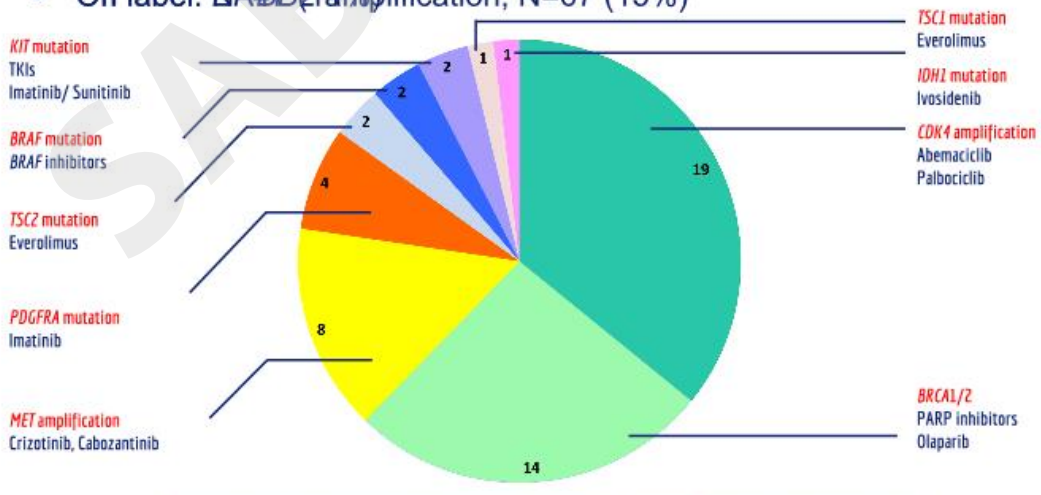
Clinical relevance - OncoKb

- Off label: ERBB2 amplification, N=67 (15%)



Conclusions

- **WGS can distinguish 42% of patients with targetable alterations:**
  - **11% – High TMB and/or MSI signatures → checkpoint inhibitors**
  - **13% – Homologous recombination deficiency →PARPi / platinum**
  - **24% – Targetable alterations (e.g. mutations, amplifications)**

- Metastatic BC is different from primary BC regarding:
  - **Driver genes:**
    - ***ESR1, NF1, FOXA1*, and *CDKN1B* more frequently affected in mBC**
    - ***GPS2* is a novel candidate driver gene in mBC**
  - **Higher** TMB in mBC
  - **Relative contribution of mutational signatures**
  - **Different signatures 1, 2, 3, 5, 13, 17**

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