NGS in solid and rare cancers

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Precision medicine in oncology

1. Patient characteristics
2. Cancer type
3. Immunohistochemistry markers (ER)
4. Genotype
5. Immune biomarkers

Perceived limitations of Precision

- **A minority of genotyped patients ultimately receive a targeted agent**
- **A minority of treated patients experience clinical benefit**
- **Clinical benefit often of a short duration**

Schwaederle, M. et al. Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. J. Clin. Oncol. 33, 3817–3825 (2015).

Causes of apparent low efficacy

- **Tumor heterogeneity and the development of acquired drug resistance**

- **Trials with ill-fitted drugs or drug combinations**
  - **Example Shiva trial**

    Le Tourneau, C. *et al.* Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol.* **16**, 1324–1334 (2015)

Past evidence on Precision

- **Phase II studies : 570 studies, 32,149 patients**

- Treatment allocated using a **personalized approach:**
  - **Higher median response rate** (RR) (31% versus 10.5%; *P* < 0.0001)
  - **Prolonged median PFS duration** (5.9 months versus 2.7 months, *P* <0.0001)
  - **Extended OS duration** (median 13.7 months versus 8.9 months; *P* = 0.0001).

- Treatment based on the presence of a **genomic biomarker:**
  - **Higher median RRs and longer median PFS and OS** (all *P* ≤ 0.05) than for patients treated based on the presence of a protein biomarker

Schwaederle, M. *et al.* Impact of precision medicine in diverse cancers: a meta-analysis of phase II clinical trials. *J. Clin. Oncol.* **33**, 3817–3825 (2015).

More accurate targeting in prospective trials

- NCI Molecular Profiling based Assignment of Cancer Therapeutics (M-PACT) study (NCT01827384)
- MD Anderson IMPACT-2 study (NCT02152254)
- Lung Cancer Master Protocol (LungMap) study (NCT02154490)44
- NCI–MATCH trial (NCT02465060)
- FOCUS4 study24
- Novartis 'Signature' trial25
- Genentech 'My Pathway' trial (NCT02091141)
- Stand Up to Cancer melanoma study
- ASCO Targeted Agent and Profiling Utilization (TAPUR) trial (NCT02693535)
- **Belgian Precision basket trials**

Likely to provide more information on the clinical value of matching targeted agents to genomic alterations

Real world evidence in registries

- Molecular Evidence Development Consortium (MED-C, CureOne)
- Multiple Myeloma Research Foundation COMMPASS registry
- Pancreatic Cancer Action Network Know Your Tumor program
- Bladder Cancer Action Network Bladder Cancer Genomics Consortium
- AACR Project GENIE

Belgian Society of Medical Oncology

The Belgian Molecular Profiling Program of Metastatic Cancer for Clinical Decision and Treatment Assignment

PRECISION

in collaboration with Belgian university and network-hospitals, Sciensano and pharmaceutical industry to give cancer patients access to a broader spectrum of cancer medicines

Made possible by grants from the Foundation Against Cancer and Kom op tegen Kanker

Why Precision?

Targeted drugs are developed and registered in the **most frequent genotype-cancer-type** associations

In rare cancers, if homogeneously mutated (GIST, CML)

Rare mutations in frequent cancer types or rare cancer type-genotype associations do not enter such a development path

Specific actionable mutations can occur in any cancer type, not just in the registered cancer type

Rare cancers are 20% of the cancers we treat

High plausibility that the same drugs could work in off-label indications, but patients remain without access to these treatments for a very long time

NGS Convention gene list (2022) for reimbursed indications

Colorectal	Lung DNA	Lung RNA	GIST	Melanoma	Ovarian
BRAF	**BRAF**	**ALK**	**c-KIT**	**BRAF**	**BRCA1**
KRAS	**EGFR**	**MET**	**PDGFRA**	**c-KIT**	**BRCA2**
NRAS	**KRAS**	**NTRK**		**NRAS**	
	MET	**RET**		TERTpromotor	
	HER2	**ROS1**			
Medulloblastoma	**Glioma DNA**	**Glioma RNA**	**Thyroid**	**Breast**	**Pancreas**
WHO list	**IDH1**	**BRAF**	**BRAF**	**ESR1**	GNAS
	IDH2	MYB	**KRAS**	**PIK3CA**	**BRCA1**
	H3F3A	MYBL1	HRAS		**BRCA2**
	BRAF		NRAS		
	TERTpromotor		**RET**		
	FGFR1		**NTRK1,2,3**		
			PAX8/PPARγ		
			TERTpromotor		
			p53		

Updated dec 1, 22 by Aline Hebrant

NGS Convention gene list (2022) for reimbursed indications

Sarcoma	Endometrial cancer	Prostate
FUSION GENES	**POLE**	**BRCA1**
PDGFRβ	**TP53**	**BRCA2**
MYOD1		
IDH1/2		
CTNNB1		
APC		
GNAS		

Updated dec 1, 22 by Aline Hebrant

Notable agnostic therapeutic targets

- **NTRK gene fusions**
- **FGFR gene fusions**
- **RET gene fusions**
- **ROS gene fusions**
- **BRAF V600**
- **Tumor mutation burden (TMB) ≥10 mutations/megabase (mut/Mb)**
- **…..**

Tumor-agnostic comprehensive NGS can find all actionable mutations

1. **Rare mutations in common cancers**
2. **Common mutations (of frequent cancers) that occur in rare cancers**

The Precision initiative was conceived to precisely address this issue, in addition to maximizing access to quality NGS for all patients

Precision components

1. **Precision 1**
   - **Implementing comprehensive NGS of advanced cancers**
   - **Data storage, data-sharing and reporting logistics**

2. **Precision 2**
   - **Open-label phase II basket studies** in which patients with an actionable genetic alteration are treated with a drug therapeutically addressing this alteration provided if not covered by a registered treatment or clinical trial in Belgium

Molecular Tumor Board

- **Experts from participating centres:**
  - **Oncologists**
  - **Molecular pathologists**
  - **Geneticists**
  - **Bio-informaticians**
  - **Scientists**

- **Scope of work:**
  - **Provide guidance on “actionable” alterations via electronic consultation**
  - **Advise interruption and initiation of cohorts in PRECISION 2**

Treatment Options

1- « Empirical » available approved treatment (for example chemotherapy, immunotherapy)

2- Genotype driven standard of care

3- Inclusion in genotype matched clinical trial

4- Inclusion in PRECISION 2 if options 2/3 not available

Molecular Tumor Board members

UZ Gent	☐ Dr. Sylvie Rottey	☐ Dr. Karen Geboes	☐ Dr. Ir. Kathleen Claes
	☐ Dr. Ir. Joni Van der Meulen	☐ Dr. Suzanne Vanhauwaert	
AZ Klina	☐ Dr. Alice Van Goethem	☐ Dr. Wim Demey	
UZA	☐ Dr. Patrick Pauwels	☐ Dr. Marika Rasschaert	
AZ Nikolaas	☐ Dr. Willem Lybaert		
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	☐ Dr. Jacques De Grève		
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GHDC	☐ Dr. Jean-Luc Canon	☐ Dr. Javier Carrasco	
Jessa	☐ Dr. Jeroen Mebis	☐ Dr. Annelies Requilé	☐ Dr. Brigitte Maes

A study to examine the value of broad NGS panel testing in the treatment of metastatic cancer: a Belgian Precision study of the BSMO in collaboration with the Cancer Center

BSMO 2020 - 1 study (GeNeo)

Sponsor: BSMO
Study PI: dr Philippe Aftimos
Collaboration: Sciensano/Cancer Centre & Healthdata
Sequencing: Foundation medicine, Roche

PRINCIPAL INVESTIGATORS

n°	***Participating Center***	***PI***
1.	Institut J. Bordet	**Dr Philippe AFTIMOS**
2.	UZ Brussel	Dr Lore DECOSTER
3.	Cliniques Universitaires Saint Luc	Dr Cédric VAN MARCKE DE LUMMEN
4.	UZ Gent	Dr Sylvie ROTTEY
5.	CHU Liege	Dr Joelle COLIGNON
6.	GZA	Dr Luc DIRIX
7.	ZNA	Dr Joanna VERMEIJ
8.	AZ Klina	Dr Wim DEMEY
9.	UZ Leuven	Dr Sabine TEJPAR
10.	UZA	Dr Marc PEETERS
11.	Grand Hospital de Charleroi	Dr Jean-Luc CANON
12.	AZ Nikolaas	Dr Willem LYBAERT
13.	Jessa Zikenhuis	Dr. Jeroen Mebis

Study Population

- **1000 patients with metastatic solid tumors** recruited at thirteen Belgian hospitals, both academic and non-academic (also participating in Precision 1):
- **Recruitment period: 24 months**
- **Patient follow-up is three years**

Inclusion criteria

1. **Adult patients** (18 years and above)
2. Patients **with metastatic solid tumors are that candidates for systemic therapy**

   Numbers will be capped for frequent tumor types :
   - Breast cancer: 150 patients
   - NSCLC: 150 patients
   - Colorectal cancer: 150 patients
   - 200 patients with rare tumors or tumors with rare histology
3. Patients enrolled following three clinical scenarios:
   a) patients **eligible for local NGS testing** (reimbursed or local practice)
   b) patients that are **not eligible for reimbursed or local NGS testing**
   c) patients **with insufficient archival tissue: FMI liquid biopsy testing (exploratory cohort)**.

Study Endpoints

- **Number/prevalence of level 1, 2, 3 and 4 alterations using comprehensive panel testing versus "real-world" practice in the three cohorts included**

- **Patient journey**:
  - % of patients with **MTB recommendation**
  - % of patients accessing genotype-informed treatment
  - Turnaround time from sample pick-up to MTB recommendation (% of patients with a turnaround time of 28 days: 14 days for the testing result and 14 days for the MTB recommendation)
  - The **proportion of patients accessing molecular guided therapy or immune checkpoint inhibitors based on the result of Foundation Medicine testing.**
  - Timing of treatment imitation following MTB recommendation
  - The proportion of deviations from treatment recommendations and reasons (patient ineligible, treatment unavailable, physician decision, patient choice)

Study Endpoints

- **Percentage of patients with successful comprehensive panel testing**
  - composite of no technical failures and results available within 14 days

Exploratory:

- **Prevalence of level 1, 2, 3 and 4 alterations detected using liquid biopsies**
- **Percentage of patients with a treatment recommendation based on a liquid biopsy**
  - **Available drug**
  - **Clinical trial**
  - **Germline testing**

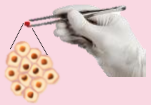
GeNeo study data analysis

Gordana Raicevic, Aline Hebrant, Els van Valckenborgh, Maïté de Hemptinne and Julie Maetens

Study: clinical specimen, NGS testing & MTB

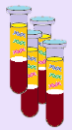
- 1000 patients have been recruited in 19 months:

CLINICAL SPECIMENS



Tumor tissue 904

Liquid biopsy



96

Technical failures

61

2

- Insufficient tissue
- Insufficient DNA
- Failed in sequencing
- Overdue collection date

NGS TESTING

FMI reports issued

843

94

FMI reports NOT discussed

15

4

- No "Star" alteration
- Death

MOLECULAR TUMOR BOARD

FMI reports discussed

828

90

COHORTS (successful FMI testing)

Liquid biopsy

Tissue Biopsy

Cohorts	Nb of patients (% compared to the total test number)	Nb of tests performed on Liquid (% compared to nb of tests per cohort)	Nb of tests performed on Tissue (% compared to nb of tests per cohort)	Biopsy of primary tumors	Biopsy of metastasis
Bladder	36 (4%)	4 (11%)	32 (89%)	22	10
Bone	7 (1%)	1 (14%)	6 (86%)	3	3
Brain	23 (2%)	0 (0%)	23 (100%)	23	0
Breast	137 (15%)	**23 (17%)**	**114 (83%)**	41	73
Cervix	19 (2%)	2 (11%)	17 (89%)	6	11
Cholangiocarcinoma /galbladder	57 (6%)	**9 (16%)**	48 (84%)	38	10
Colon-rectum	128 (14%)	6 (5%)	**122 (95%)**	67	55
Endometrial	22 (2%)	0 (0%)	22 (100%)	14	8
Head & Neck	22 (2%)	1 (5%)	21 (95%)	15	6
Kidney	15 (2%)	0 (0%)	15 (100%)	4	11
Liver	2 (~0%)	1 (50%)	1(50%)	0	1
Lung	46 (5%)	3 (7%)	43 (93%)	23	20
Neuroendocrine	7 (1%)	0 (0%)	7 (100%)	3	4
Oesophagus	15 (2%)	1 (7%)	14 (93%)	10	4
Ovarian	45 (5%)	3 (7%)	42 (93%)	9	33
Pancreas	68 (7%)	**13 (19%)**	**55 (81%)**	24	31
Prostate	8 (1%)	7 (87%)	1 (13%)	0	1
Rare tumors*	100 (11%)	3 (3%)	**97 (97%)**	53	44
Skin	25 (3%)	1 (4%)	24 (96%)	8	16
Soft Tissue**	48 (5%)	4 (8%)	44 (92%)	16	27
Stomach	32 (3%)	0 (0%)	32 (100%)	22	10
Testis	2 (~0%)	0 (0%)	2 (100%)	1	1
Thyroid	14 (2%)	0 (0%)	14 (100%)	7	7
Unknown primary	52 (6%)	**11 (21%)**	41 (79%)	0	41
Vulva/vagina	7 (1%)	1 (14%)	6 (86%)	6	0
Total	**937**	**94 (10%)**	**843 (90%)**	**415**	**427**

(*) For the rare tumors, the most frequent one is prostate acinar adenocarcinoma (26%) (see Annexes III in the CSR);

(**) For one patient it was not mentioned whether the biopsy has been taken from the primary tumor or metastasis.

FMI tests: Turn-around-time (TAT)

	≤14 DAYS	15 - 20 DAYS	21 - 25 DAYS
TAT samples received - report issued	**612 (67%)**	168 (18%)	53 (6%)
TAT report issued - MTB recommendation sent	**443 (48%)**	292 (32%)	87 (9%)
	≤ 28 DAYS	**29 - 37 DAYS**	**37 - 45 DAYS**
Total TAT (samples received - MTB recommendation sent)	416 (45%)	322 (35%)	87 (9%)

TAT report issued – recommendation sent

- Bias in TAT calculation. The date mentioned in the FMI report and which is the one taken into account in this TAT calculation, is not the date of the posting of the report on the portal. Some reports were only available for downloading and processing a 1-2 days later on the portal which adds to TAT.
- It was expected that around 70% of the patients would have been discussed at the MTB, based on a “star alterations” list that the members had pointed before the study; this was actually 98 % which resulted in a large number of patients to discuss in one MTB session.
- Conflictual agenda’s with conferences or educational events, some MTBs were cancelled, resulting in a delay in the processing of released reports.

Molecular Tumor Board

918 patients discussed at the MTB

	Number of patients (% compared to the total number of patients discussed in MTB)	Number of patients with a test on tissue (% with total number of patients with a tissue biopsy result discussed in MTB as denominator)	Number of patients with a test on liquid biopsy (% with total number of patients with a liquid biopsy result discussed in MTB as denominator)
No recommendation	342 (37%)	300 (36%)	42 (47%)
1 recommendation	**407 (44%)**	**368 (44%)**	**39 (43%)**
2 recommendations	129 (14%)	124 (15%)	5 (6%)
3 recommendations	30 (3%)	27 (3%)	3 (3%)
4 recommendations	7 (1%)	6 (1%)	1 (1%)
5 recommendations	3 (<1%)	3 (<1%)	0 (%)
TOTAL	**918**	**828**	**90**

- **63% (576 patients of 918)** received **at least one recommendation** for therapy based on the alterations found in the FMI test;
- **37% (342 patients of 918)** received **no recommendations**;
- **11% (99 patients of 918)** received a recommendation with a referral to **genetic counseling**

MTB treatment recommendation

90 Liquid biopsy

	Number of patients (% compared to the total number of patients discussed in MTB)	Number of patients with a test on tissue (% with total number of patients with a tissue biopsy result discussed in MTB as denominator)	Number of patients with a test on liquid biopsy (% with total number of patients with a liquid biopsy result discussed in MTB as denominator)
No recommendation	342 (37%)	300 (36%)	42 (47%)
1 recommendation	407 (44%)	368 (44%)	39 (43%)
2 recommendations	129 (14%)	124 (15%)	5 (6%)
3 recommendations	30 (3%)	27 (3%)	3 (3%)
4 recommendations	7 (1%)	6 (1%)	1 (1%)
5 recommendations	3 (<1%)	3 (<1%)	0 (%)
TOTAL	**918**	**828**	**90**

- **53%** (**48** patients out of 90) **at least one recommendation** for therapy based on the alterations found in the FMI test
- **47%** (**42** patients out of 90) **no recommendations**
- **12%** (**11** patients of 90) received a recommendation for referral to **genetic counseling**

Driving alteration analysis

Altered genes (*all types of alterations are merged*) and genomic signatures that were most frequently the driving alteration for MTB recommendations

-main alteration type for driving alteration for MTB recommendation is **single nucleotide variant (SNV)**

-oncoKB test level for these alterations are mainly in the order: **4, 1 and 3b**

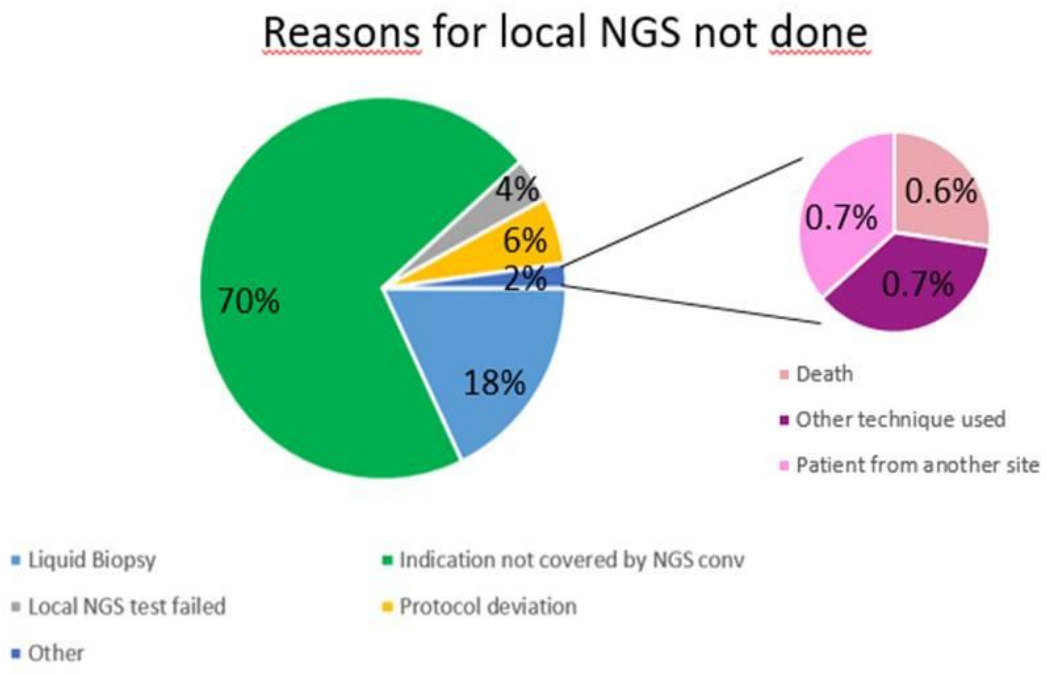
Gene	Frequency
KRAS	96
PIK3CA	67
ERBB2	49
ARID1A	34
NF1	33
CDKN2A/B	30
BRAF	25
PTEN	25
ATRX	14
FGFR3	14
BRCA2	13
FGFR2	13
MTAP	13
TSC1	13
BRCA1	12
TP53	12
BAP1	11
EGFR	11
MDM2	11
MET	11
CHEK2	10
Genomic signature	**Frequency**
TMB	61
MSI	14

Analysis versus local NGS tests

1000 patients enrolled and tested with FoundationOne

469 patients with local NGS test

531 patients with no local NGS test



Added value of FMI test vs local NGS

For the cohorts with more than **10 patients/cohort**:

> 75% of the patients received an additional recommendation :

- Lung
- Brain
- Ovarian

Cohorts	Total nb of patients with at least one FMI recommendation and a local NGS test done	Nb of patients having at least one additional recommendation based on the FMI test vs local NGS results
Bladder	8	7 (88%)
Bone	1	1 (100%)
Brain	10	10 (100%)
Breast	43	30 (70%)
Cervix	2	1 (50%)
Cholangiocarcinoma/galbladder	7	7 (100%)
Colon-rectum	59	35 (59%)
Endometrial	6	6 (100%)
Head & Neck	4	3 (75%)
Kidney	0	0 (0%)
Liver	1	1 (100%)
Lung	20	16 (80%)
Neuroendocrine	2	1 (50%)
Oesophagus	4	4 (100%)
Ovarian	13	11 (85%)
Pancreas	19	10 (53%)
Prostate	0	0 (0%)
Rare tumors	19	14 (74%)
Skin	15	8 (53%)
Soft Tissue	4	4 (100%)
Stomach	4	4 (100%)
Thyroid	7	6 (86%)
Unknown primary	11	8 (73%)
Vulva/vagina	2	1 (50%)
TOTAL	**261**	**188 (72%)**

Added value of FMI test vs local NGS

For the cohorts with more than **10 patients/cohort**:

<75% of the patients received an additional recommendation :

- Breast
- Colon-rectum
- Pancreas
- Rare tumors
- Skin
- Unknown primary

Cohorts	Total nb of patients with at least one FMI recommendation and a local NGS test done	Nb of patients having at least one additional recommendation based on the FMI test vs local NGS results
Bladder	8	7 (88%)
Bone	1	1 (100%)
Brain	10	10 (100%)
Breast	43	30 (70%)
Cervix	2	1 (50%)
Cholangiocarcinoma/galbladder	7	7 (100%)
Colon-rectum	59	35 (59%)
Endometrial	6	6 (100%)
Head & Neck	4	3 (75%)
Kidney	0	0 (0%)
Liver	1	1 (100%)
Lung	20	16 (80%)
Neuroendocrine	2	1 (50%)
Oesophagus	4	4 (100%)
Ovarian	13	11 (85%)
Pancreas	19	10 (53%)
Prostate	0	0 (0%)
Rare tumors	19	14 (74%)
Skin	15	8 (53%)
Soft Tissue	4	4 (100%)
Stomach	4	4 (100%)
Thyroid	7	6 (86%)
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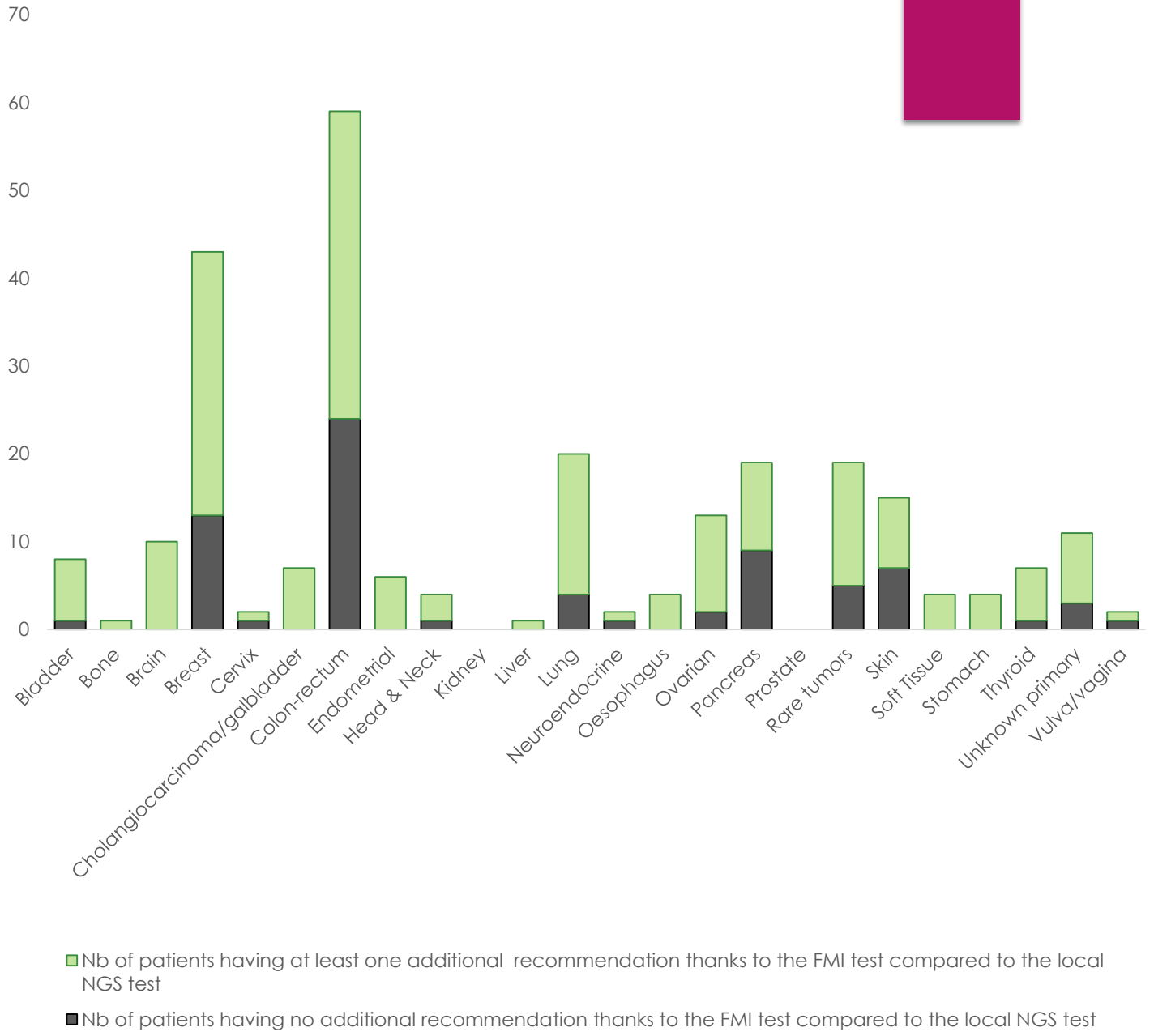
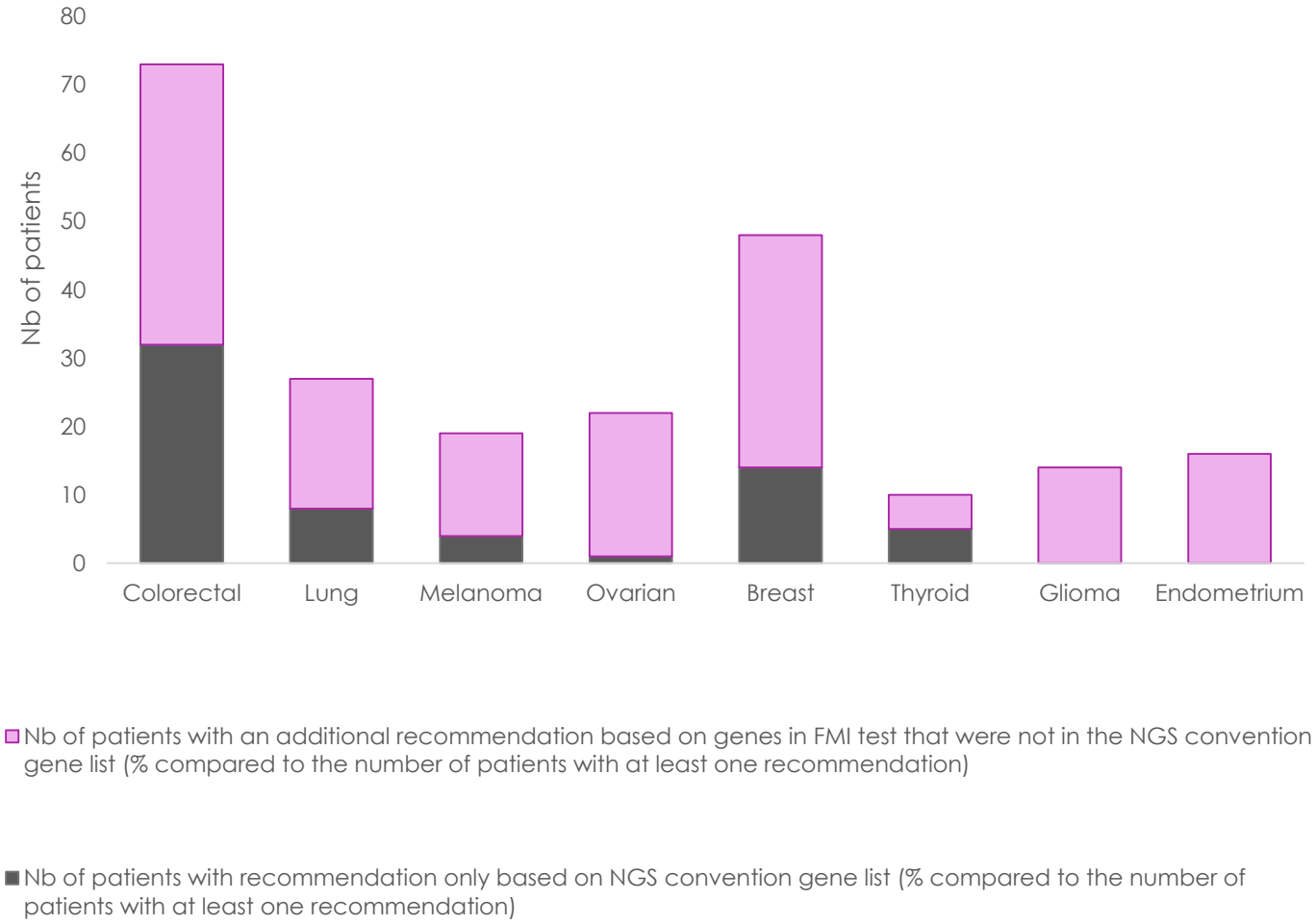
Added value of FMI test vs local NGS



Comparison FMI test versus NGS convention gene list

Number of patients /cohort who received an **additional treatment recommendation based on genes detected by the FMI test** that were not included in the NGS **convention gene list** for that indication.



Value of FMI test for patients who didn't have access to the local NGS

Number of patients who received at least one MTB treatment recommendation thanks to the FMI test

Cohorts	Nb of patients having at least one recommendation thanks to the FMI test
Bladder	21
Brain	4
Breast	50
Cervix	7
Cholangiocarcinoma/galbladder	33
Colon-rectum	14
Endometrial	10
Head & Neck	9
Kidney	6
Liver	1
Lung	7
Neuroendocrine	2
Oesophagus	4
Ovarian	9
Pancreas	28
Prostate	6
Rare tumors	46
Skin	4
Soft Tissue	15
Stomach	14
Thyroid	3
Unknown primary	19
Vulva/vagina	3
TOTAL	**315**

MTB recommendation uptake

	Nb of patients	Percentage
Pts with MTB treatment recommendation	**629**	**100%**
Nothing beyond SOC or treatment already received	21	3%
Pts where MTB treatment recommendation was <u>followed</u>	**123**	**20%**
Molecular guided therapy	91	74%
Immune checkpoint inhibitors	32	26%
Pts where MTB treatment recommendation <u>was not followed</u>	**485**	**77%**
Not yet in FU	4	0,8%
Patient Choice	21	4%
Physician Decision	116	24%
Patient Ineligible for recommended treatment	133	27%
No disease progression	*50*	
Palliative care	*13*	
No treatment due to liver failure/renal insufficiency	*2*	
Treatment unavailable	109	22%
Death	77	16%
Lost to follow-up	20	4%

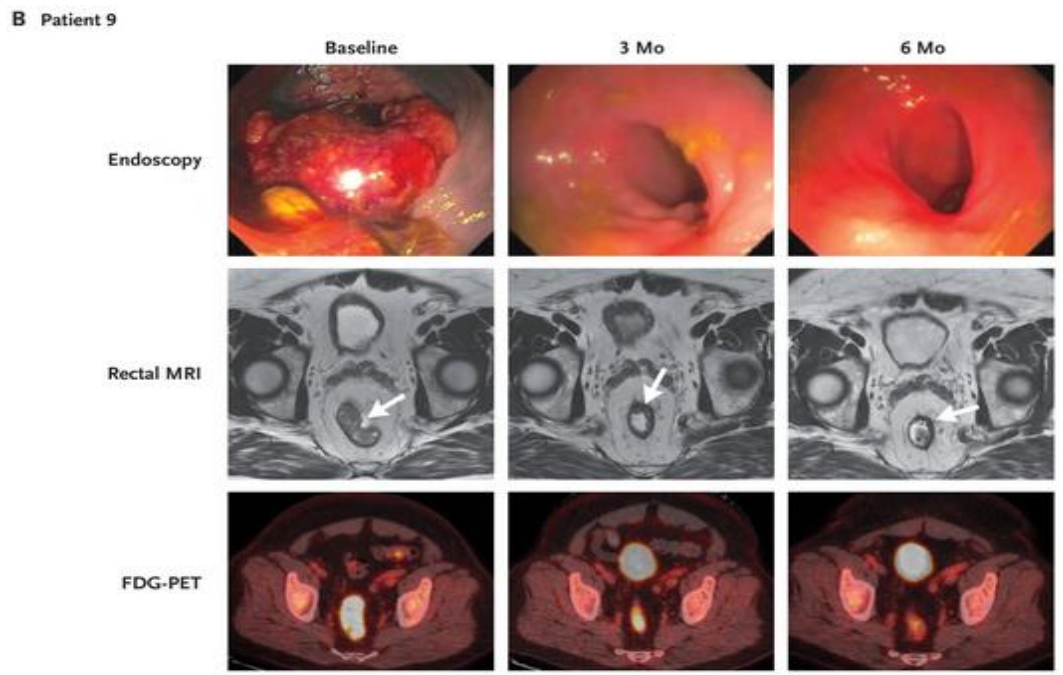
Conclusion

- Comprehensive NGS outperforms reimbursed NGS in identifying actionable mutations
  - Comprehensive NGS identifies actionable mutations for cancers without a reimbursed NGS
  - Comprehensive NGS identifies additional actionable mutations in cancers with reimbursed NGS
- A majority of patients received at least one MTB recommendation for therapy
- A minority of patients with at least one MTB recommendation have been treated according to the received MTB recommendation
  - Implementing comprehensive NGS earlier in the patient journey might increase the impact

Role of NGS in a neoadjuvant setting

- **Targeted therapy for actionable gene fusions in sarcoma and other cancers**
- **Immunotherapy**

MSI-H locally advanced rectal cancer



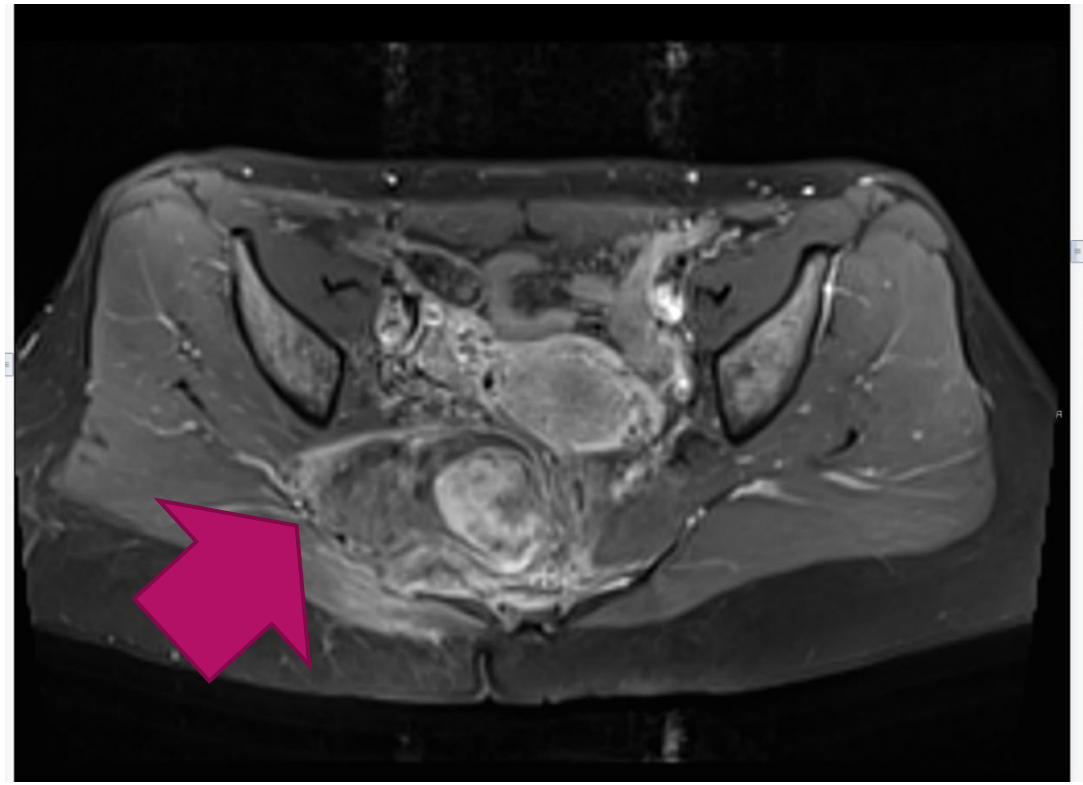
Cercek A, et al. N Engl J Med. 2022 Jun 23;386(25):2363-2376

Neoadjuvant options, targeted therapy

- **Female, 40**
- **Gluteal MPNST** involving bone and soft tissue and sciatic nerve, unresectable unless severe morbidity (12/21)
- **Important pain problem, Tradonal**
- **NGS: Somatic RET exon 12-KIF5B exon fusion**
- **Neoadjuvant chemotherapy Epi-ifo: SD**
- **Retsevmo (Selpercatinib)**, (Thyroid and NSCLC approved)
- **PR and resolution of pain, free of pain medication**
- **Continued FU to possible surgery**

Neoadjuvant options, Targeted therapy

02/03/2022



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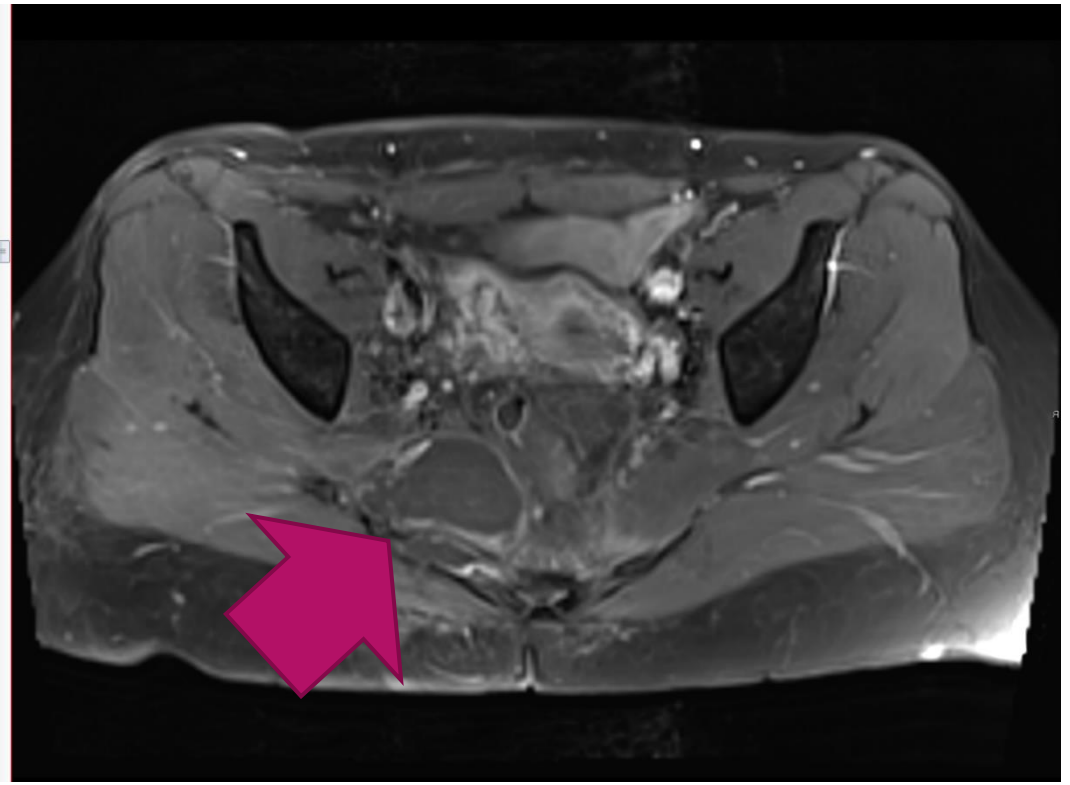


Approved targeted therapies

https://www.cancer.gov/about-cancer/treatment/

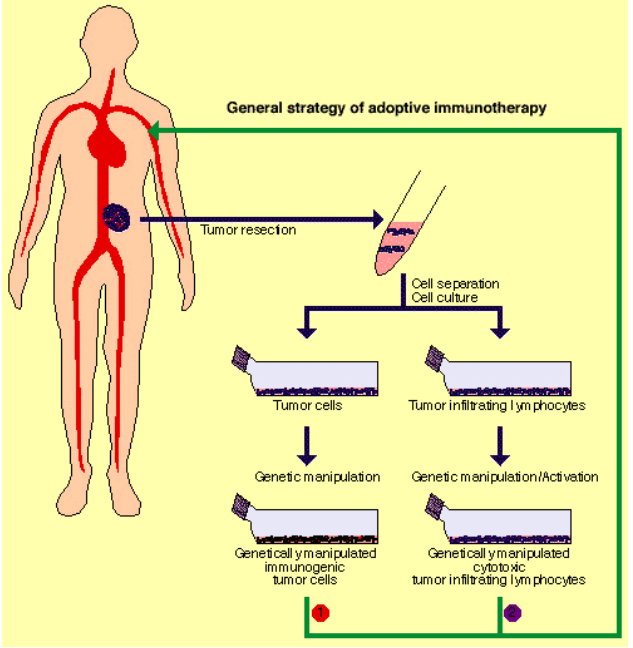
How to copy therapies from more frequent cancers to rare cancers

- Randomized controlled trials may be infeasible
- Extrapolating evidence from targeted therapies used for common cancers to rare biomarker-defined cancers
  - Relevance of biomarkers might differ from one tissue type to another
  - Extrapolation of treatments from adult to pediatric populations has been used, and guidelines exist
  - Extrapolation from common to rare cancers sharing the same predictive biomarker has also been documented without guidelines (Dabrafenib)
- European Medicines Agency (EMA) extrapolation framework (for medicines in general)
- Statistical recommendations for extrapolation
  - adaptive designs, including Bayesian approaches using prior information from the common cancer

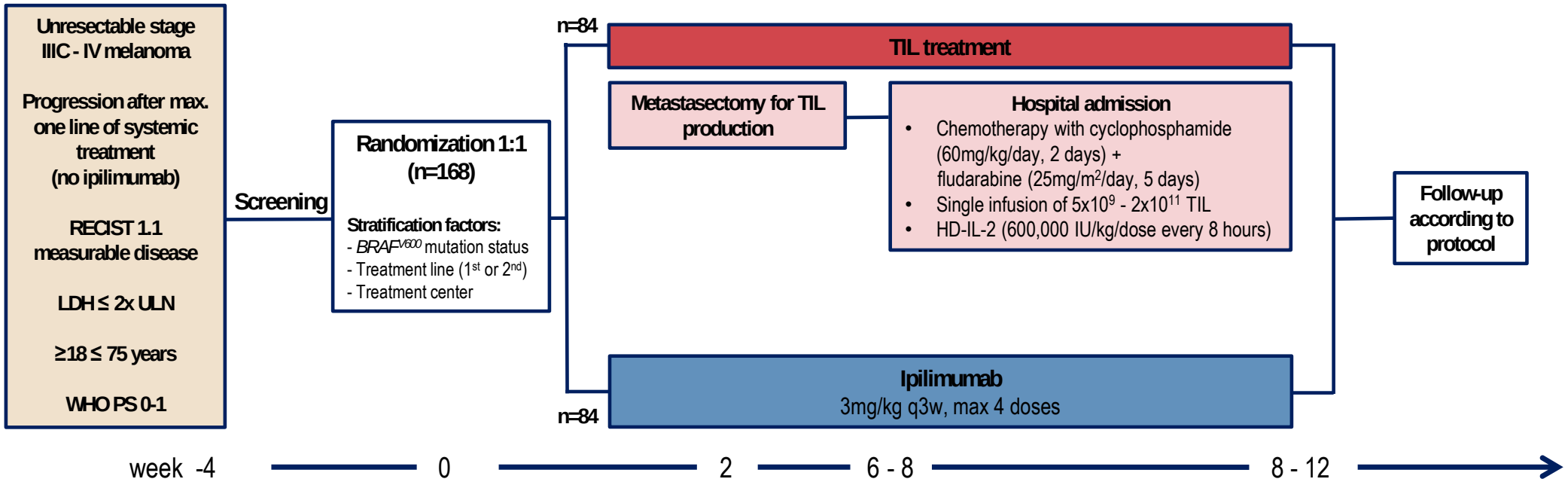
Cho D, Cheyne S, Lord SJ, Simes J, Lee CK. BMJ Open. 2022 Jul 12;12(7):e058350

Further progress can be made

- **Adequate financing for comprehensive somatic NGS**
- **Move up NGS to localized and locoregional cancer before any therapy**
- **Mutanome-directed cell therapies**



Trial design

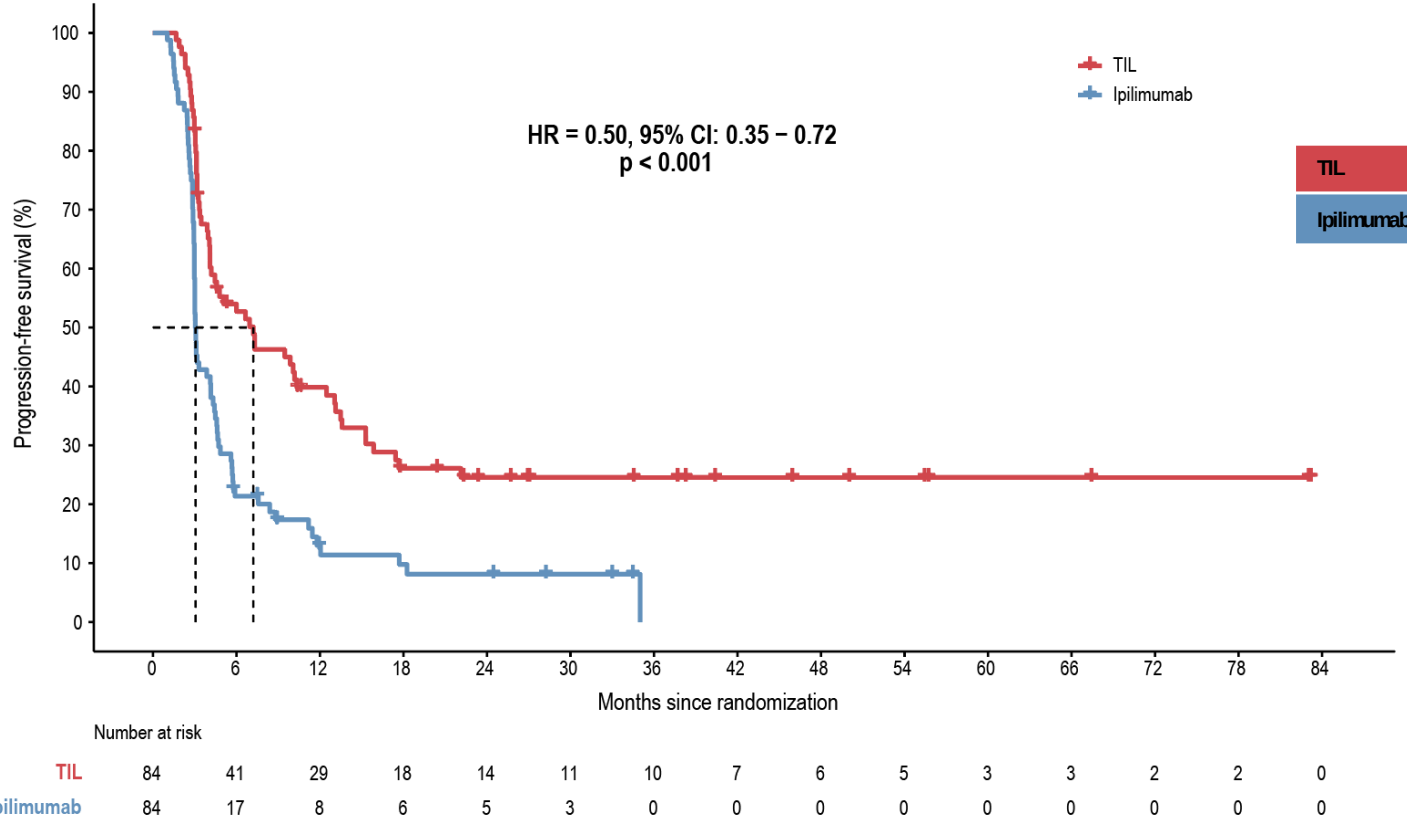


Primary endpoint: Progression-free survival (PFS) according to RECIST 1.1 per investigator review in the intention-to-treat population (ITT)*

*Using the stratified (unweighted) log-rank test and the stratified cox regression model. The study was considered to be positive when PFS after TIL is significantly longer than ipilimumab, based on the log-rank test with a two-sided p-value below 0.05.

Results (1)

Progression-free survival according to RECIST 1.1 in the ITT population



	Median follow-up (months)	Median PFS (months)	95% CI	6 month PFS (%)	95% CI
TIL	33.5	7.2	4.2 - 13.1	52.7	42.9 - 64.7
Ipilimumab	33.0	3.1	3.0 - 4.3	21.4	14.2 - 32.2

PARIS 2022 ESMO congress

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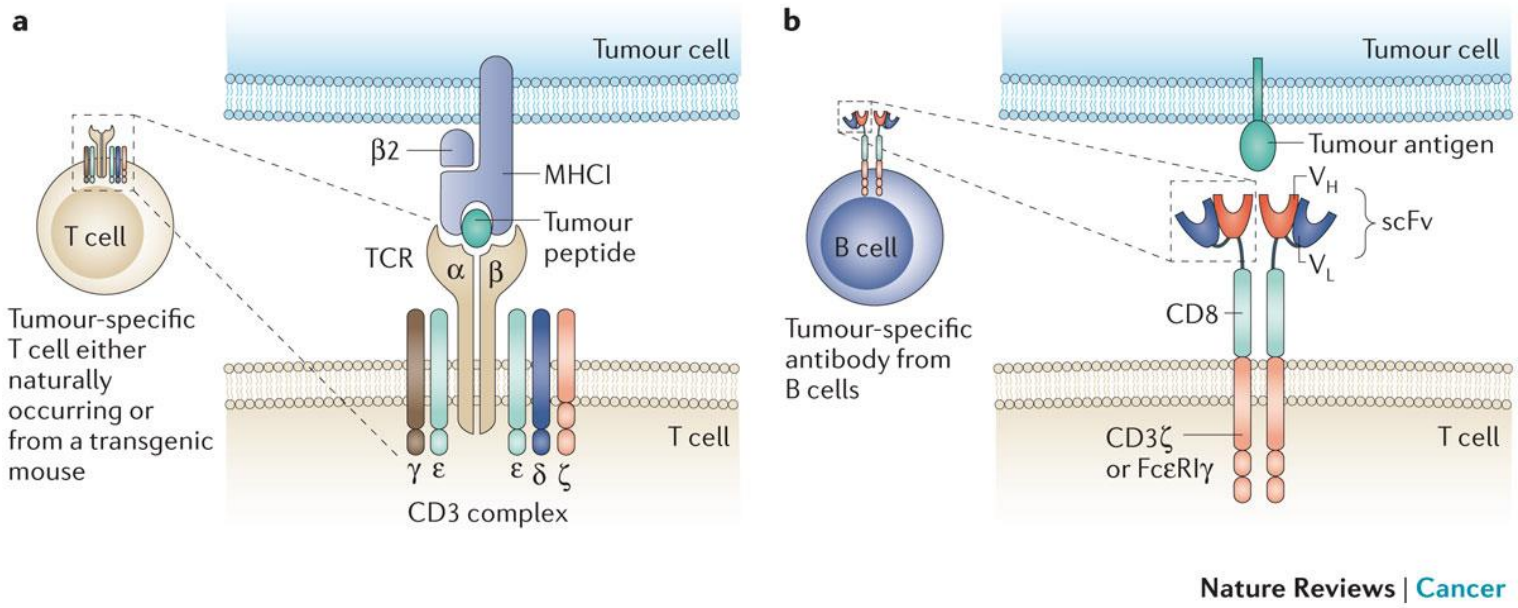
Genetically manipulated T-cells



Original T-cell receptors

Chimeric antigen receptors or CAR

M. Kershaw, Nature Reviews Cancer 13, 525-41, 2013

Mutanome-directed cell therapies

- **Based on immunogenic mutations (mutanome, WGS)**
  - **CAR-T cells recognizing immunogenic epitopes**
  - **Recruit and expand autologous T-cells reactive to immunogenic epitopes**

- **Only two studies are running in Belgium, three if counting dendritic cell vaccination !**
  - **NEO-PTC-01 in Patients With Advanced or Metastatic Melanoma**
    - **Biontech, UZBrussel;** NCT04625205
  - **A Phase 1/2, First-in-Human, Open-Label, Two-Part Clinical Trial of TK-8001 in Patients With HLA-A*02:01 Genotype and Advanced-Stage/Metastatic MAGE-A1+ Solid Tumors (IMAG1NE)**
    - **UZGent;** NCT05430555
  - **Autologous Dendritic Cell Vaccination in Mesothelioma (MESODEC)**
    - **UZA;** NCT02649829

- **TALK to your hematologist! It is the next stage for progress**