REGION

ProTarget – a pragmatic clinical study exploring precision cancer medicine

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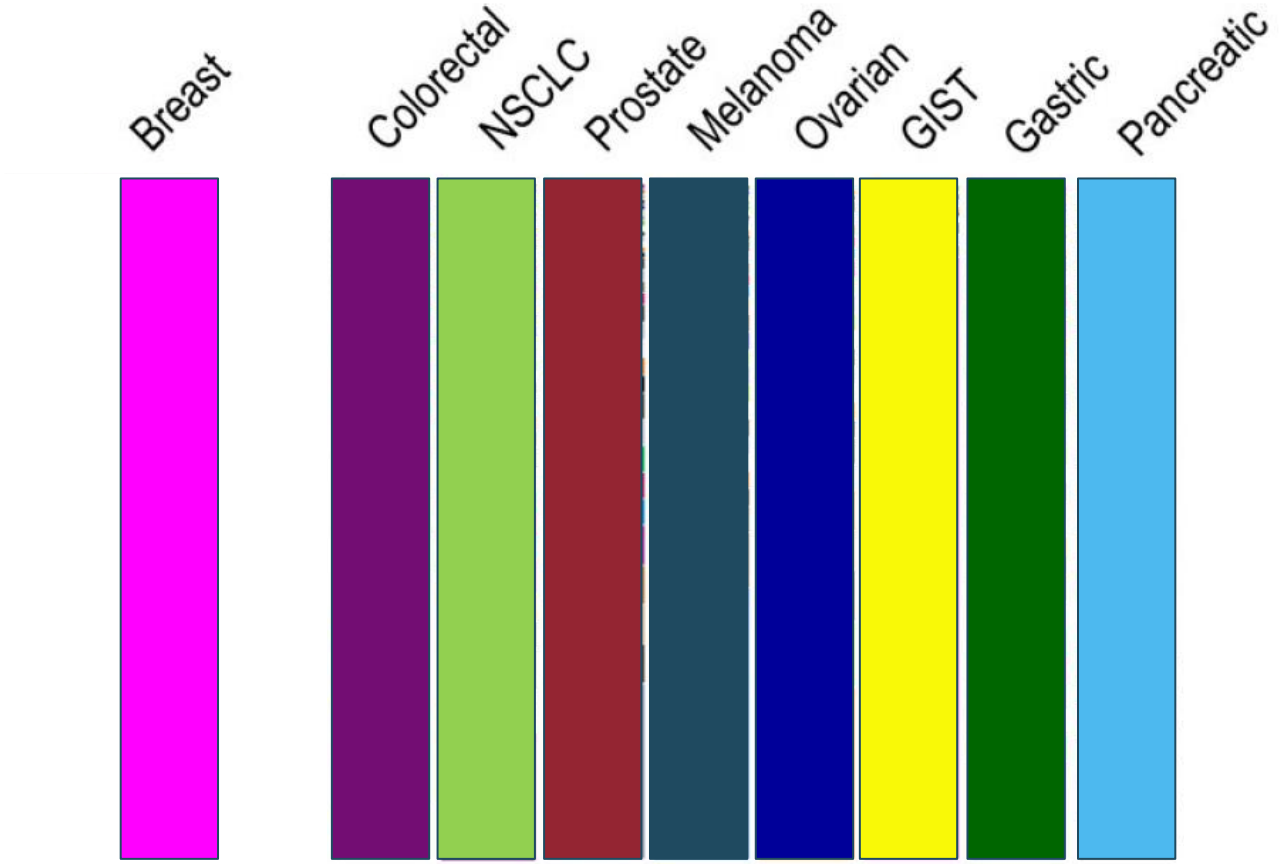
COI

- Bayer, Invited Speaker, Personal
- Amgen, Invited Speaker, Personal
- Lilly, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Roche/Genentech, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Bristol-Myers Squibb, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Symphogen, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Pfizer, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Novartis, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Bayer, Other, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Alligator Bioscience, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Incyte, Other, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Genmab, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Puma Biotechnology, Other, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Orion Clinical, Other, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Bioinvent, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.
- Monta Bioscience, Coordinating PI, Financial interest, Institutional, Compensation for conduction of clinical trial.

Paradigme shift

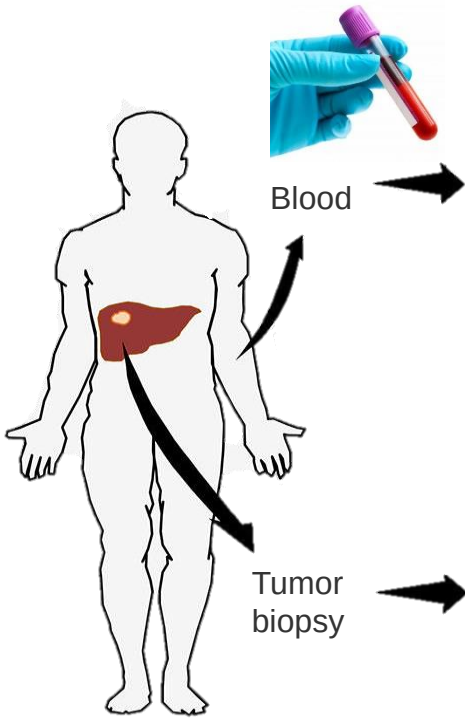


Copenhagen **P**rospective **P**ersonalized **O**ncology (**CoPPO**):

Does genomic profiling improve outcome in phase 1 trials?

Tuxen IV, Rohrberg KS, Oestrup O, Ahlborn LB, Schmidt AY, Spanggaard I, Hasselby JP, Santoni-Rugiu E, Yde CW, Mau-Sørensen M, Nielsen FC, Lassen U. Clin Cancer Res. 2019 Feb 15;25(4):1239-1247. doi: 10.1158/1078-0432.CCR-18-1780.

Setup for genomic profiling



Blood

Tumor biopsy

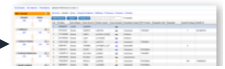
Whole genome sequencing

Whole genome sequencing

RNAseq

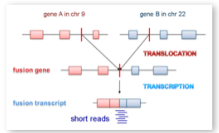
SNP array
Expression array

Germline variants



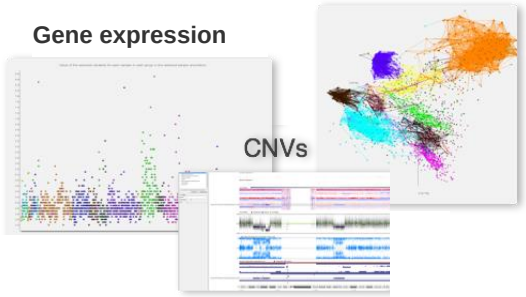
Somatic mutations

Gene fusions



Gene expression

Classification



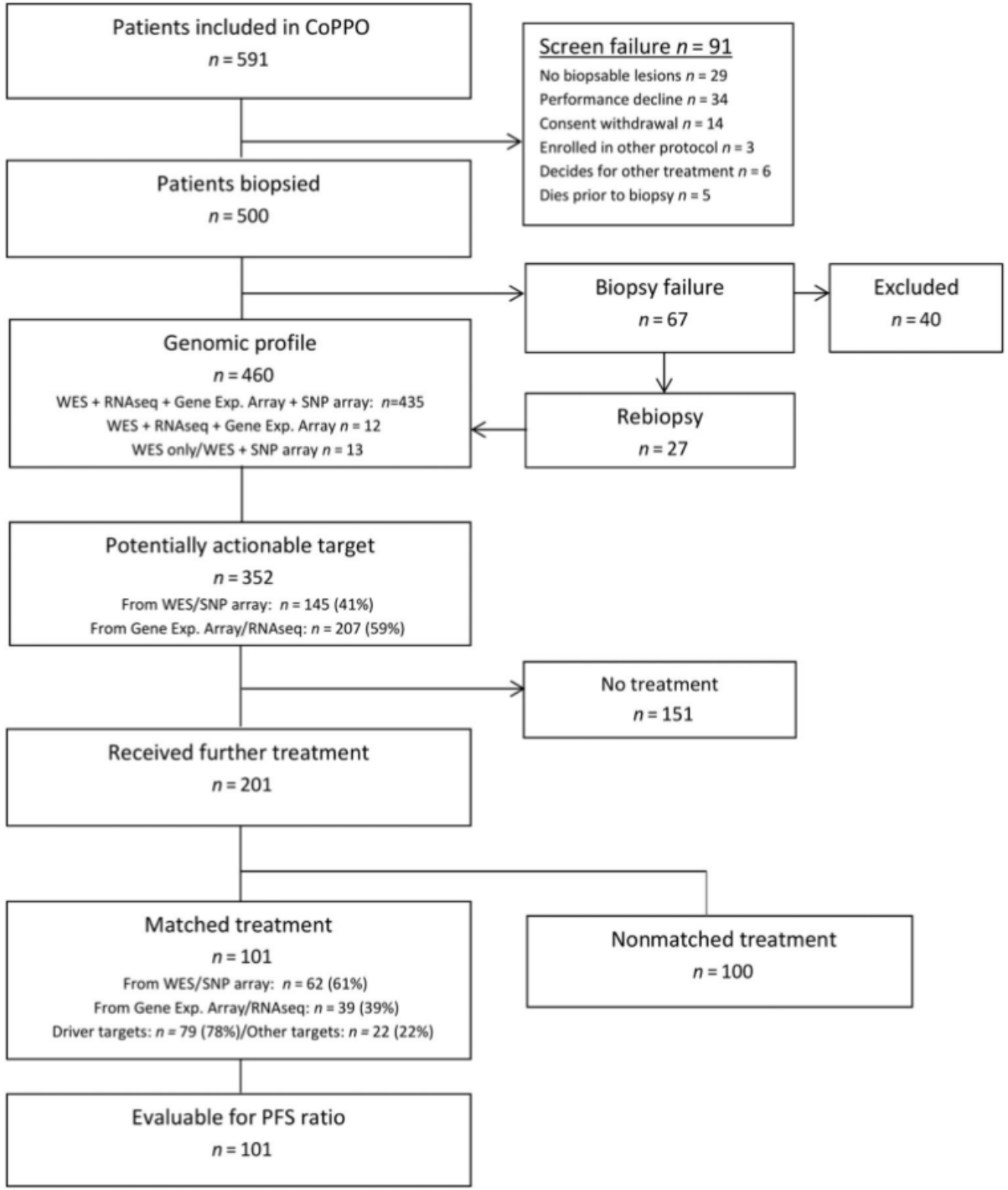
Currated by real people

Integrate into clinical report

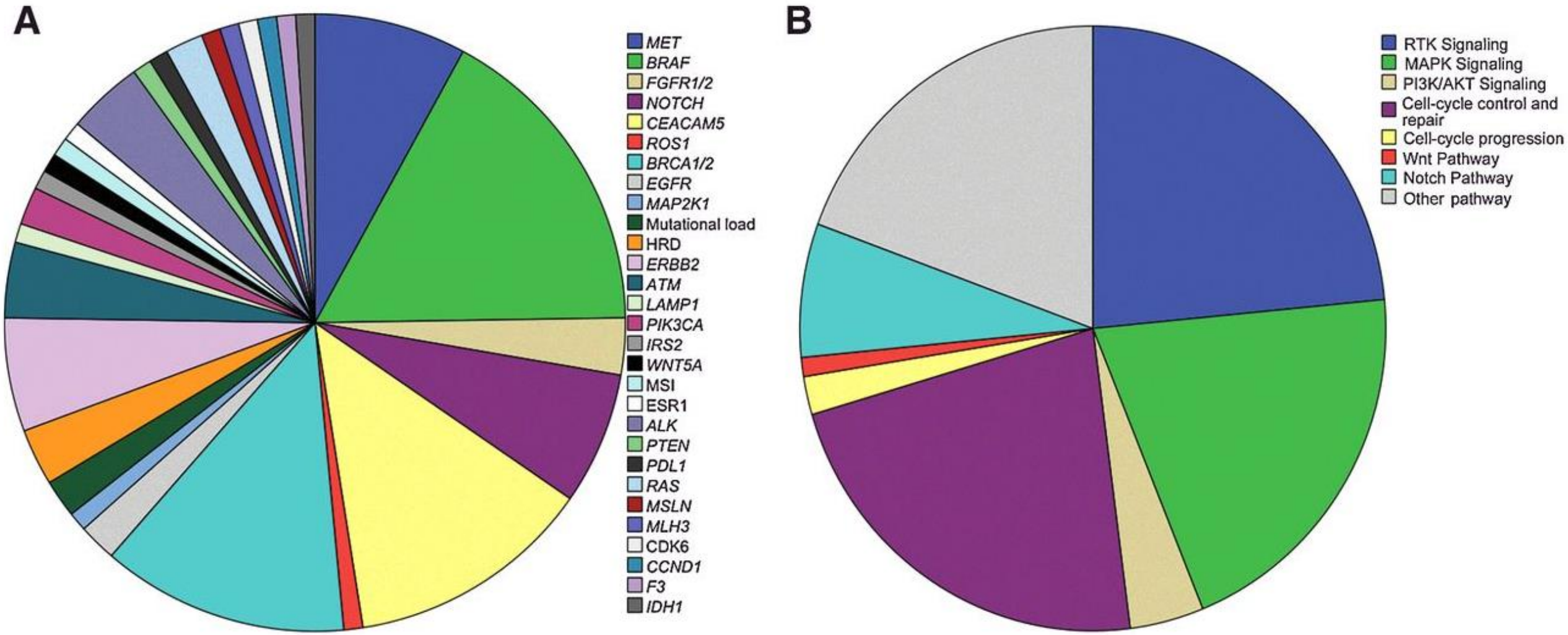
Weekly national MDT (tumor board)

Treatment - outcome after TBM

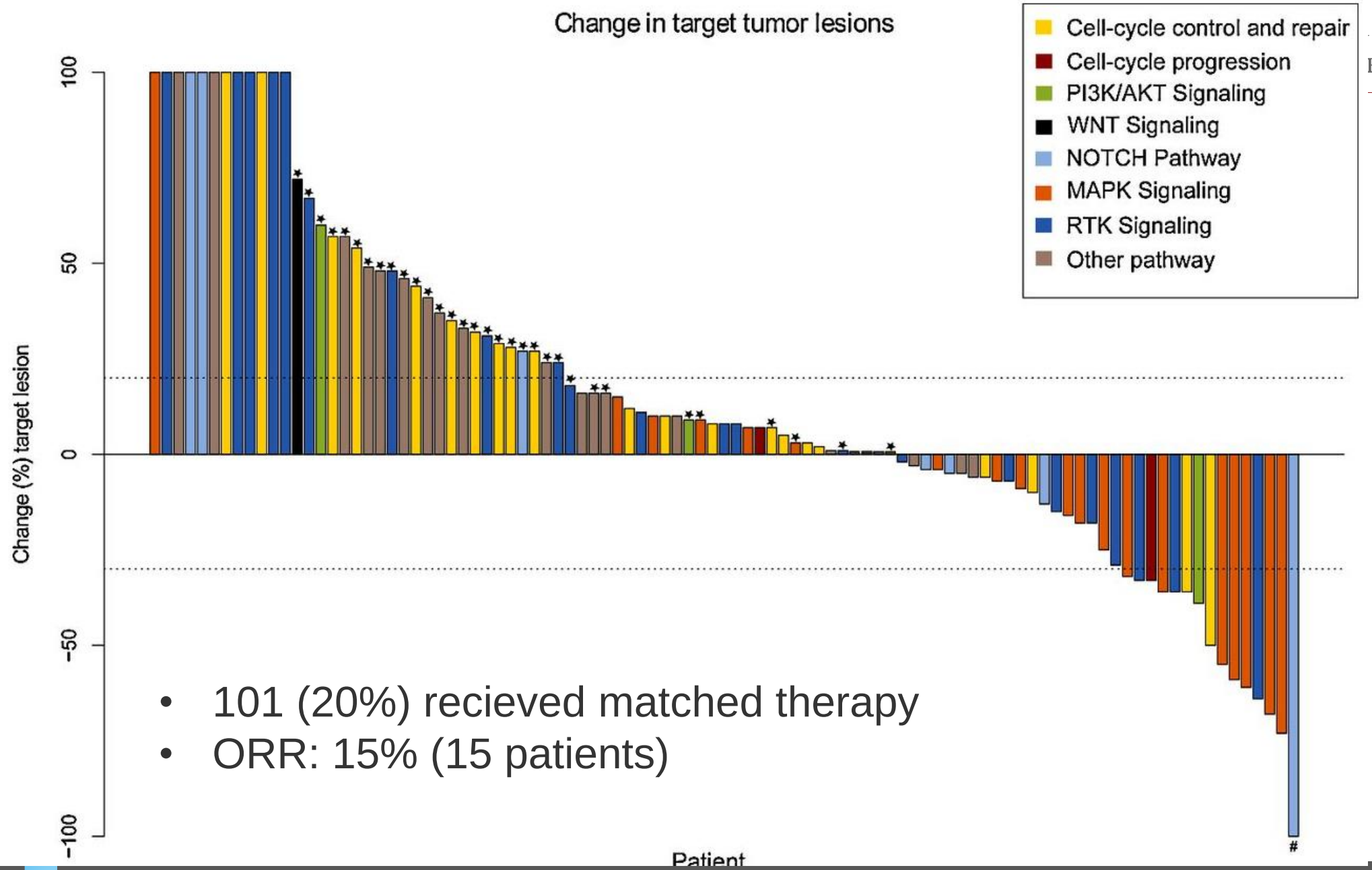
- Phase 1/2 trial (Rigshospitalet)
  - > 40 trials in the Phase 1 Unit
- Phase 1/2 trial (other departments in DK or other countries)
- FDA/EMA approved targeted therapy – Off-lable
- Named patient program – not approved treatment
- Change of diagnose – new treatment options



Clin Cancer Res. 2019 Feb 15;25(4):1239-1247

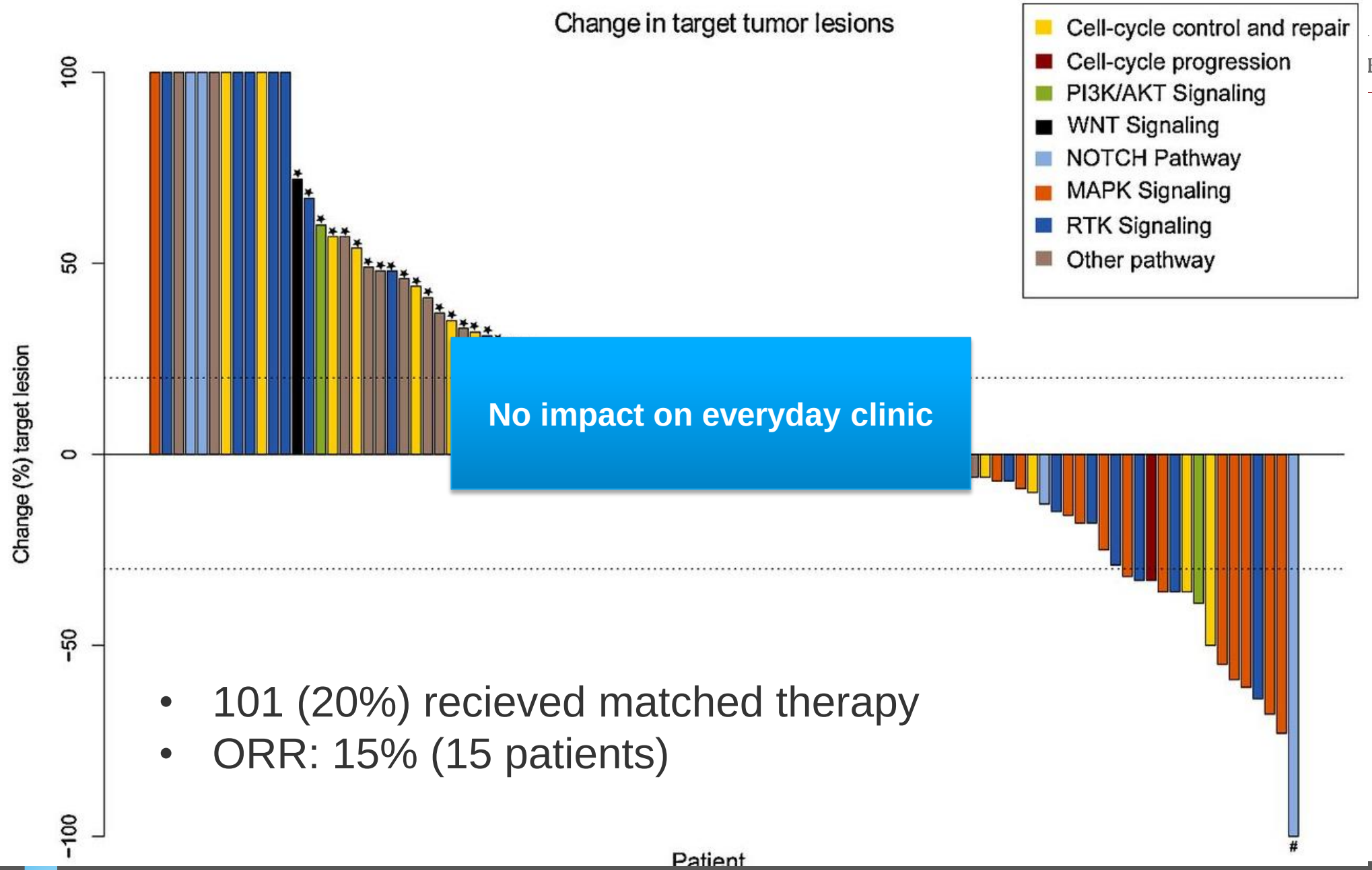


Clin Cancer Res. 2019 Feb 15;25(4):1239-1247



- 101 (20%) recieved matched therapy
- ORR: 15% (15 patients)

Clin Cancer Res. 2019 Feb 15;25(4):1239-1247

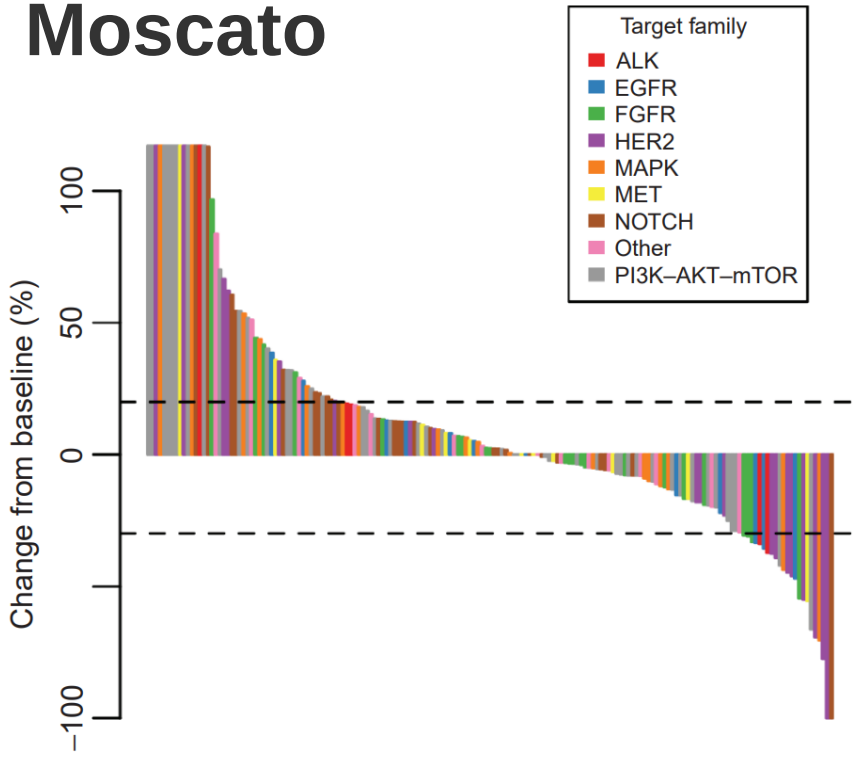


No impact on everyday clinic

- 101 (20%) recieved matched therapy
- ORR: 15% (15 patients)

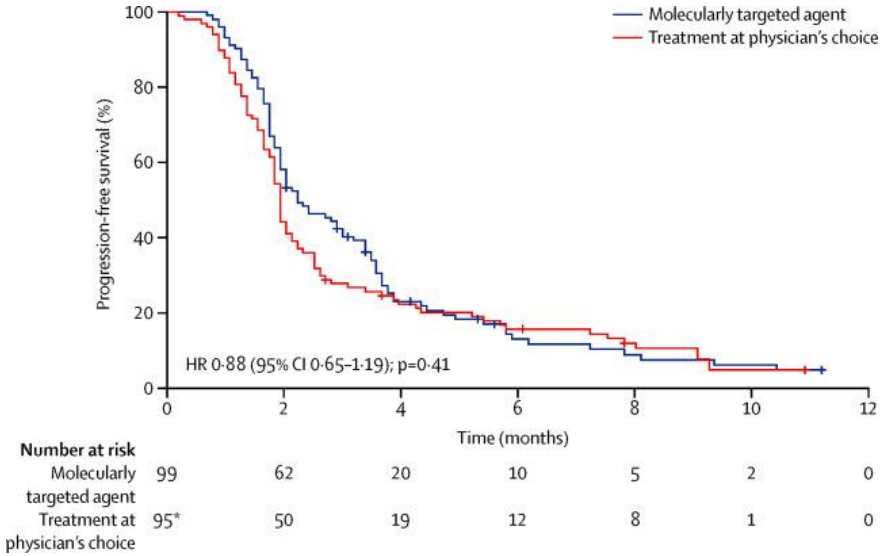
Clin Cancer Res. 2019 Feb 15;25(4):1239-1247

Moscato

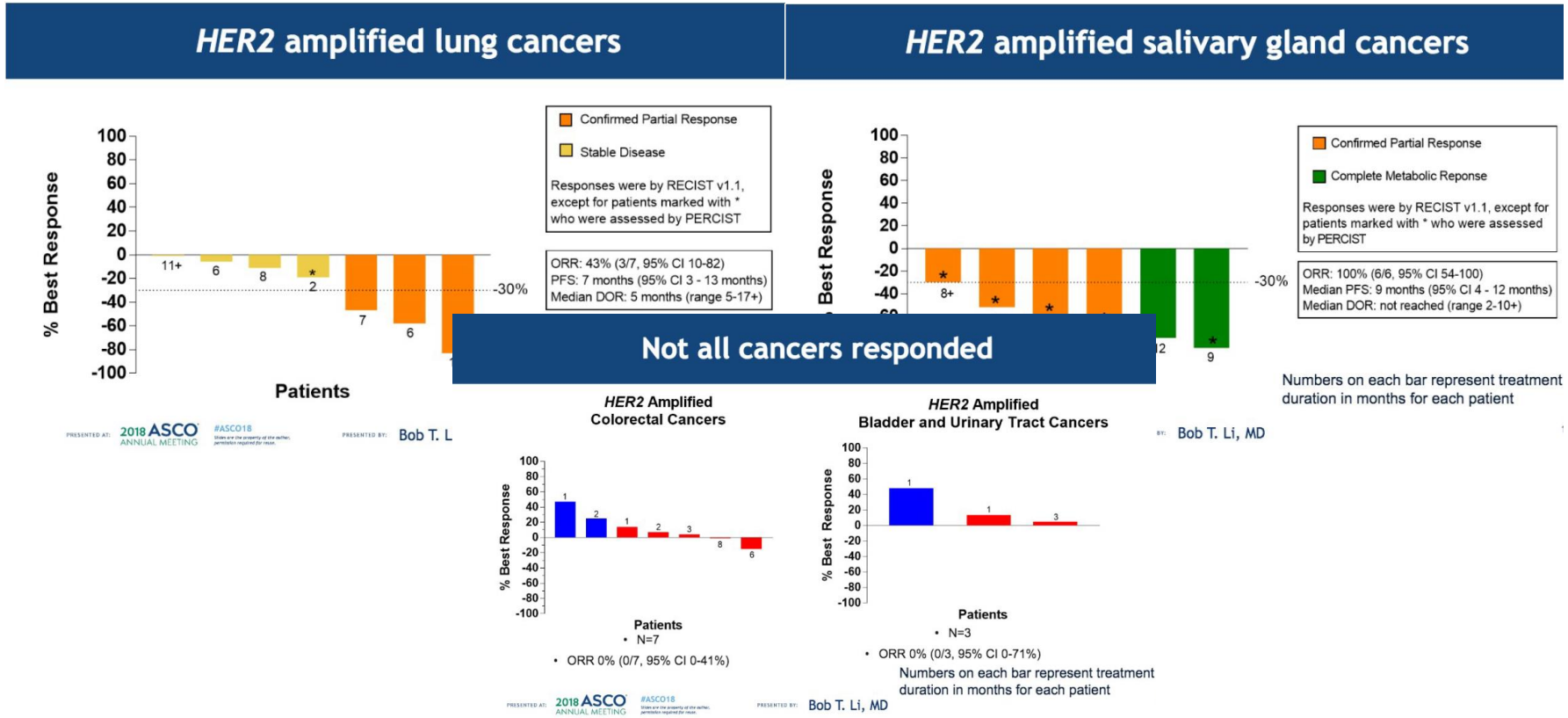


- 199 out of 948 biopsied patients treated with matched therapy
- ORR: 11% (22 patients)

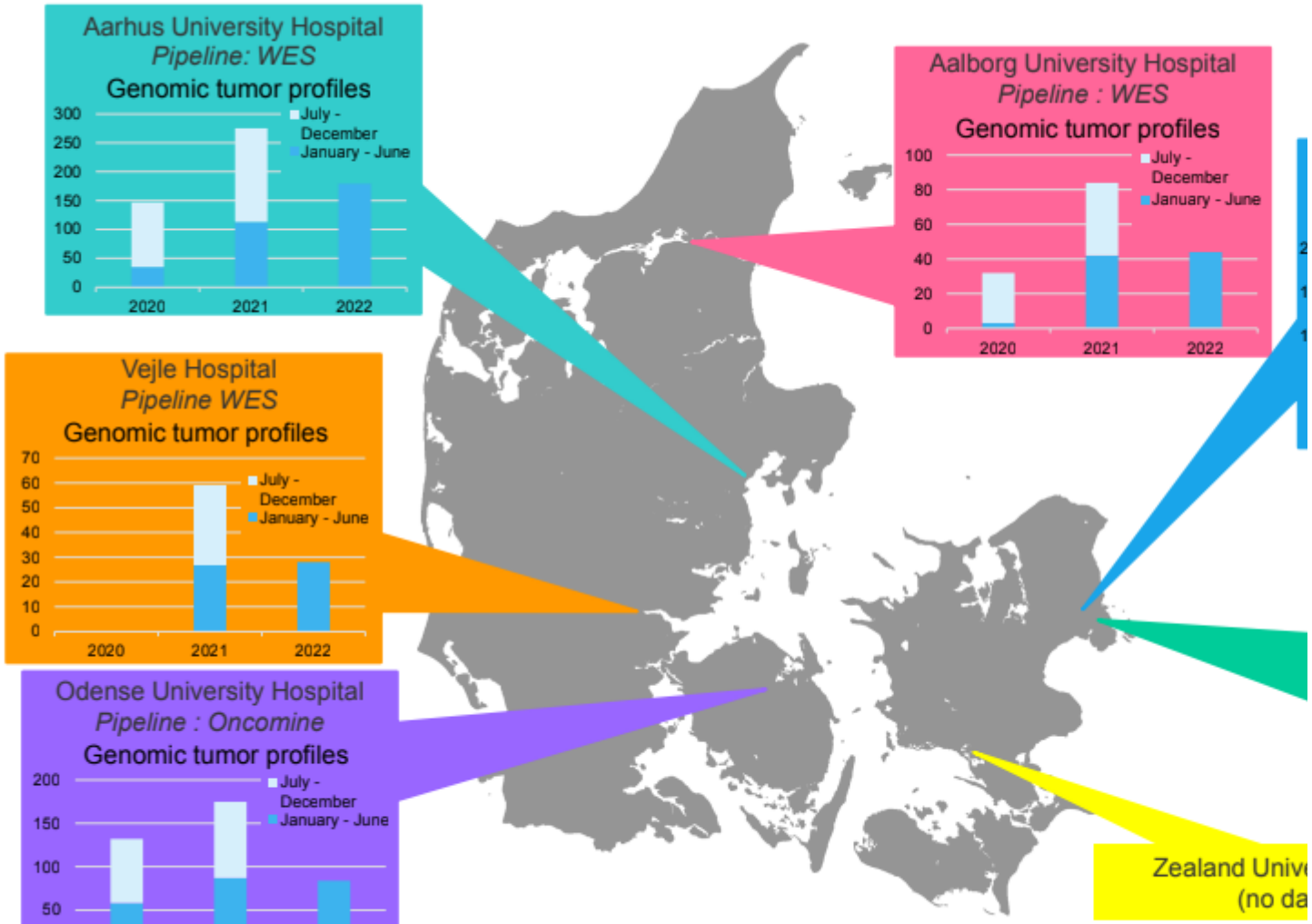
SHIVA



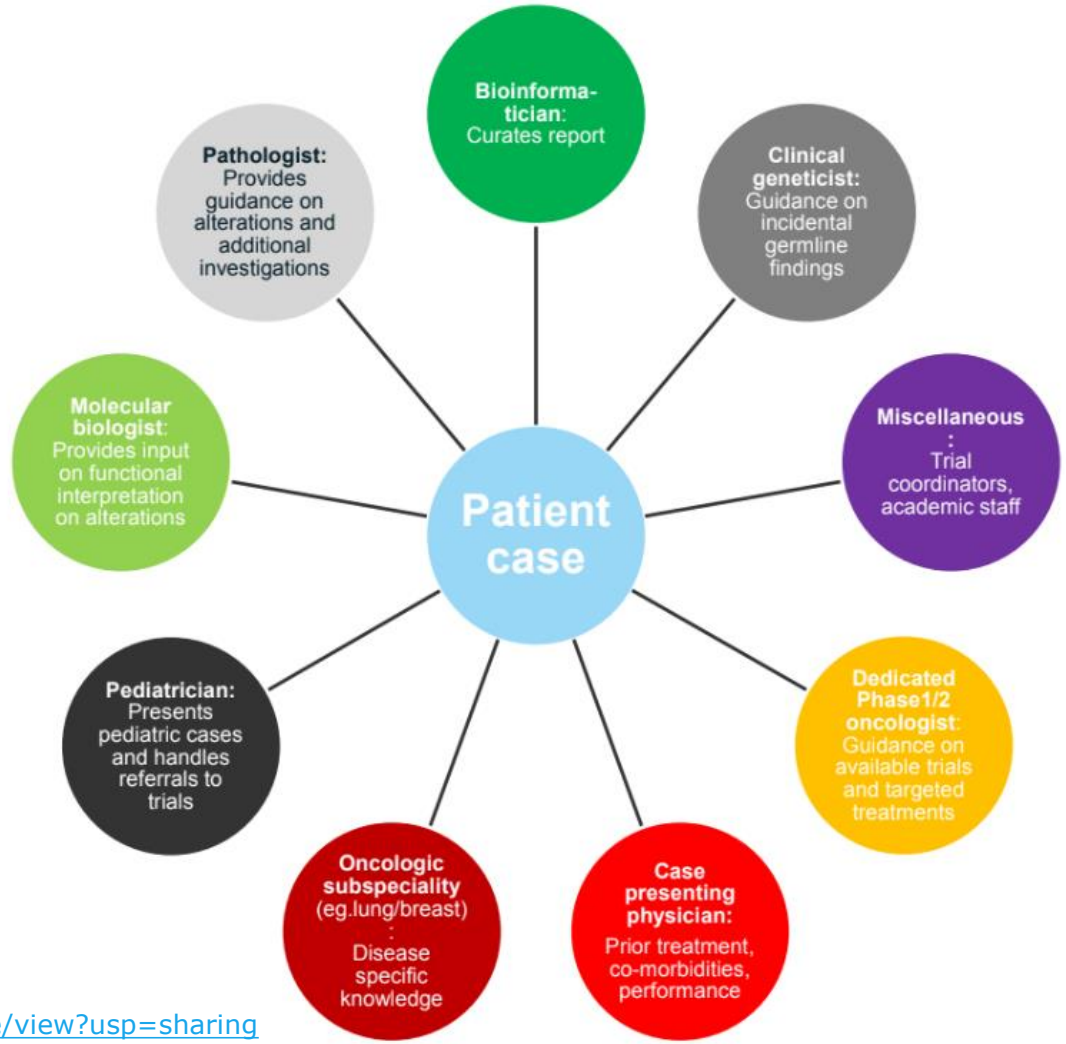
NCI-MATCH – Trastuzumab-entamcin in HER-2 amplified cancer



Genomic profiling in Denmark



National weekly tumorboard
30-40 patient cases/week



https://drive.google.com/file/d/17Kn1nhn3M_peTOTc0YbcxI7uVDyJQZge/view?usp=sharing

ProTarget: A Danish Nationwide Clinical Trial on Targeted Cancer Treatment based on Genomic Profiling

Primary Objectives:

To evaluate the anti-tumor activity and toxicity of commercially available, targeted anti-cancer drugs used for treatment of patients with an advanced solid tumor, multiple myeloma or B cell non-Hodgkin lymphoma that harbours a genomic- or protein expression variant known to be a drug target or to predict sensitivity to a drug.

ProTarget

Challenges designing a trial

- Multiple targets
- Multiple diagnoses
  - ➢ Rare indications
- Multiple detection methods
  - Panels
  - WES
  - WGS
  - IHC

- Several different pharmaceutical companies
- Different hospitals
- Different regional legal entities
- Data sharing

Challenges designing a trial

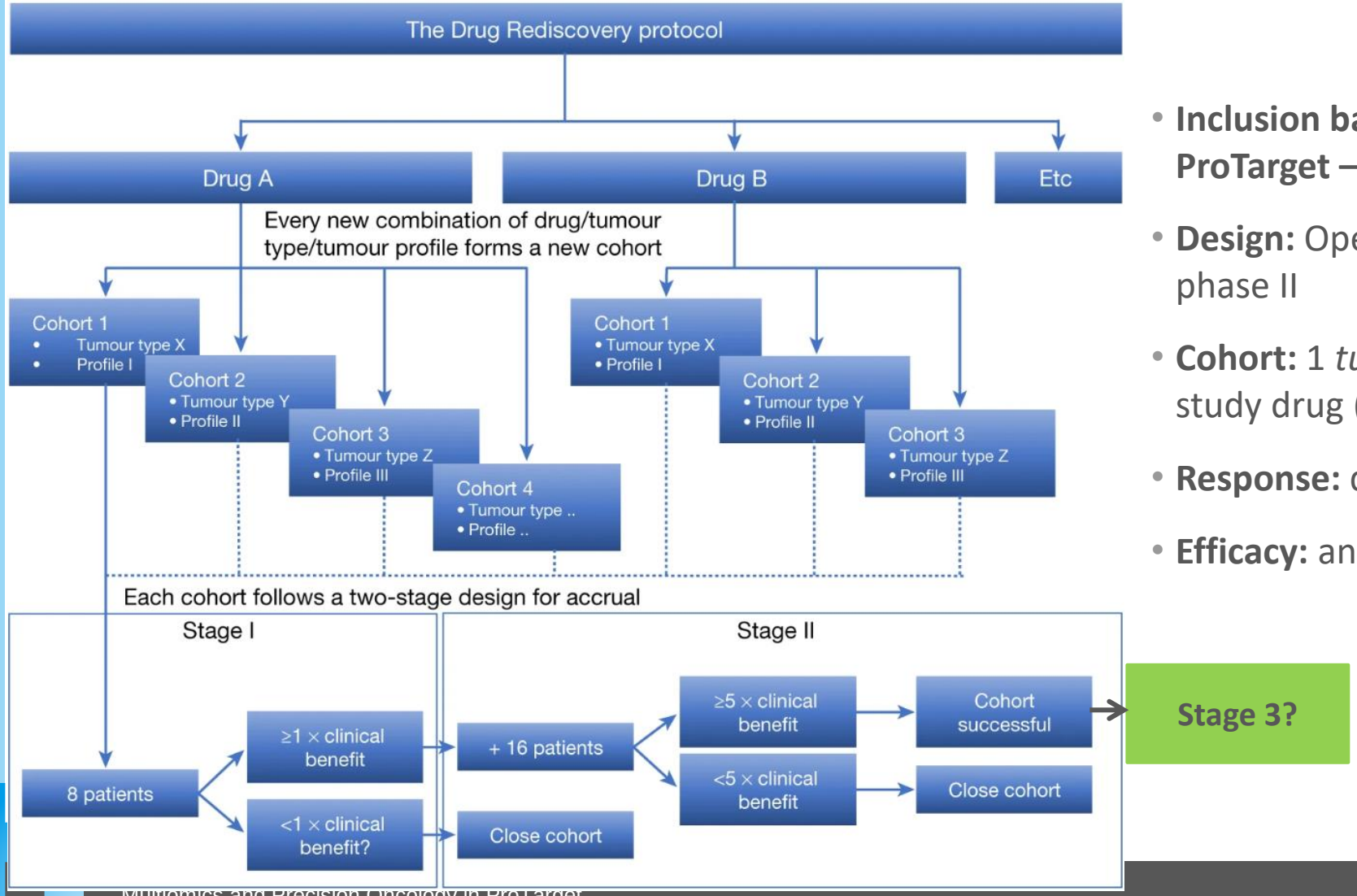
- Multiple targets
  - As many collaborators as possible
- Multiple diagnoses
  - Take into account potential differences in response in different diagnoses
- Rare indications
  - Share data with other European trials
- Multiple detection methods
  - Enroll patients on any method at any time
    - Retrospective validation with fresh biopsy and WGS + RNAseq
- Several different pharmaceutical companies
  - Separate contracts
- Different hospitals
  - Contract negotiations
  - Initiate based on wishes and abilities
- Different regional legal entities
  - Political effort to harmonize across the countrie
- Data sharing
  - Important intention to share data in Europe

ProTarget - Design

- **Tumor board is the core**
- Pragmatic opening of cohorts
- Decision regarding molecular eligibility decided by the tumor board
  - Relevant driver
  - Absence of resistance variant
- National collaboration on pipelines
- National collaboration on variant classification

ProTarget

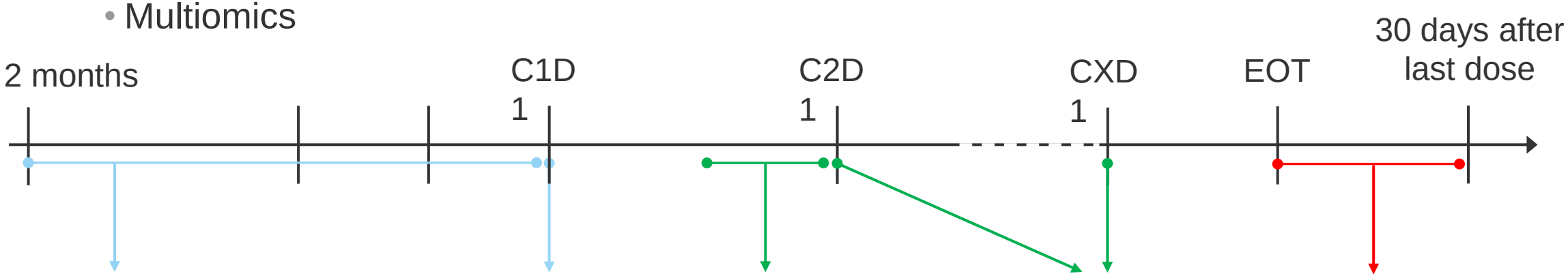
Cohort design and efficacy analyses



- **Inclusion based on genomic test outside of ProTarget – approved by tumor board**
- **Design:** Open label, single arm, multi center phase II
- **Cohort:** 1 *tumor type* + 1 molecular profile + 1 study drug (or combination)
- **Response:** defined as CR, PR or SD ≥16 weeks
- **Efficacy:** analyzed per cohort

Translational workup

- Focus on:
  - Clonal evolution
  - Intrinsic and acquired resistance
  - Multiomics



Screening:
≤2 mdr. prior to C1D1
- WGS and RNAseq
- FFPE
- Germline

C1D1
- ctDNA (STRECK)

OT, Cycle1 follow-up:
Day 15-28 in C1
- WGS and RNAseq
- 1 biopsi til patologi

On treatment CXD1
- ctDNA (STRECK)

PD/EOT:
<30 days after EOT
- WGS and RNAseq
- ctDNA (STRECK)

ProTarget – available IMPs

Roche

- ALECTINIB – ALK/ROS1
- ATEZOLIZUMAB – TMBh/MSI/dMMR
- ERLOTINIB - EGFRmut
- COBIMETINIB and VEMURAFENIB BRAF V600E
- TRASTUZUMAB and PERTUZUMAB – HER2
- TRASTUZUMAB EMTANSIN – HER2
- VISMODIGIB – PTCH1

Pfizer

- AVELUMAB – TMBh/MSI/dMMR
- AXITINIB – VGFR1-3

GSK

- NIRAPARIB – BRCA1-2/ATM/ATR/HRD

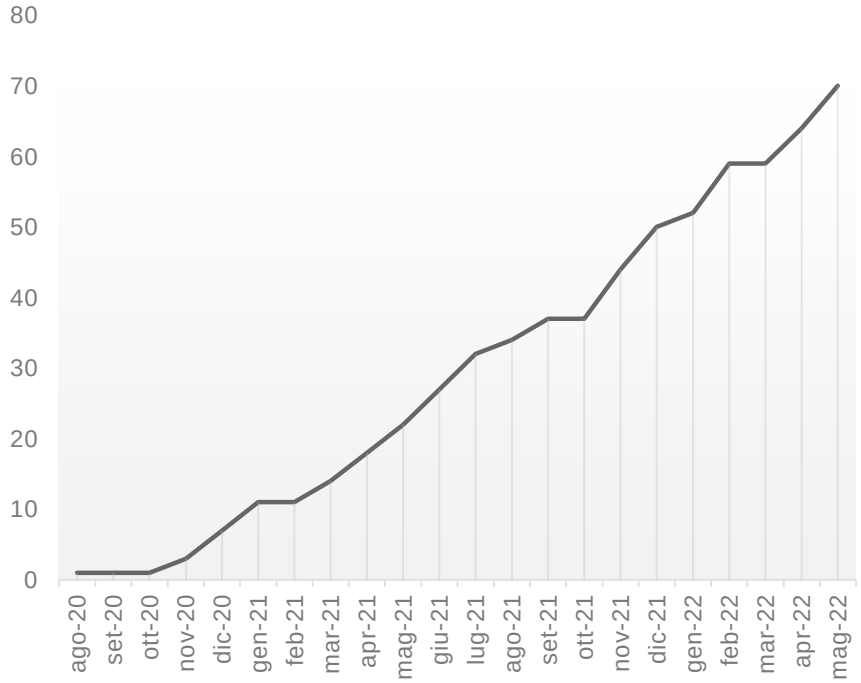
Incyte

- PEMIGATINIB – PDGFR/FGFR

Two more from other company after ammendment

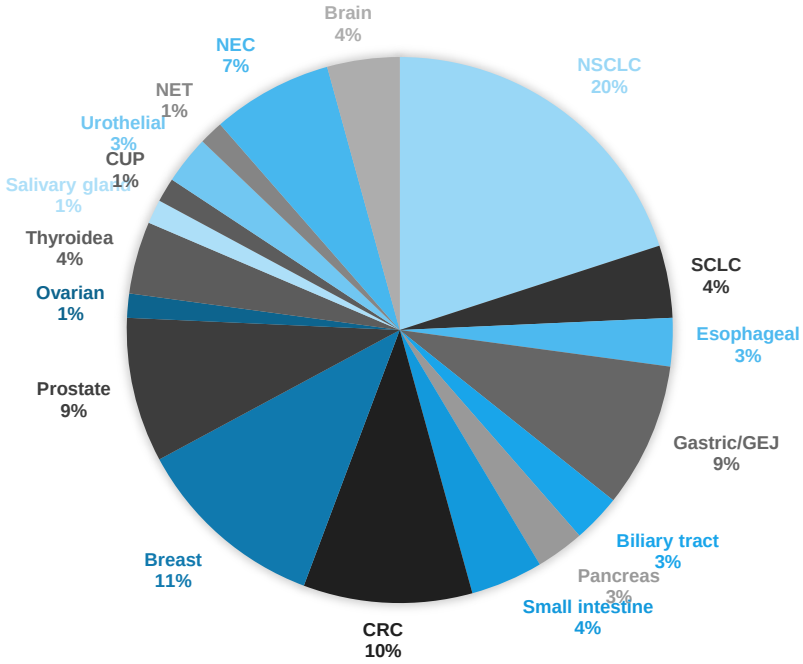
Inclusion in ProTaget

Accumulated inclusion

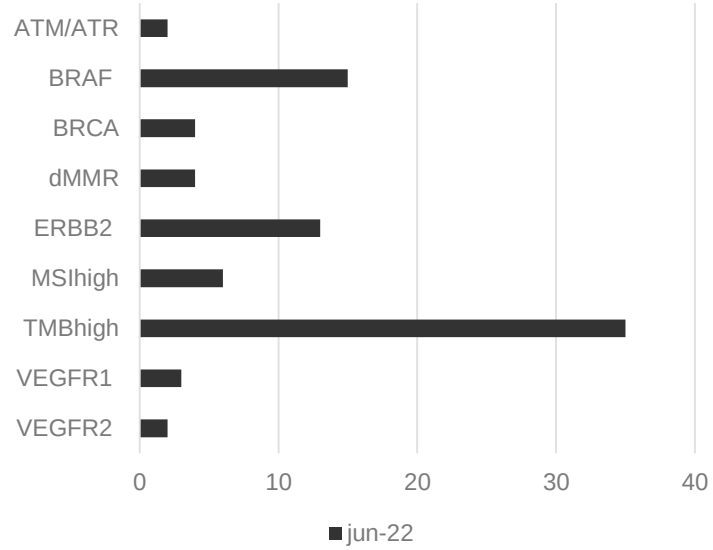


Total: 87 pts
44 cohorts
Sept. 1st 2022

PRIMARY TUMOR TYPE



ProTarget druggable variants



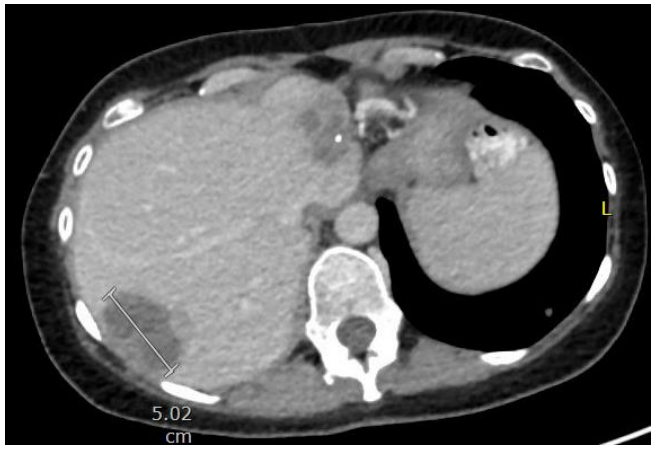
HER2 amplified CRC

- Exhausted treatment options
- Treated with HER-2 dual inhibition

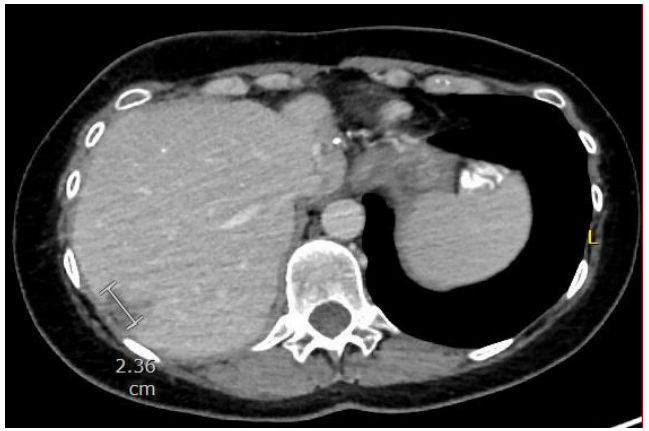
Opsummering af Resultater

Cancer-associerede mutationer[1]:	Særlige kromosomale forandringer[2]:	Særlige genekspressionsfund[3]:
APC: c.3871C>T, p.Q1291*	ACF[6]: 66 %	Klassificeret som[4]: *colon c.*
PTEN: c.706_707delinsTT, p.D236F	HRD	Proliferationsindex[5]: 8,19
	Amplifikation: *ERBB2*	Der er **høj** ekspression af: *AREG, CEACAM5, ERBB2, ETV4, EREG*
	Deletion og LOH: *NOTCH2, JAG2, TP53, BRCA1*	Der er **lav** ekspression af: *PD-L1, NRG1, WNT5A*

Baseline



After 4 months

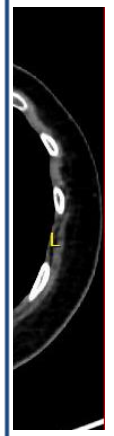


HER2 ampli

- Slow progressi

Opsummering af Resultater

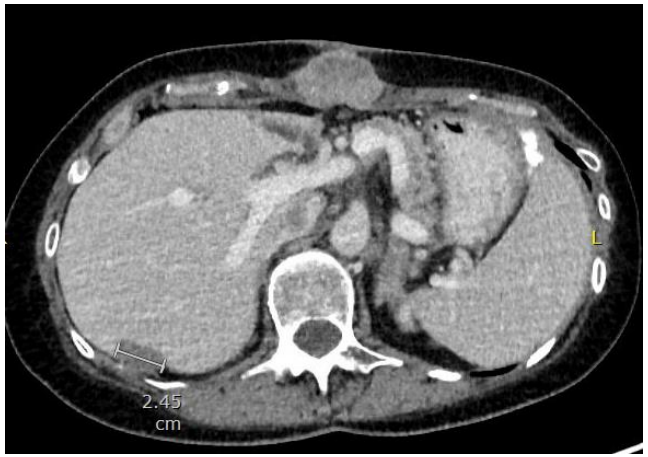
Cancer-associerede somatiske mutationer[1]:	Særlige kromosomale forandringer[2]:	Særlige genekspressionsfund[3]:
APC: c.3871C>T, p.Q1291*	Amplifikation: *ERBB2*	Klassificeret som[4]: colon c.
PTEN: c.706_707delinsTT, p.D236F	Deletion og LOH: *TP53, NOTCH2, JAG2, BRCA1*	Proliferationsindex[5]: 7,34
TP53: c.844C>T, p.R282W	*HRD*	Der er **høj** ekspression af: *AREG, ERBB2, ETV4, CEACAM5, EREG, GNAS*
Der er ikke identificeret nogen klinisk relevant		Der er **lav** ekspression af: *F3, WNT5A, NRG1*



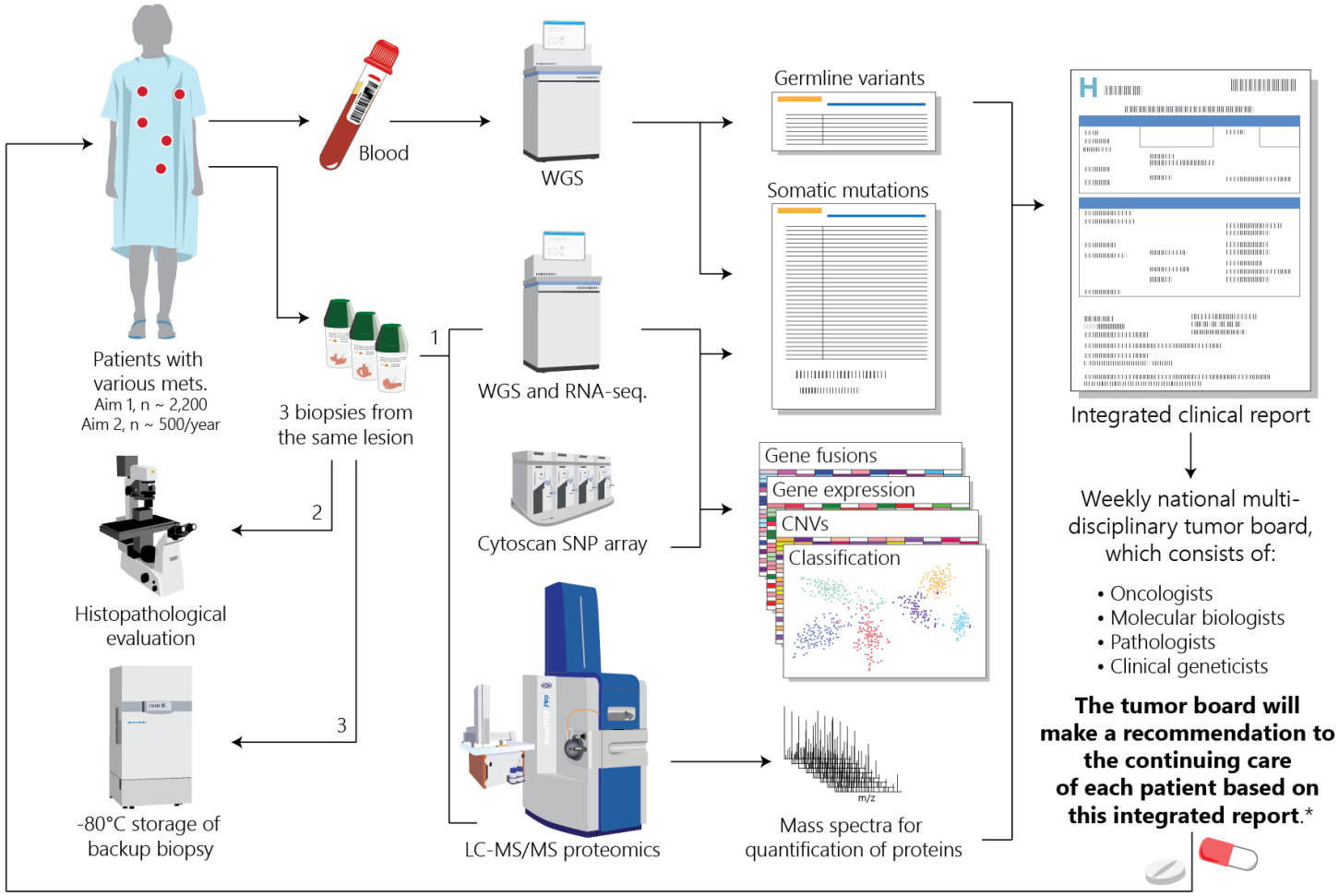
Op

Cancer-associerede mutationer[1]:	Særlig forandringer[2]:	
APC: c.3871C>T, p.Q1291*	ACF[6]: 66 %	Klassificeret som[4]: *colon c.*
PTEN: c.706_707delinsTT, p.D236F	HRD	Proliferationsindex[5]: 8,19
	Amplifikation: *ERBB2*	Der er **høj** ekspression af: *AREG, CEACAM5, ERBB2, ETV4, EREG*
	Deletion og LOH: *NOTCH2, JAG2, TP53, BRCA1*	Der er **lav** ekspression af: *PD-L1, NRG1, WNT5A*

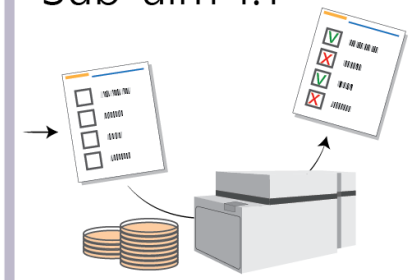
After 18 months



Aims 1 (retrospective) and 2 (prospective): the multi-omics approach

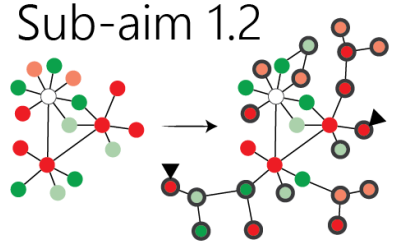


Sub-aim 1.1



We will validate targets from the multi-omics approach in patient-derived organoids using high-throughput drug screenings.

Sub-aim 1.2



We will add phosphoproteomics on selected cohorts from aim 1 and aim 2 to better understand resistance mechanisms and clonal evolution as well as potentially identify targets to overcome resistance.

* In aim 2, recommendations have already been made for the retrospective samples (Tuxen et al., 2019)

ProTarget: A Danish Nationwide Clinical Trial on Targeted Cancer Treatment based on Genomic Profiling

- Integration of other methods
  - Drug screen on patient derived organoids
  - Proteomics
  - Phospho-proteomics
  - Kinase assays

ProTarget

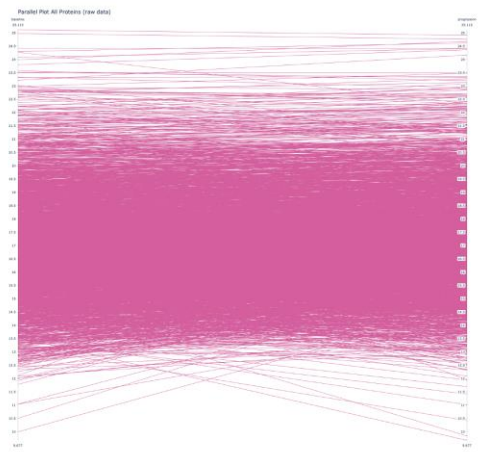
Rigshospitalet
Centre for Cancer and Organ Diseases

Prioritizing drug targets and candidates in phase1

- N = 1
- Samples = 2 (Baseline and progression)

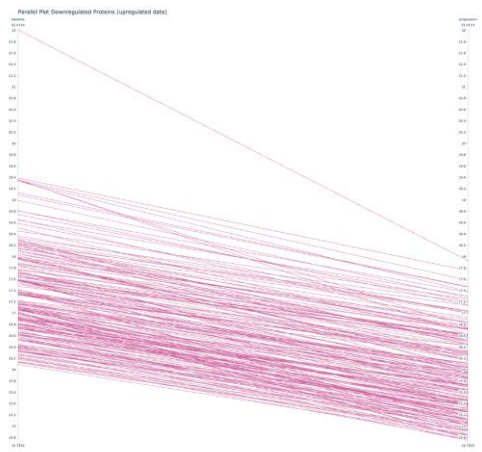
All proteins

Baseline Progression



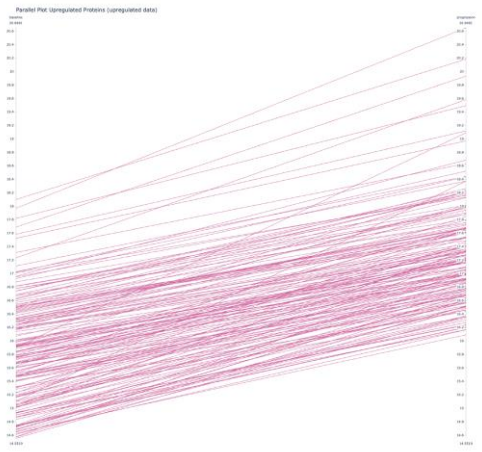
Down regulated

Baseline Progression



Up regulated

Baseline Progression



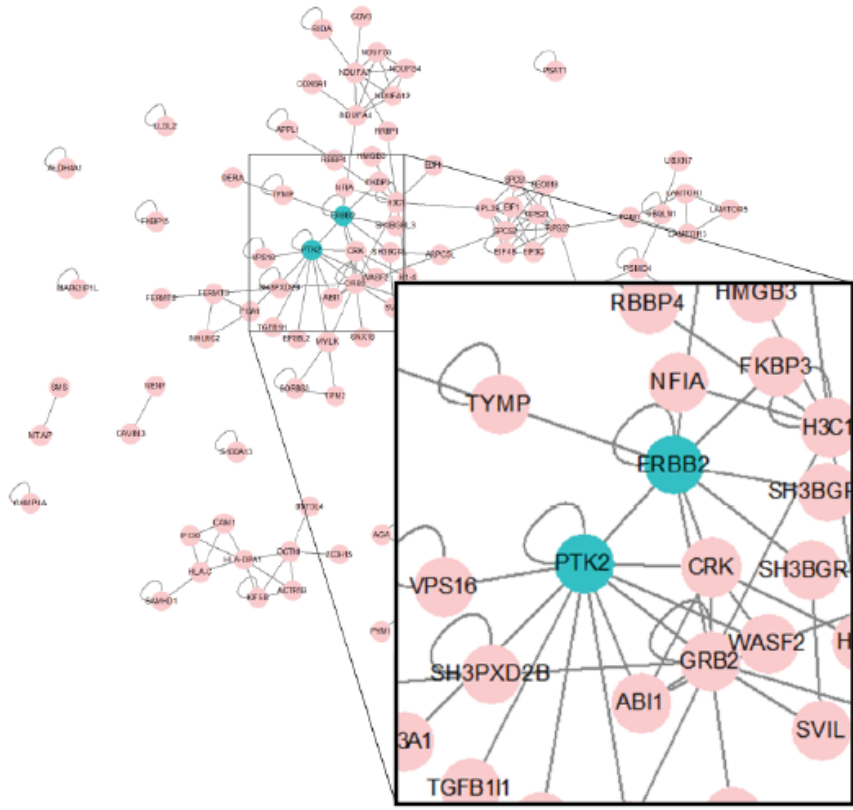
jupyter **Report notebook: HER2 pilot**

HER2 amplified colon cancer with unknown recistance

- Treatment: lapatinib + trastuzumab
- Samples: baseline and progression

Filter proteins to identify candidate recistance mechanism

		Proteins
[1]:	Regulated proteins from baseline to progression	370
[2]: +	upregulated proteins	176
[3]: +	associated wtih colon or liver cancer	74
[4]: +	in the ERBB2 (HER2) pathway	1



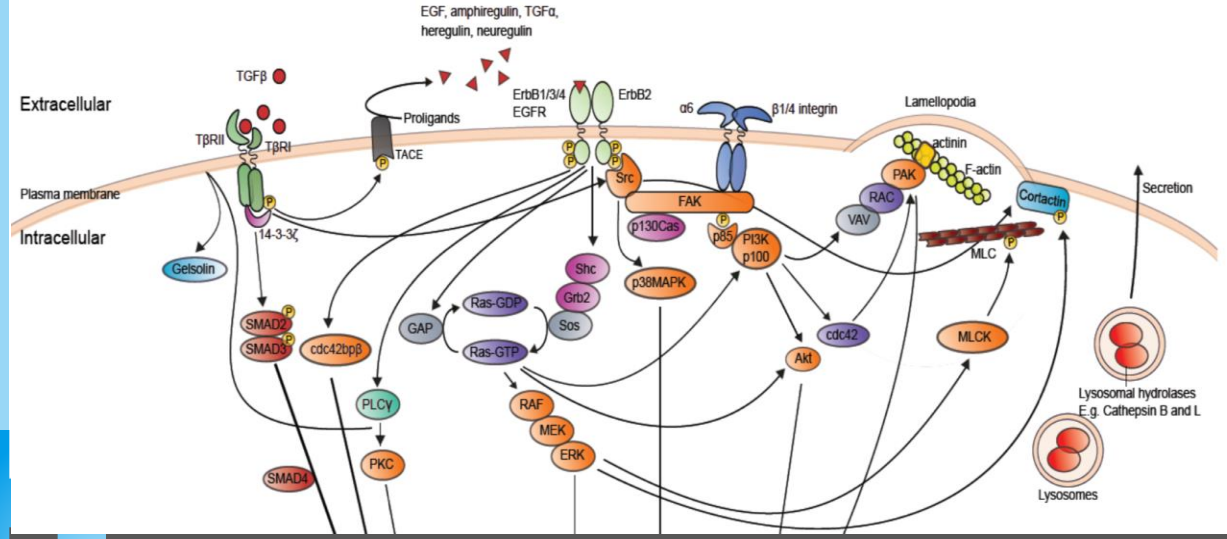
Unpublished data, in collaboration with Annelaura Bach Nielsen, Postdoc, Mann group
NNF Center for Protein Research, Faculty of Health and Medical Sciences, University of Copenhagen

HER2 amplified colon cancer with unknown resistance

- Treatment: Dual HER-2 inhibition
- Samples: Baseline and progression

PTK2: Protein Tyrosine Kinase 2

Alias: FAK



Research

This paper is available on line at http://www.mcponline.org

Quantitative Proteomics with siRNA Screening Identifies Novel Mechanisms of Trastuzumab Resistance in HER2 Amplified Breast Cancers*

Alaina P. Boyer‡§, Timothy S. Collier‡§, Ilan Vidavsky¶, and Ron Bose‡‖**

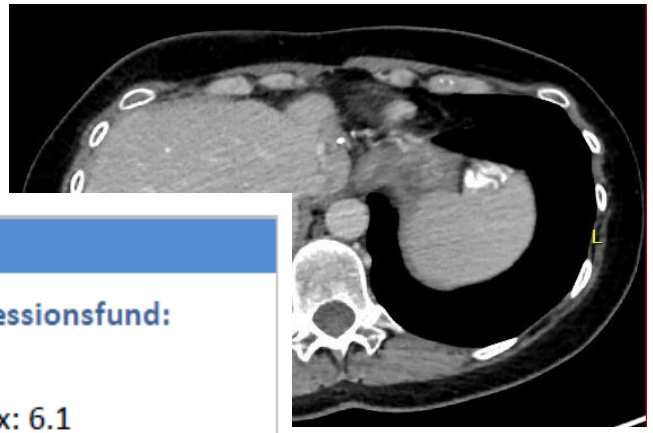
FAK (PTK2/FAK) and Paxillin (PXN) also showed significantly increased protein ratios. FAK and PXN localize to focal adhesions, play a key role in integrin signaling, and affect cell migration and cell adhesion (50, 51). FAK is a cytoplasmic tyrosine kinase, and it can form a complex with Src family kinases (50). Dephosphorylation or down-regulation of FAK and PXN by EGFR and HER2 signaling has been previously reported in two phosphoproteomic studies (24, 52). Activation of FAK occurs in pancreatic and other cancers, and FAK inhibitors are undergoing drug development (53, 54).

HER2 amplified CRC

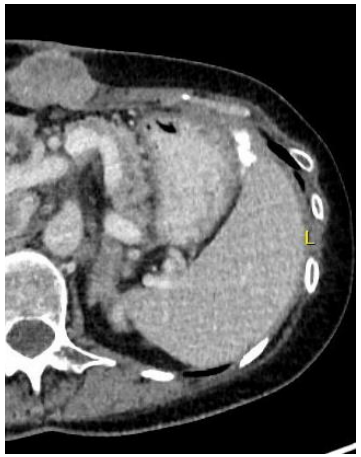
- Slow progression -> re-biopsy
- Res
- Prot
- FAK
  - Ir
  - S

Opsummering af Resultater		
Cancer-associerede somatiske mutationer: *TP53* *c.844C>T, p.R282W* *(loss of function)* *APC* *c.3871C>T, p.Q1291** *(mulig loss of function)* *PTEN* *c.706_707delinsTT, p.D236F* *(VUS)*	**Særlige kromosomale forandringer:** Amplifikation: ***PIK3CA,*** *HES1, PDE4D,* 7p22.3p14.2, *DKK4, FGF9, CDK8, RFC3, KL, FOXO1,* 13q21.33q31.1, ***CDK12***, ***ERBB2***, 20q Deletion og LOH: ***RAD17, RAD51B, FGFR1*** HRD	**Særlige genekspressionsfund:** Proliferationsindex: 6.1 Der er **høj** ekspression af: *ERBB2* Der er **lav** ekspression af: *APC, ATM, CD40, CDK6, CTLA4, EGFR, ESR1, FGFR2, FLT1, GNAS, HAVCR2, HGF, IL2RA, JAG1, MDM2, MTOR, NOTCH2, NRG1, PTCH1, PTEN, RAF1, RB1, RET, TLR7, TNFRSF9, WEE1,WNT5A*
Fusioner:	*TNS4->ERBB2* *TOP2A->IGFBP4*	
Germline varianter:	Der er IKKE påvist patogene varianter i de udvalgte gener.	

After 4 months



ths



Future development and challenges

Challenges

- Lower inclusion rate than expected
  - Competing trials
  - Detection of resistance mutations on WGS/RNAseq
- Inclusion of patients without measurable disease
- Inclusion of patients without biopsy
- Financial
- Capture data from EMR to eCRF
- Integration with genomic data

Development

- Including more targeted agents
- Opening of stage 3
  - Reluctance from authorities
- Doing translational research on collected tissue
  - IO cohorts mature for initial investigations
- Opening trial combining targeted agents
  - Obstacles:
    - Pharma
    - Site experience in phase 1b trials
    - N of 1 trials

Copenhagen Master Observational Trial (C-MOT)

- The *master observational trial protocol* seeks to combine the depth of molecularly based master protocols (e.g. basket and umbrella trials) with the breadth of real-world data
- C-MOT is a prospective, investigator-initiated, non-interventional study
  - Aims to describe the safety and efficacy of standard of care or available clinical trials of targeted anti-cancer drugs
- C-MOT prospectively includes 1200 patients with lung or breast cancer
  - Genomic analysis at base, 1st and 2nd evaluation for each treatment course
  - Patient reported outcomes, QoL, PRO-CTCAE
  - Data from EHRs, including dosing of anti-neoplastic drugs, cancer supportive care drugs, comorbidities, biochemistry, microbiology, repeated measurements of vital signs, pathology, and radiology workup

Acknowledgements

Thanks to all the patients and their relatives

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Innovation Fund Denmark

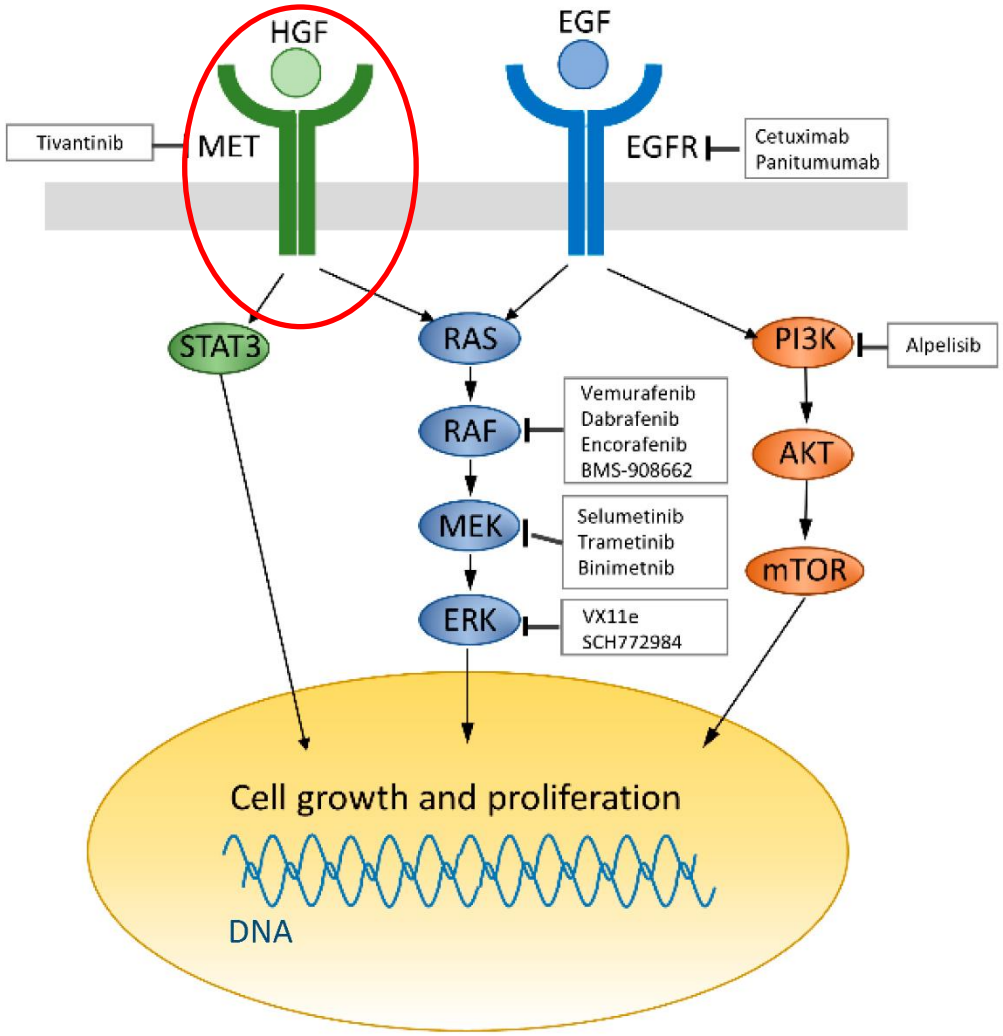
Arvid Nilssons Fond

REGION The Capital Region of Denmark

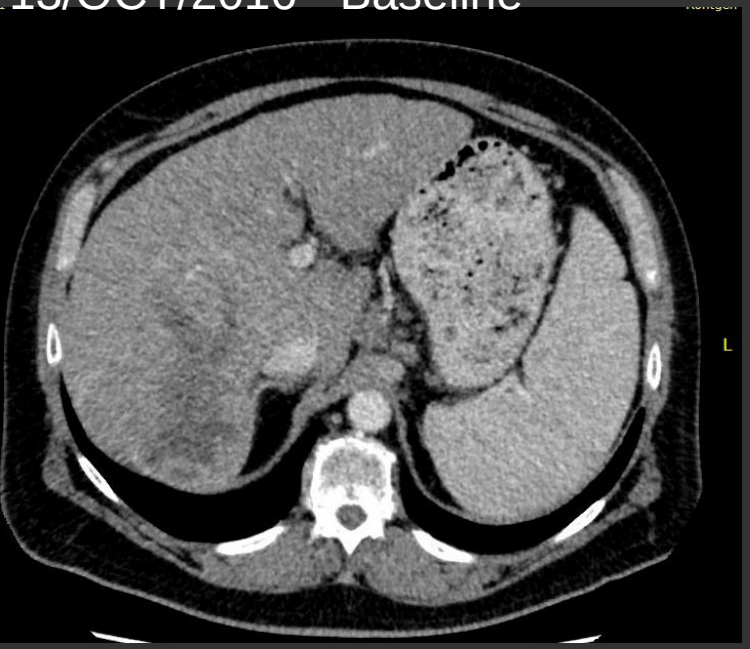
novo nordisk fonden

MET-amplified Pancreatic Cancer

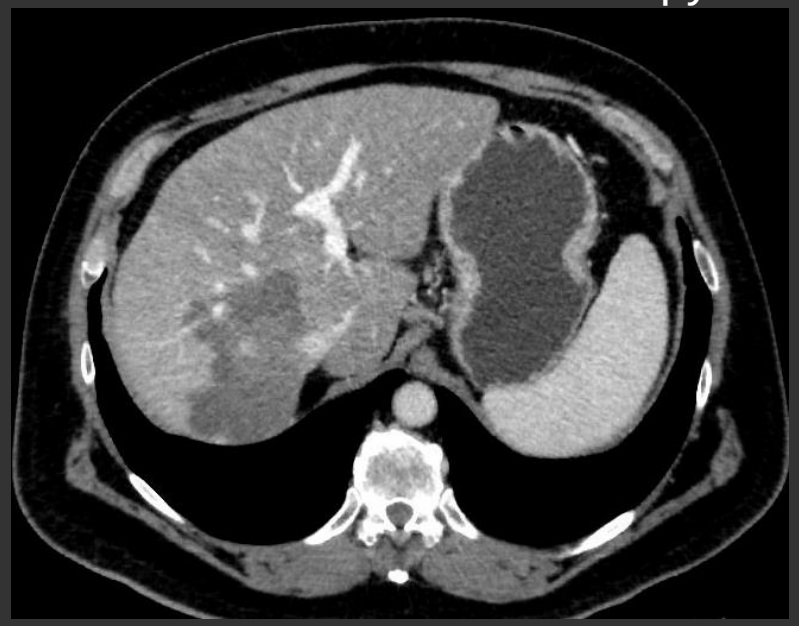
- 60-year-old male
- Previous therapy:
  - FOLFIRINOX
  - Gemcitabine + nab-paclitaxel
- Enrolled into DDI part of capmatinib trial
- Treatment:
  - Capmatinib 400 mg BID
  - (Midazolam 2.5 mg)
  - (Caffein 100 mg)



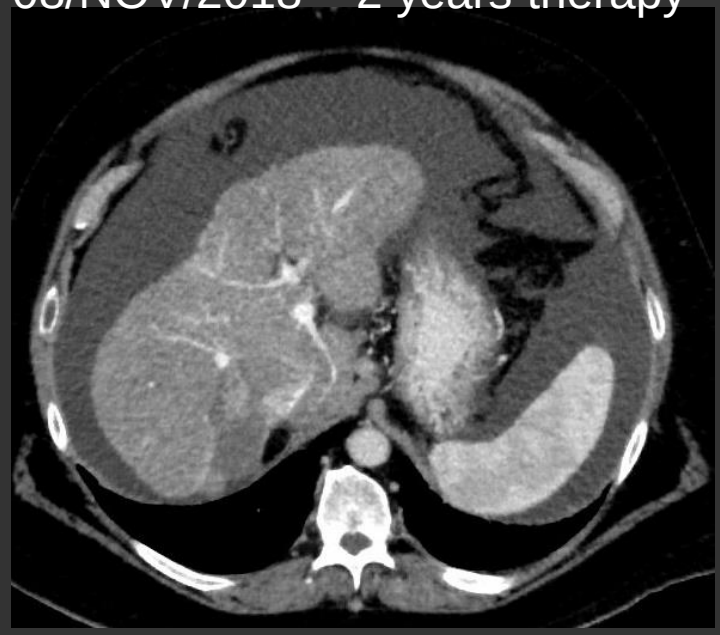
13/OCT/2016 - Baseline



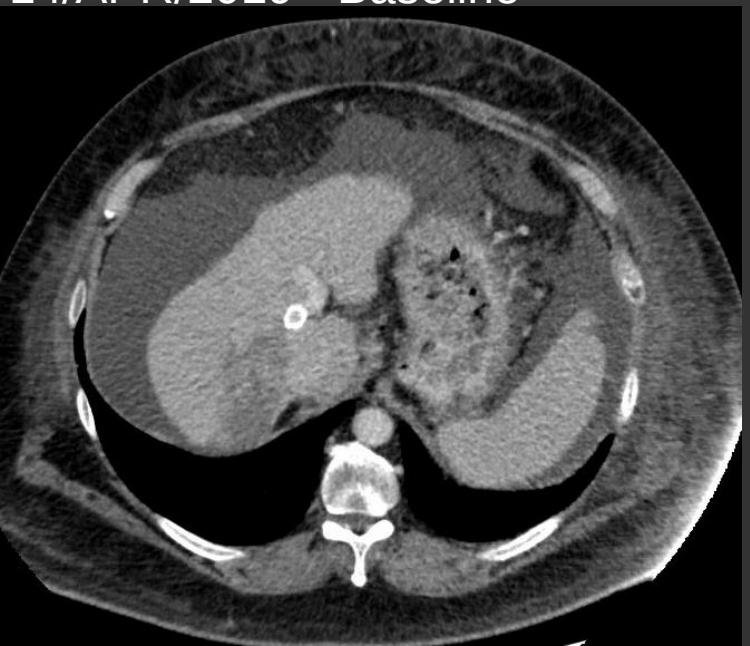
15/DEC/2016 – 6 Weeks therapy



08/NOV/2018 – 2 years therapy

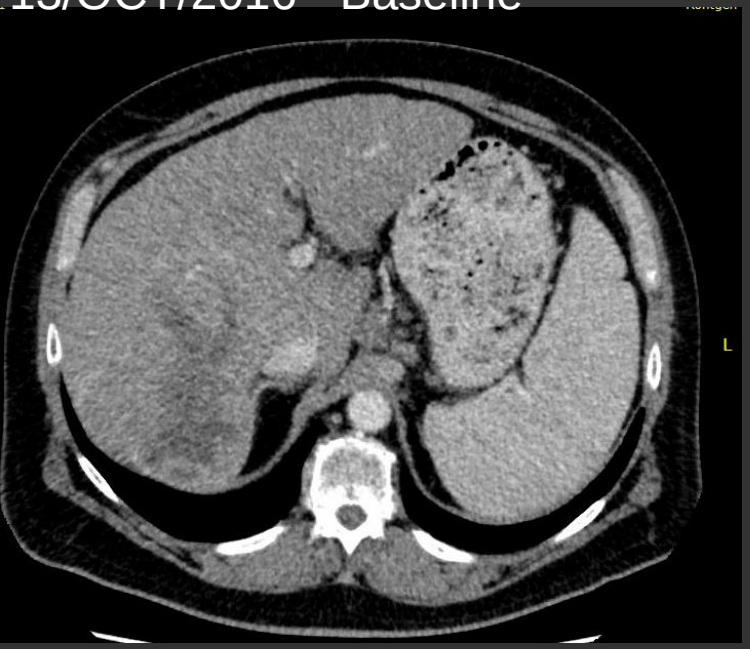


14/APR/2019 - Baseline

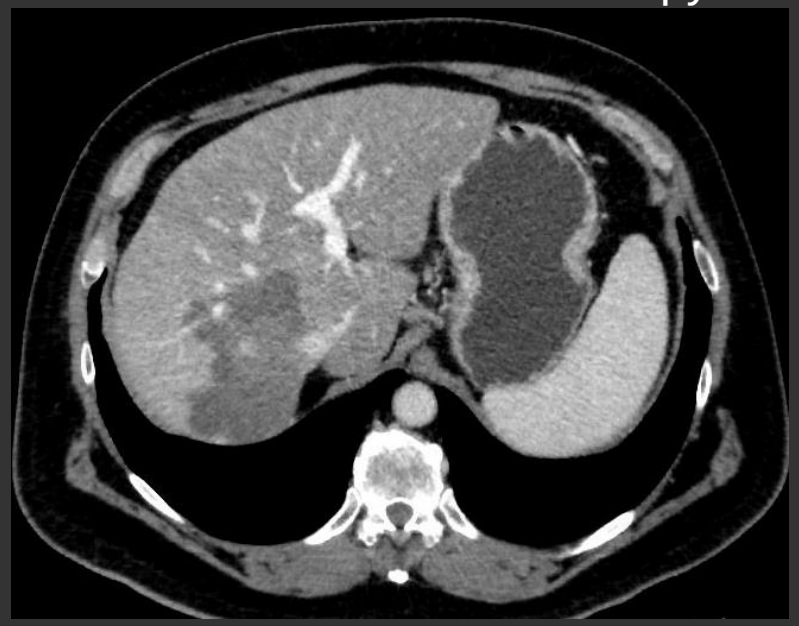


- Ongoing PR
- Develops liver cirrhosis
  - Discontinues capmatinib

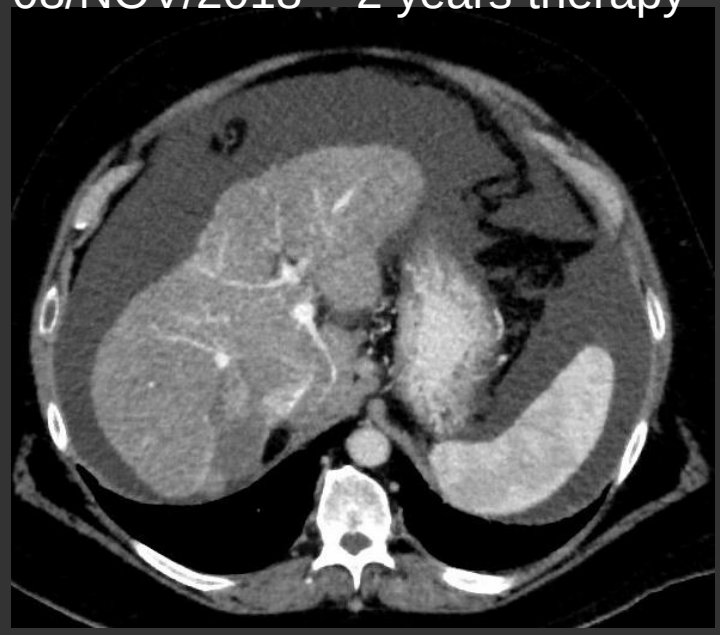
13/OCT/2016 - Baseline



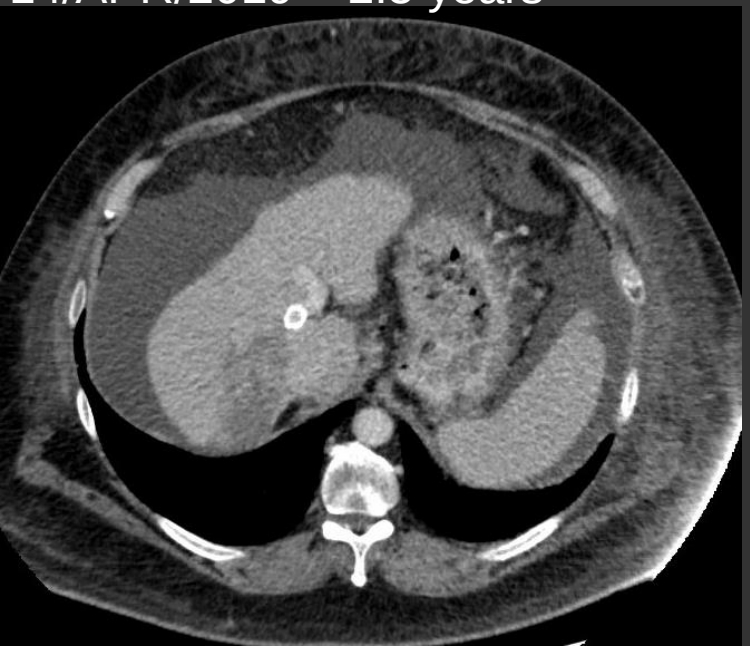
15/DEC/2016 – 6 Weeks therapy



08/NOV/2018 – 2 years therapy



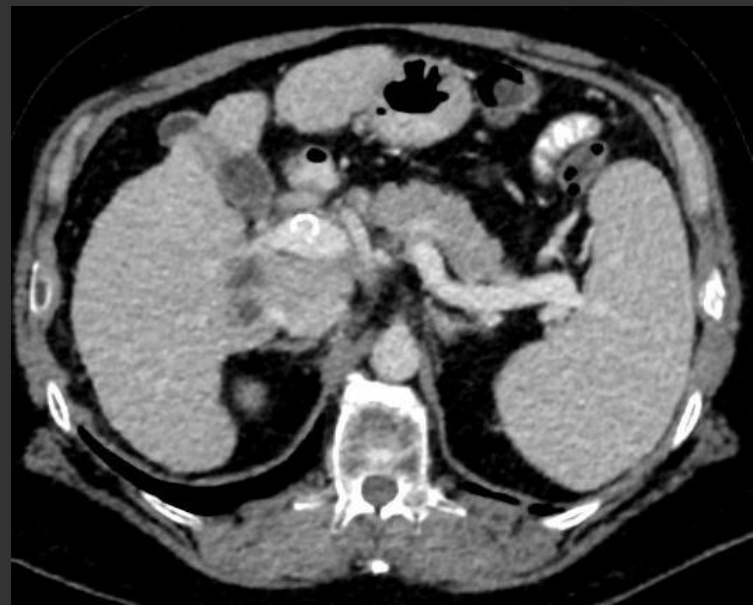
14/APR/2019 – 2.5 years



- Ongoing PR
- Develops liver cirrhosis
  - Discontinues capmatinib

- PD after 4 months off treatment
  - New biopsy

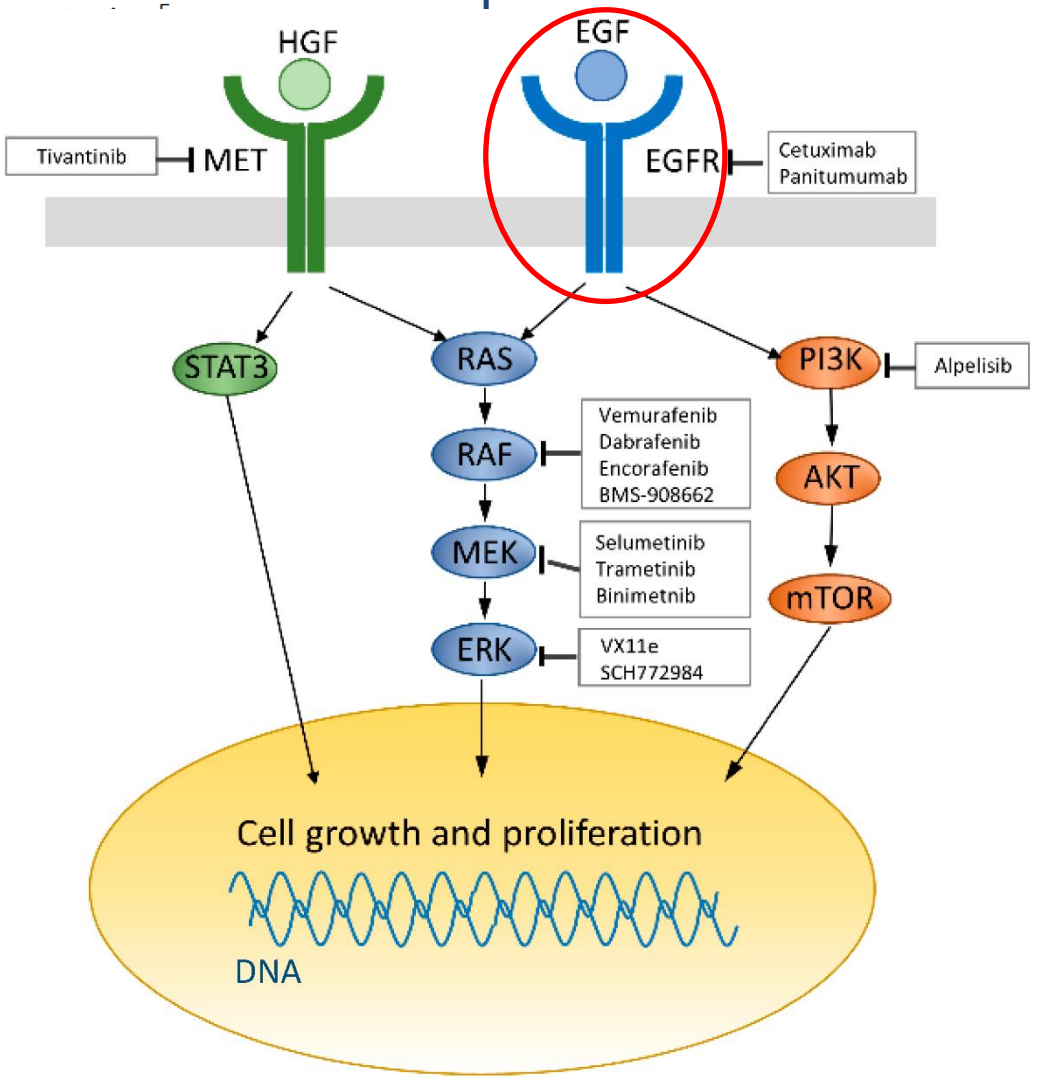
28/AUG/2019 – almost 3 years



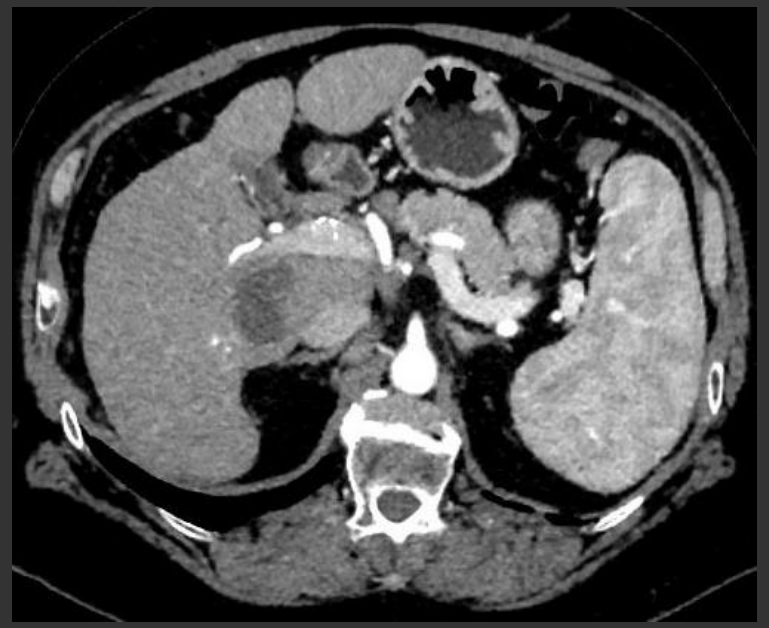
Opsummering af Resultater

Cancer-associerede somatiske mutationer[1]:	Særlige kromosomale forandringer[2]:	Særlige genekspressionsfund[3]:
TP53: c.706T>G, p.Y236D *Klinisk relevant fusion ikke identificeret.*	Amplifikation: *EGFR*	Klassificeret som[4]: *cholangiocarc.* Proliferati Der er **høj** *AREG, EG* *CTLA4*
Germline varianter[6]:	Der er ikke fundet nogen patogene varianter i de uc	

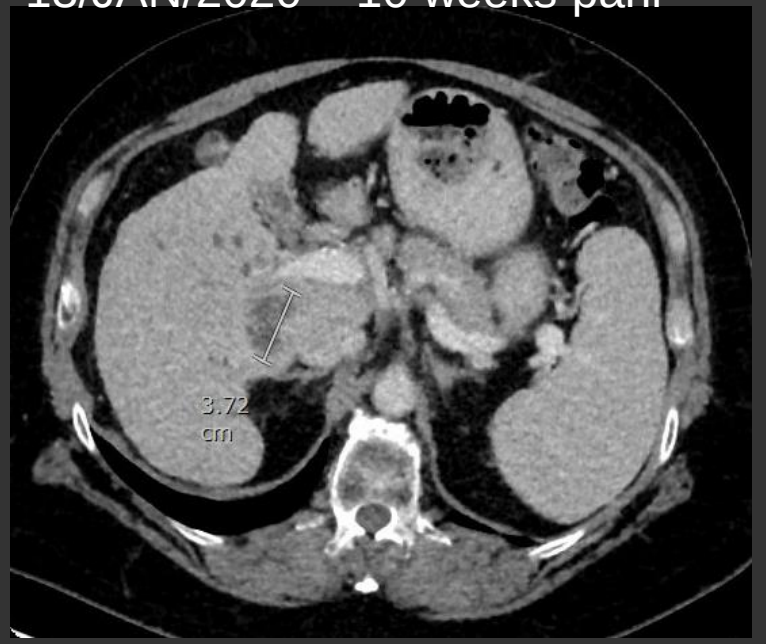
- Panitumumab – αEGFR mAB



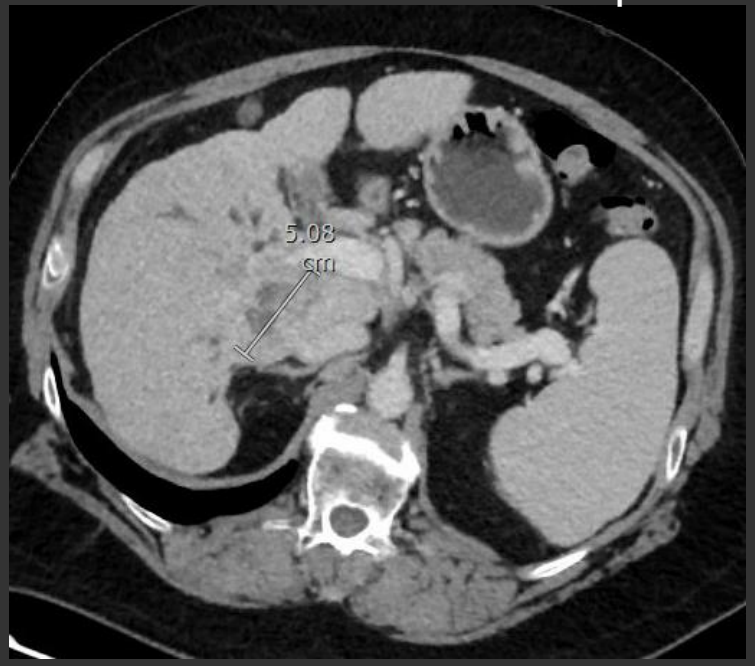
30/OCT/2019 – Baseline Pani



13/JAN/2020 – 10 weeks pani



19/MAR/2020 –18 weeks pani



- Response after 10 weeks of αEGFR mAB
- Progressive disease after 18 weeks of αEGFR mAB

Opsummering af Resultater

Cancer-associerede somatiske mutationer[1]:	Særlige kromosomale forandringer[2]:	Særlige genekspressionsfund[3]:
TP53: c.706T>G, p.Y236D *Klinisk relevant fusion ikke identificeret.*	Amplifikation: *EGFR*	Klassificeret som[4]: *cholangiocarc.* Proliferationsindex[5]: 7,68 Der er **høj** ekspression af: *AREG, EGFR, EREG, FGF2, HGF, CTLA4*
Germline varianter[6]:	Der er ikke	

- Resistance mechanism to αEGFR mAB not detected

Opsummering af Resultater

Cancer-associerede somatiske mutationer[1]:	Særlige kromosomale forandringer[2]:	Særlige genekspressionsfund[3]:
TP53 c.706T>G, p.Y236D *Der er ikke identificeret nogen klinisk relevant fusion.*	Amplifikation: *EGFR, FHIT, CDK1* Deletion og LOH: *MYC, CDKN2A, BRCA2, JAG2* Muligt HRD	Klassificeret som[4]: Cholangiocarcinoma Proliferationsindex[5]: 7.66 Der er **høj** ekspression af: *AREG, FGF2, ETV4, MET, EGFR, EREG, LAMP1-p1 og LAMP1-p2*
Germline varianter[6]:	Der er IKKE påvist patogene varianter i de udvalgte gener.	

Brugerguide - Slet før anvendelse

Brug tekst typografier

Brug **TAB** for at gå frem i tekst-niveauer. Klik **ENTER**, derefter **TAB** for at skifte fra et niveau til et næste

For at gå tilbage i tekst-niveauer, brug **SHIFT+TAB**

Alternativt kan
Forøg og **Formindsk** listeniveau bruges

Ændre slide layouts

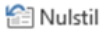
1. Klik på pilen ved siden af **Layout** for at få vist en dropdown menu af mulige slides layout

2. Vælg **Layout** for at ændre dit nuværende layout til et alternativt

Nulstil slide

1. Klik på fanen **Hjem**

2. Vælg **Nulstil** for at nulstille placering, størrelse og formatering af pladsholdere til layoutets oprindelige design



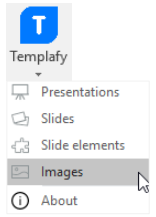
Indsæt billede

På slides med billedpladsholder eller hvilken som helst anden pladsholder, klik på pladsholderens kant. TIP: Hold Shift nede og klik på pladsholderen

A. Indsæt firma billede

1. Klik på den blå **Templafy**-knap

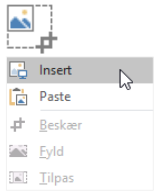
2. I drop ned menuen, vælg **Images**, eller klik på **Images**-knappen i Templafy vinduet i højre side af skærmen



B. Browse efter andre billeder

1. Klik på **Image Tools-**knappen som findes under firma fanen

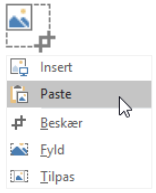
2. Klik på **Indsæt** for at browse efter et billede



C. Indsæt et kopieret billede

1. Klik på **Image Tools-**knappen som findes under firma fanen

2. Klik på **Paste** for at indsætte det kopierede billede



Beskær billede

1. Klik **Beskær** for at ændre billedets fokus/størrelse

2. Ønsker du at skalere billedet, så hold **SHIFT**-knappen nede, mens du trækker i billedets hjørner

Tips: Hvis du sletter billedet og indsætter et nyt, kan billedet lægge sig foran tekst og grafik. Hvis dette sker, højreklik på billedet og vælg **Placer bagest**

For at justere sidenummerering, dato og sidefod

Gør dette som det sidste i din præsentation, så det slår igennem på alle slides

1. Klik på fanen **Indsæt**

2. Klik **Sidehoved og Sidefod**
(Tekst kommer fra Templafy)

Vælg **Anvend på alle** eller **Anvend** hvis det kun skal være på et enkelt slide

Hjælpelinjer

For at se hjælpelinjer

1. Klik på fanen **Vis** og sæt hak ved **Hjælpelinjer**

Tips: Alt + F9 for hurtig visning af hjælpelinjer