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DISCUSSION

The Rome Trial - From Histology to Target: the Road to Personalize Targeted Therapy and Immunotherapy

A. Botticelli and colleagues

Application of ProvGigaPath, an open-weight billion-parameter foundation model based on a novel vision transformer architecture for cancer mutation prediction and TME analysis

C. Bifulco and colleagues

Federica Di Nicolantonio

University of Torino, Department of Oncology & Candiolo Cancer Institute, FPO – IRCCS

DECLARATION OF INTERESTS

Federica Di Nicolantonio

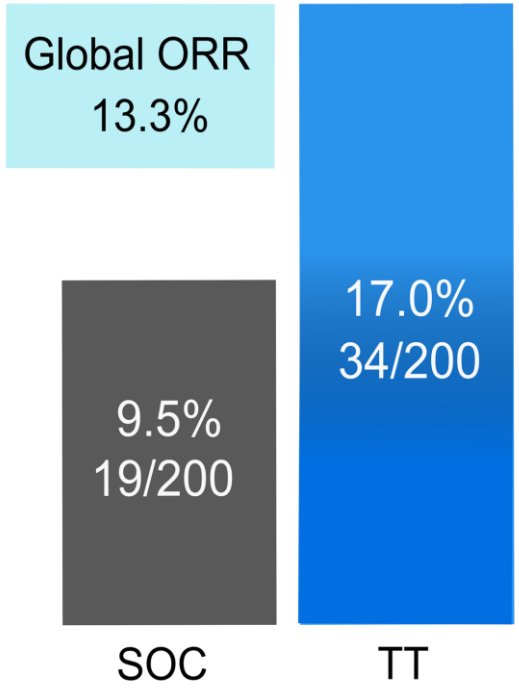
Received speaker's fees: Illumina Inc, Pierre Fabre

Research funding: The Italian Association for Cancer Research (Fondazione AIRC), Italian Ministry of Health.

The Rome Trial - From Histology to Target

The study met its ORR Primary endpoint

Best response	Arm A Standard of Care N: 200 (%)	Arm B Targeted Therapy N: 200 (%)	p value
CR	0	5 (2.5%)	
PR	19 (9.5%)	29 (14.5%)	
SD	35 (17.5%)	36 (18.0%)	
PD	147 (73.0%)	130 (65.0%)	
ORR	**9.5% [5.8-14.4]**	**17.0% [12.1-22.9]**	**0.027**



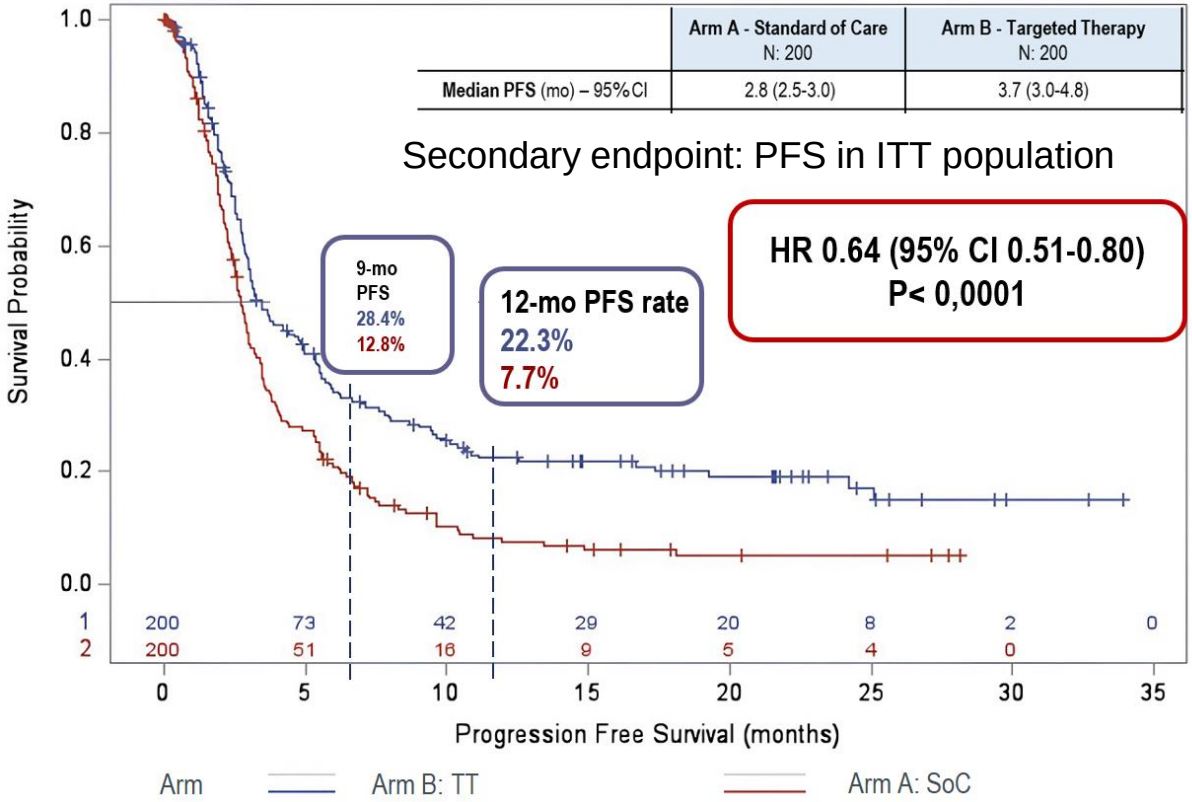
The Rome Trial - From Histology to Target

Nov 2020 – Aug 2023:
N: 1794 screened patients

N: 897 patients discussed in MTB

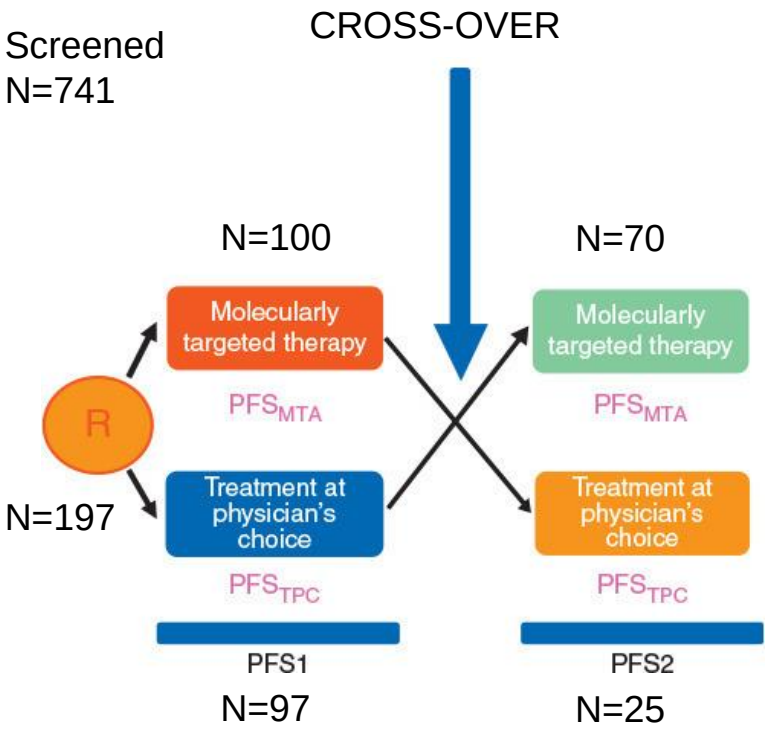
127 weekly MTB discussions

400 randomized patients

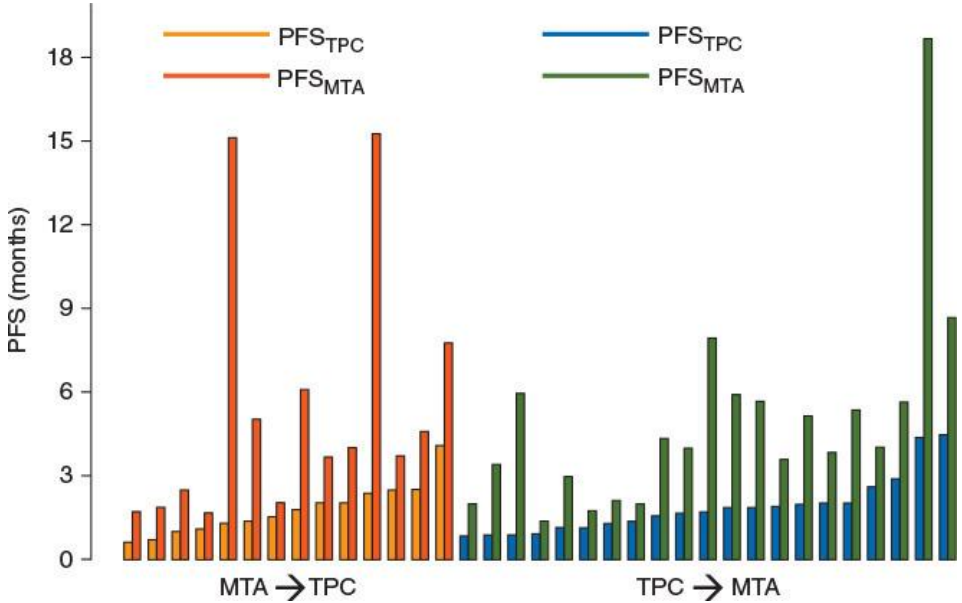


Andrea Botticelli

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA)



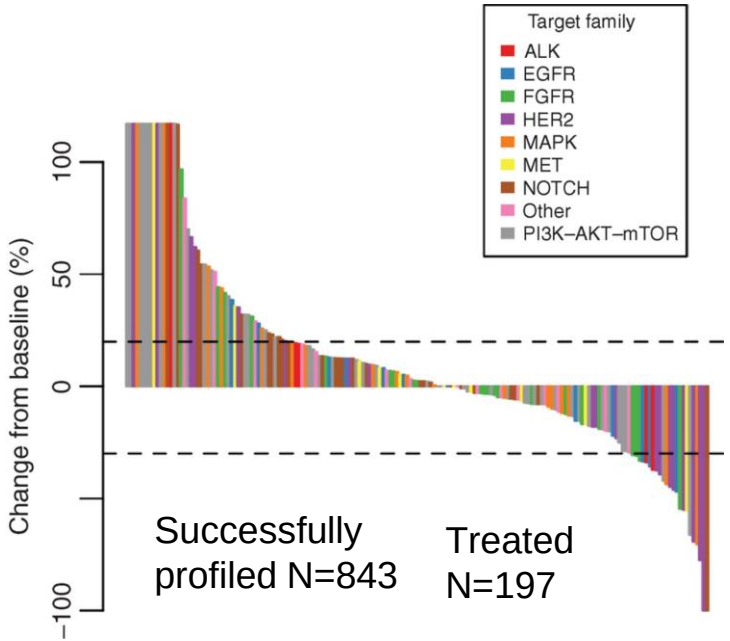
Negative for Primary Endpoint (PFS), but cross-over shows benefit in a patient subgroup



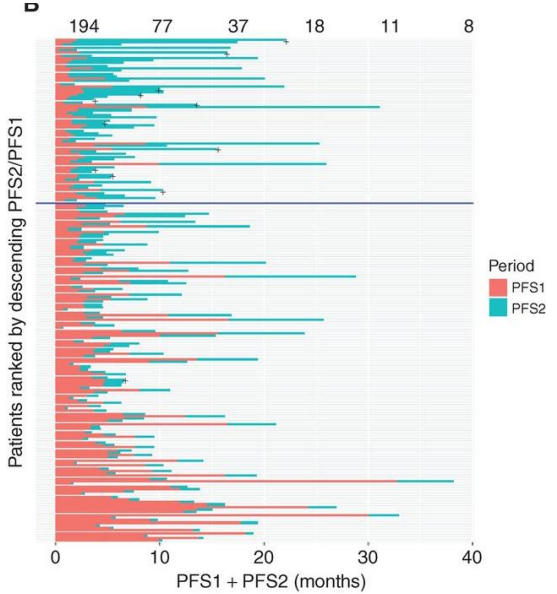
Le Tourneau et al. Lancet Oncol 2015 Oct;16(13):1324-34.
Belin L et al., Annals of Oncology 28: 590–596, 2017

High-Throughput Genomics and Clinical Outcome in Hard-to-Treat Advanced Cancers: the MOSCATO 01 Trial

% patients presenting progression-free survival (PFS) on matched therapy (PFS2) 1.3-fold longer than the PFS on prior therapy (PFS1).



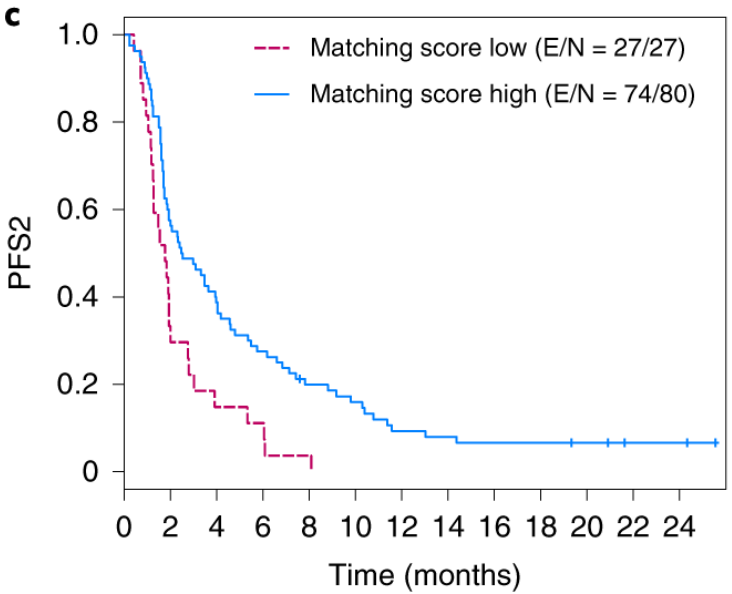
The PFS2/PFS1 ratio was >1.3 in 33% patients (63/193).



Massard C et al,Cancer Discov (2017) 7 (6): 586–595.

Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial

Screened N=303
Treated N=107



159 drugs given, 115 off-label, 22 on-label and 22 investigational

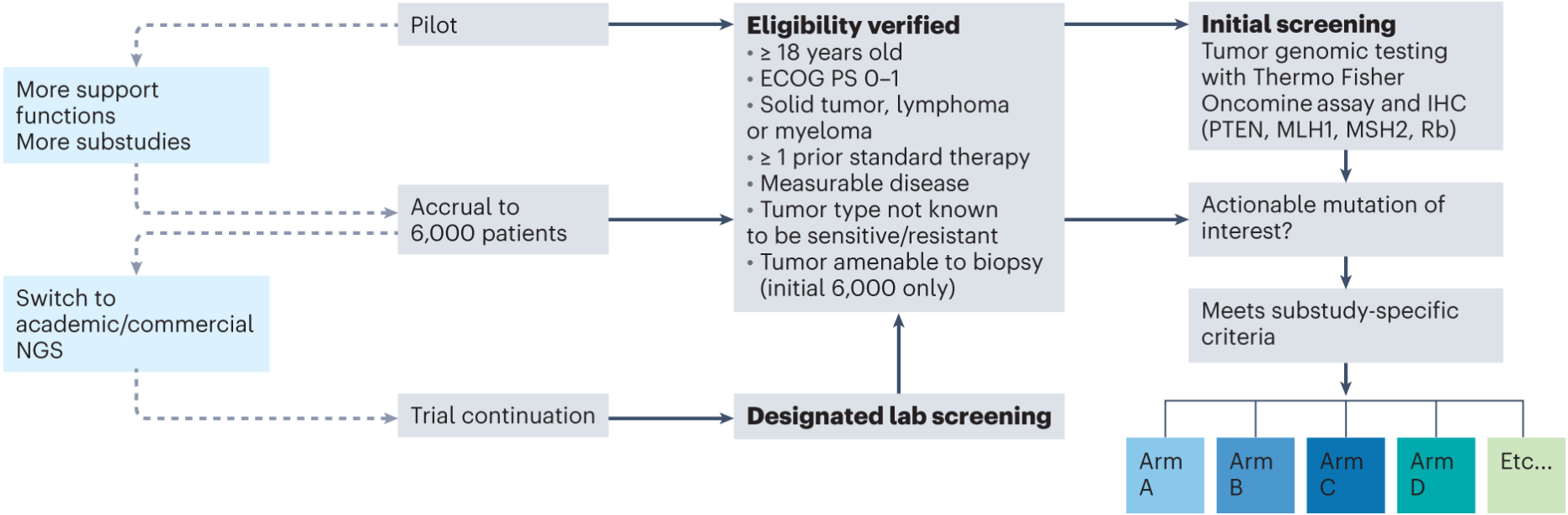
Drug targets (number of patients who received a drug that impacted designated target)***	
BRAF	2
CDK4/6	3
HER pathway (EGFR/ERBB2/ERBB3/ERBB4)	17
FGFR	9
MEK	17
MET	11
PARP	1
Pan RAF	1
PI3K/AKT/mTOR	23
RET	4
VEGFR	32
WNT	5
HORMONAL RECEPTOR	2
IMMUNE	7
OTHER	22

Rodon J et al., Nat Med. 2019 May;25(5):751-758.

The NCI-MATCH trial: lessons for precision oncology

Screened ≈ 6000; Treated N=1593

7 of the initial 27 substudies (of 38 total) in NCI-MATCH have positive outcome



Peter J O'Dwyer et al., Nat Med . 2023 Jun;29(6):1349-1357.

Federica Di Nicolantonio

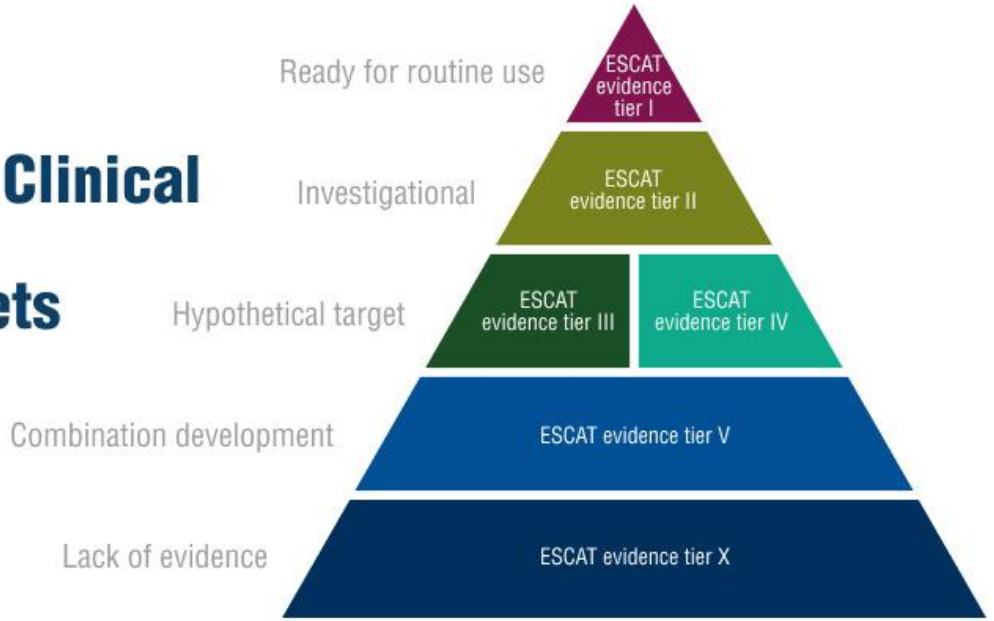
The NCI-MATCH trial

Arm	Molecular aberration	Treatment	*N*	*N* eval.	Number of responses (%)	6-month PFS	Met endpoint?
F	**ALK fusions**	**Crizotinib**	**5**	**4**	**2 (50.0%)**	**25%**	**Yes**
H	**p.Val600Glu or p.Val600Lys mutations**	**Dabrafenib/ trametinib**	**35**	**29**	**11 (37.9%)**	**68.4%**	**Yes**
K2	**FGFR mutation/fusion**	**Erdafitinib**	**35**	**21**	**3 (14.3%)**	**36.8%**	**Yes**
Q	*HER2* amplify.	Ado-trastuzumab emtansine	38	36	2 (5.6%)	23.6%	No
Y	***AKT* mutations**	**Capivasertib**	**35**	**35**	**10 (28.6%)**	**50.0%**	**Yes**
Z1D	**dMMR status**	**Nivolumab**	**47**	**42**	**15 (35.7%)**	**51.3%**	**Yes**
Z1F	**PIK3CA mutation**	**Copanlisib**	**35**	**25**	**4 (16.0%)**	**38%**	**Yes**
Z1K	***AKT* mutation**	**Ipatasertib**	**35**	**26**	**6 (23.1%)**	**52.4%**	**Yes**

Ranking genomic alterations as targets for cancer precision medicine

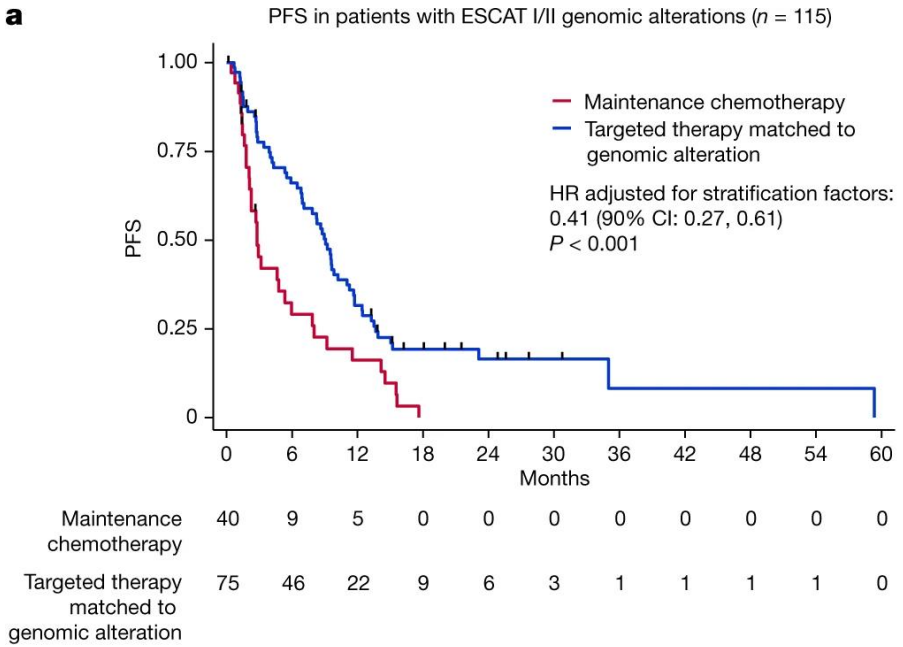
ESCAT

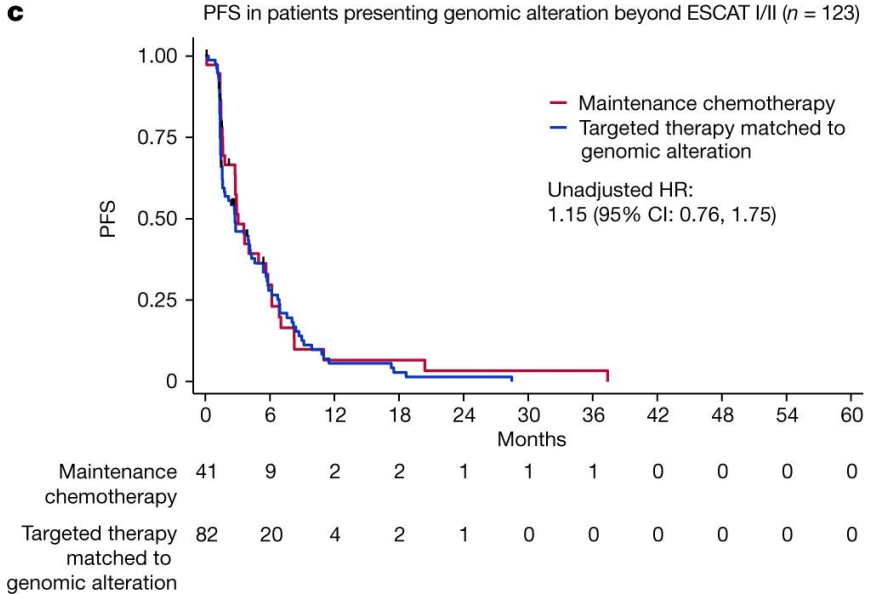
ESMO Scale for Clinical Actionability of Molecular Targets



Mateo J et al., Ann Oncol . 2018 Sep 1;29(9):1895-1902.

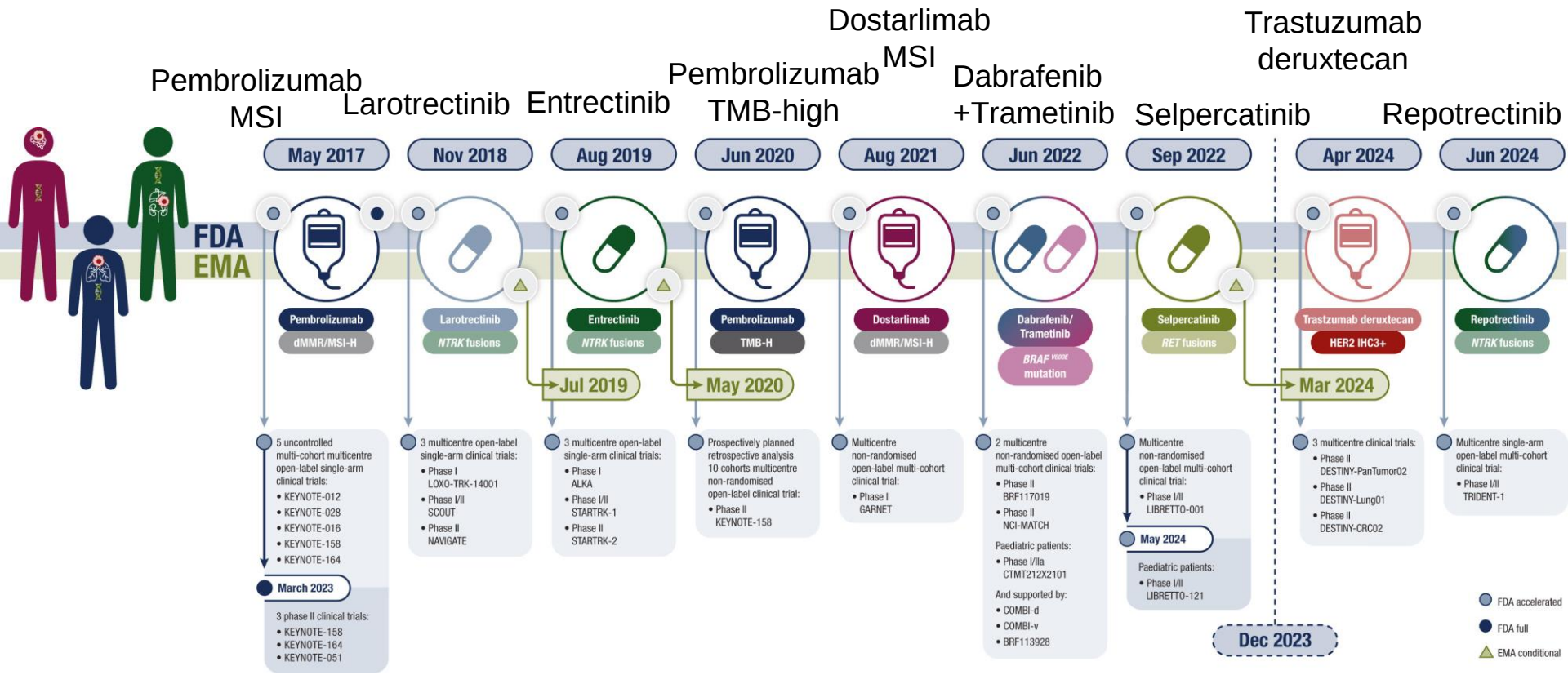
ESCAT I/II genomics alterations to select treatment for patients with metastatic breast cancer





Andre F., et al., Nature volume 610, pages343–348 (2022)

TUMOR-AGNOSTIC APPROVED DRUGS



Westphalen, C.B. et al. The ESMO Tumour-Agnostic Classifier and Screener (ETAC-S): a tool for assessing tumour-agnostic potential of molecularly guided therapies and for steering drug development. Ann Oncol 2024

The ROME trial: Available targeted treatments and pathways

Targeted Therapy	Target pathways
Erlotinib	EGFR mutations
Trastuzumab, pertuzumab, TDM1, lapatinib	ERBB2 amplification/mutations
Everolimus	mTOR mutations, AKT mutations
Vemurafenib, cobimetinib	BRAF mutations
Alectinib, brigatinib	ALK traslocations, RET alterations
Pralsetinib*, selpercatinib*	RET alterations
Palbociclib	CDK4/6, CDKN2A/B alterations
Ponatinib	Bcr-abl traslocations
Vismodegib	SMO/PTCH1 mutations
Itacitinib	JAK mutations
Pemigatinib	FGFR1/2/3 alterations
Ipatasertib, alpelisib*	Pi3k, AKT, PTEN alterations
Entrectinib*	NTRK1/2/3 fusions, ROS1
Tepotinib	METex14, MET alterations
Talazoparib	BRCA 1/2 mutations, HRD
Immunotherapy	**Biomarkers**
Nivolumab, ipilimumab, atezolizumab	MSI, high TMB**

* Drugs included in the V4 protocol amendment in 10/2022
** high TMB defined as >10 mut/mb in solid and/or liquid NGS

ESMO Recommendations for the use of tumour NGS in 2024

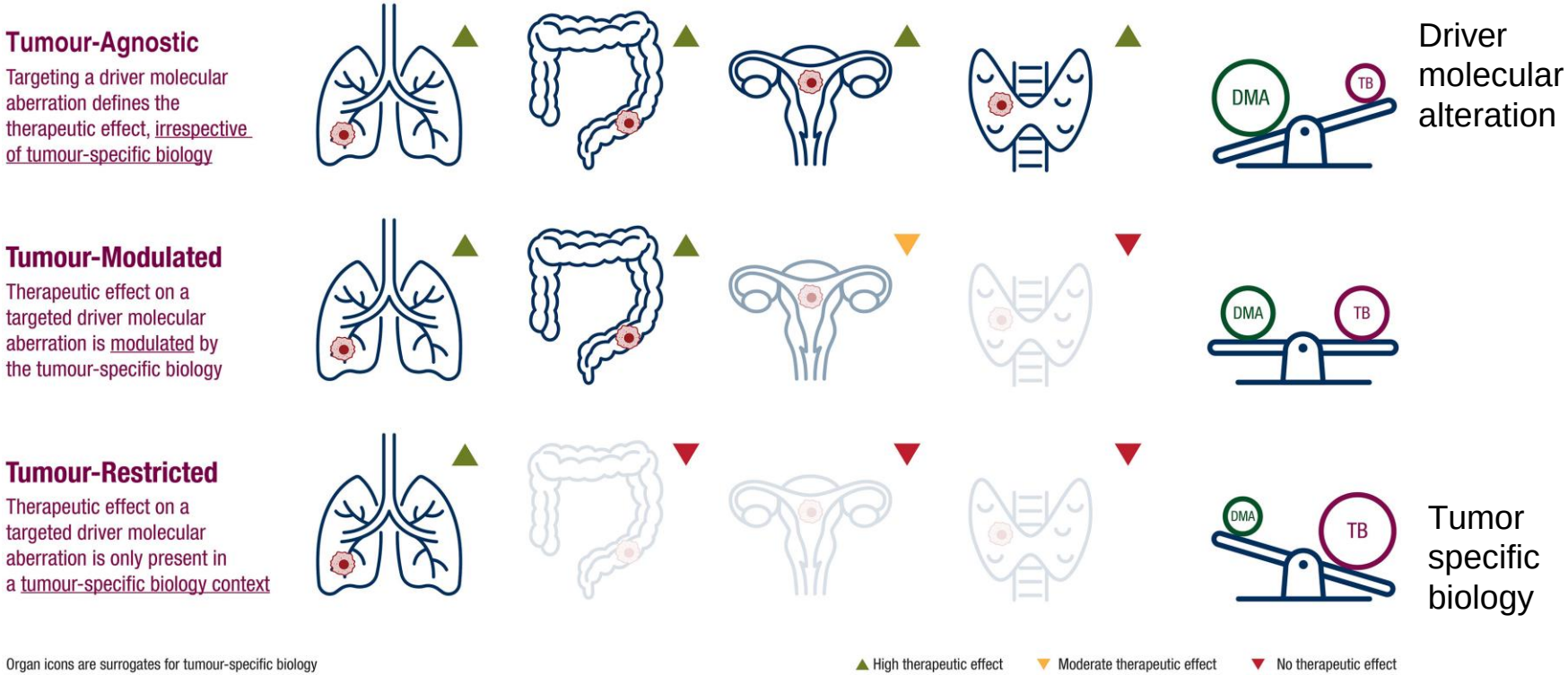
ESMO recommends to carry out **tumour NGS** to detect **tumour-agnostic alterations** in patients with **advanced cancers**, in countries where **tumour-agnostic targeted therapies are accessible (**cost-effectiveness and fusions are integrated in the panel)

The ESMO PMWG recommends running tumour NGS in patients with
advanced non-squamous NSCLC;
breast;
colorectal;
prostate;
ovarian cancer;
advanced cholangiocarcinoma;
GIST;
sarcoma;
thyroid cancer;
and unfavourable CUP.

Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group

Mosele MF et al. Annals of Oncology. 2024 ; Vol. 35, No. 7. pp. 588-606.

Proposed ESMO Tumour-Agnostic Classifier



Westphalen, C.B. et al. The ESMO Tumour-Agnostic Classifier and Screener (ETAC-S): a tool for assessing tumour-agnostic potential of molecularly guided therapies and for steering drug development. Ann Oncol 2024

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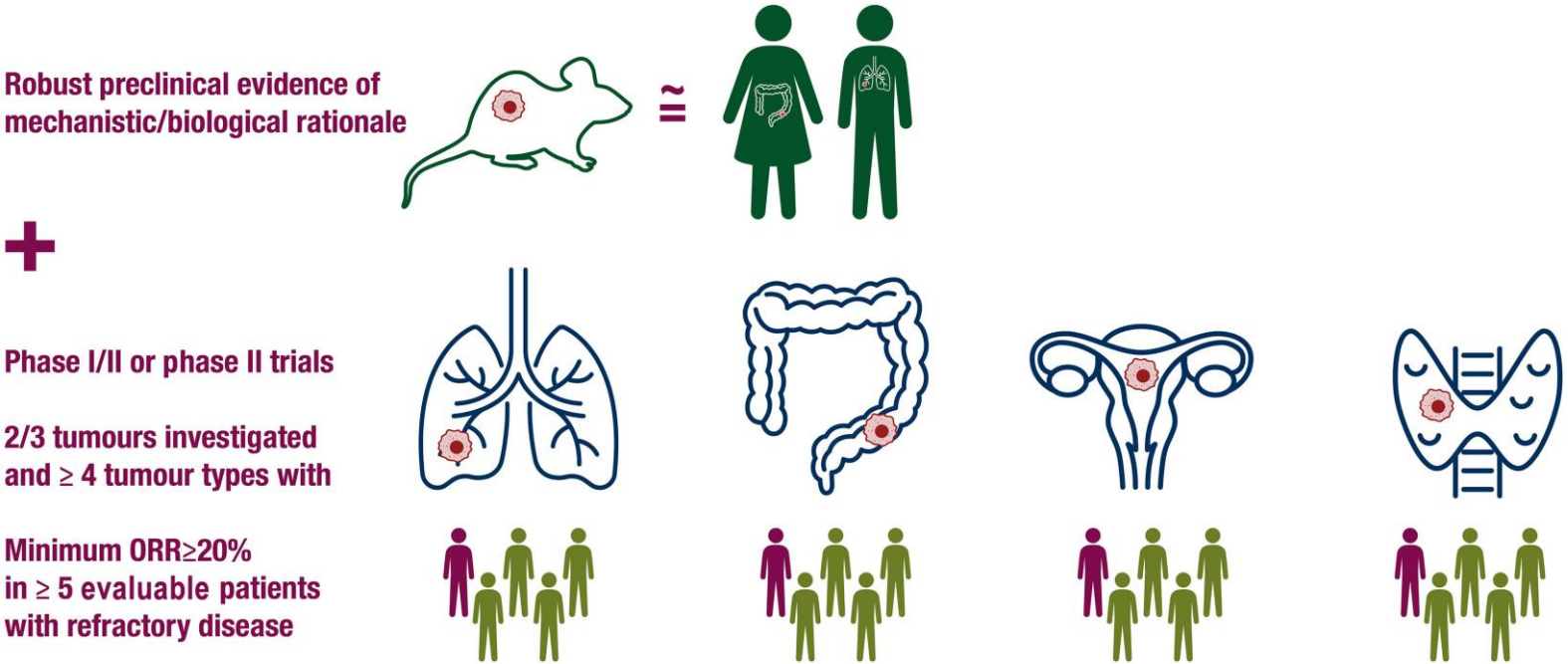
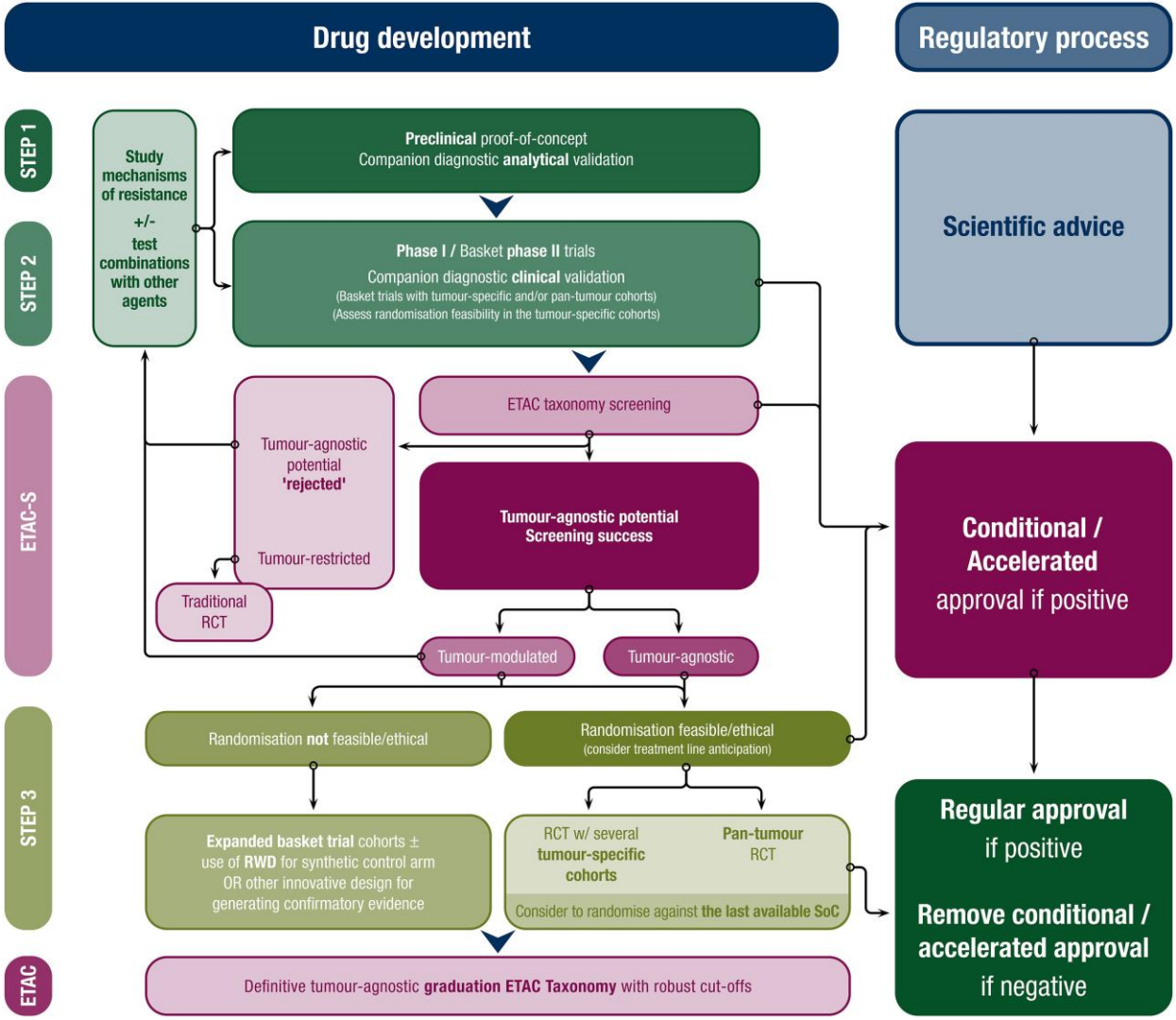
ETAC-S Proposed minimum eligibility requirements for tumour-agnostic potential



Westphalen, C.B. et al. The ESMO Tumour-Agnostic Classifier and Screener (ETAC-S): a tool for assessing tumour-agnostic potential of molecularly guided therapies and for steering drug development. Ann Oncol 2024

Proposed tumor-agnostic drug development framework



Westphalen, C.B. et al.
The ESMO Tumour-Agnostic Classifier and Screener (ETAC-S): a tool for assessing tumour-agnostic potential of molecularly guided therapies and for steering drug development.
Ann Oncol 2024

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AI tools to perform tumor agnostic clinical trials

The Rome Trial MTB

Nov 2020 – Aug 2023:
N: 1794 screened patients

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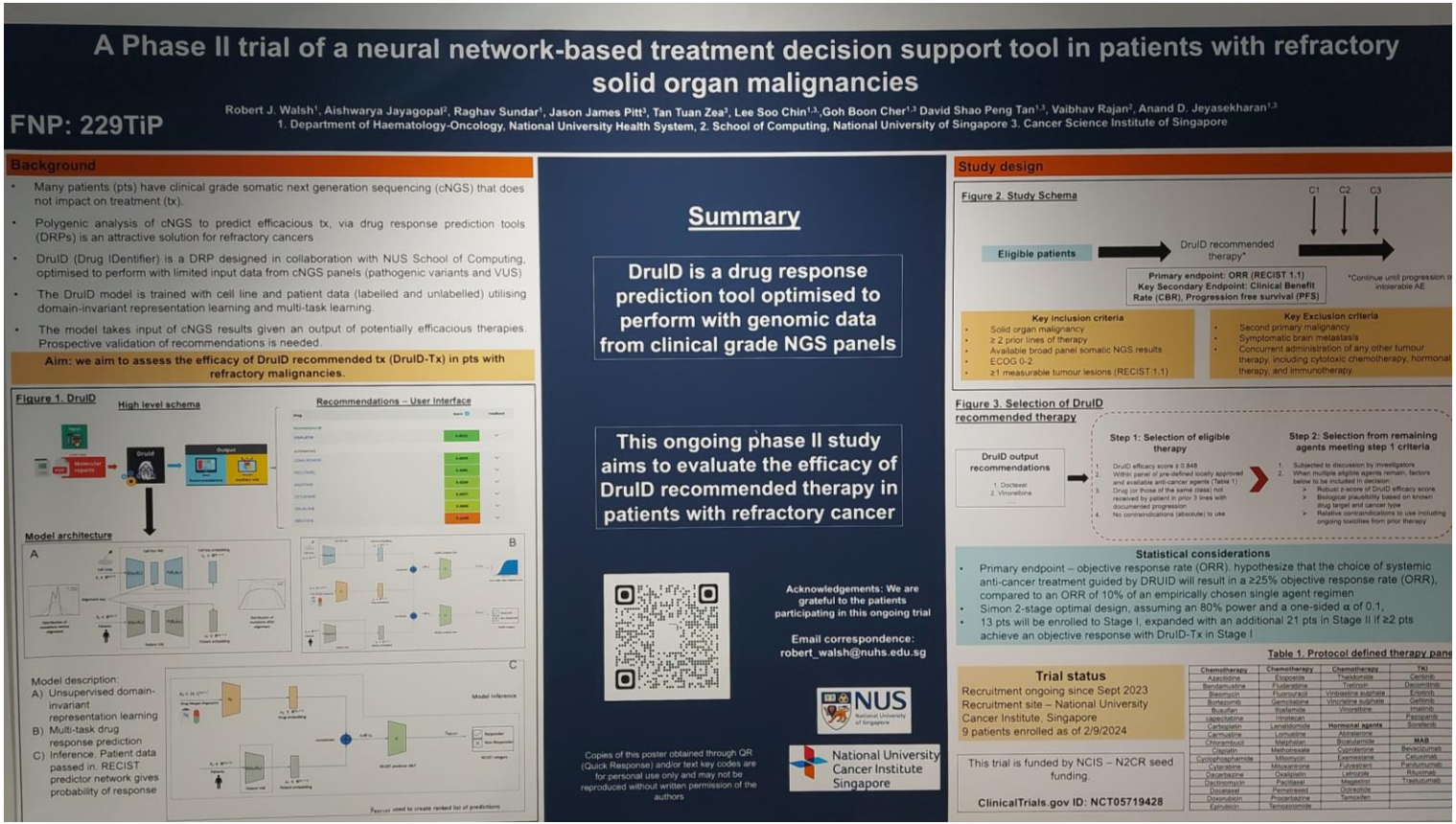
127 weekly MTB discussions

400 randomized patients



A Phase II trial of a neural network-based treatment decision support tool in patients with refractory solid organ malignancies

FNP: 229TiP

Robert J. Walsh[1], Aishwarya Jayagopal[2], Raghav Sundar[1], Jason James Pitt[3], Tan Tuan Zea[3], Lee Soo Chin[1,3],Goh Boon Cher[1,3] David Shao Peng Tan[1,3], Vaibhav Rajan[2], Anand D. Jeyasekharan[1,3]
1. Department of Haematology-Oncology, National University Health System, 2. School of Computing, National University of Singapore 3. Cancer Science Institute of Singapore

Background

- Many patients (pts) have clinical grade somatic next generation sequencing (cNGS) that does not impact on treatment (tx).
- Polygenic analysis of cNGS to predict efficacious tx, via drug response prediction tools (DRPs) is an attractive solution for refractory cancers
- DruID (Drug IDentifier) is a DRP designed in collaboration with NUS School of Computing, optimised to perform with limited input data from cNGS panels (pathogenic variants and VUS)
- The DruID model is trained with cell line and patient data (labelled and unlabelled) utilising domain-invariant representation learning and multi-task learning.
- The model takes input of cNGS results given an output of potentially efficacious therapies. Prospective validation of recommendations is needed.

Aim: we aim to assess the efficacy of DruID recommended tx (DruID-Tx) in pts with refractory malignancies.

Figure 1. DruID

High level schema

Recommendations – User Interface

Model architecture

Model description:
A) Unsupervised domain-invariant representation learning
B) Multi-task drug response prediction
C) Inference. Patient data passed in. RECIST predictor network gives probability of response

Summary

DruID is a drug response prediction tool optimised to perform with genomic data from clinical grade NGS panels

This ongoing phase II study aims to evaluate the efficacy of DruID recommended therapy in patients with refractory cancer

Acknowledgements: We are grateful to the patients participating in this ongoing trial

Email correspondence:
robert_walsh@nuhs.edu.sg

NUS National University of Singapore

National University Cancer Institute Singapore

Study design

Figure 2. Study Schema

Eligible patients → DruID recommended therapy* (C1, C2, C3)

Primary endpoint: ORR (RECIST 1.1)
Key Secondary Endpoint: Clinical Benefit Rate (CBR), Progression free survival (PFS)

*Continue until progression or intolerable AE

Key inclusion criteria

- Solid organ malignancy
- ≥ 2 prior lines of therapy
- Available broad panel somatic NGS results
- ECOG 0-2
- ≥1 measurable tumour lesions (RECIST 1.1)

Key Exclusion criteria

- Second primary malignancy
- Symptomatic brain metastasis
- Concurrent administration of any other tumour therapy, including cytotoxic chemotherapy, hormonal therapy, and immunotherapy.

Figure 3. Selection of DruID recommended therapy

DruID output recommendations
1. Doctexel
2. Vinorelbine

Step 1: Selection of eligible therapy
1. DruID efficacy score ≥ 0.848
2. Within panel of pre-defined locally approved and available anti-cancer agents (Table 1)
3. Drug (or those of the same class) not received by patient in prior 3 lines with documented progression
4. No contraindications (absolute) to use

Step 2: Selection from remaining agents meeting step 1 criteria
1. Subjected to discussion by investigators
2. When multiple eligible agents remain, factors below to be included in decision:
   - Robust z-score of DruID efficacy score
   - Biological plausibility based on known drug target and cancer type
   - Relative contraindications to use including ongoing toxicities from prior therapy

Statistical considerations

- Primary endpoint – objective response rate (ORR). hypothesize that the choice of systemic anti-cancer treatment guided by DRUID will result in a ≥25% objective response rate (ORR), compared to an ORR of 10% of an empirically chosen single agent regimen
- Simon 2-stage optimal design, assuming an 80% power and a one-sided α of 0.1,
- 13 pts will be enrolled to Stage I, expanded with an additional 21 pts in Stage II if ≥2 pts achieve an objective response with DruID-Tx in Stage I

Trial status

Recruitment ongoing since Sept 2023
Recruitment site – National University Cancer Institute, Singapore
9 patients enrolled as of 2/9/2024

This trial is funded by NCIS – N2CR seed funding.

ClinicalTrials.gov ID: NCT05719428

Table 1. Protocol defined therapy panel

Chemotherapy	Chemotherapy	Chemotherapy	TKI
Azacitidine	Enocitabine	Thalidomide	Cediranib
Bendamustine	Fludarabine	Tretinoin	Dacomitinib
Bleomycin	Fluorouracil	Vinblastine sulphate	Gefitinib
Bortezomib	Gemcitabine	Vincristine sulphate	Imatinib
Busulfan	Ifosfamide	Vinorelbine	Lapatinib
Capecitabine	Irinotecan		Pazopanib
Carboplatin	Lenalidomide	**Hormonal agents**	Sorafenib
Carmustine	Lomustine	Abiraterone	
Chlorambucil	Melphalan	Bicalutamide	**MAB**
Cisplatin	Methotrexate	Cyproterone	Bevacizumab
Cyclophosphamide	Mitomycin	Exemestane	Cetuximab
Cytarabine	Mitoxantrone	Fulvestrant	Panitumumab
Dacarbazine	Oxaliplatin	Letrozole	Rituximab
Dactinomycin	Paclitaxel	Megestrol	Trastuzumab
Docetaxel	Pemetrexed	Octreotide	
Doxorubicin	Procarbazine	Tamoxifen	
Epirubicin	Temozolomide		

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Robert J Walsh, ESMO 2024, Poster Presentation Number 229TiP, NCT05719428

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DISCUSSION

The Rome Trial - From Histology to Target: the Road to Personalize Targeted Therapy and Immunotherapy

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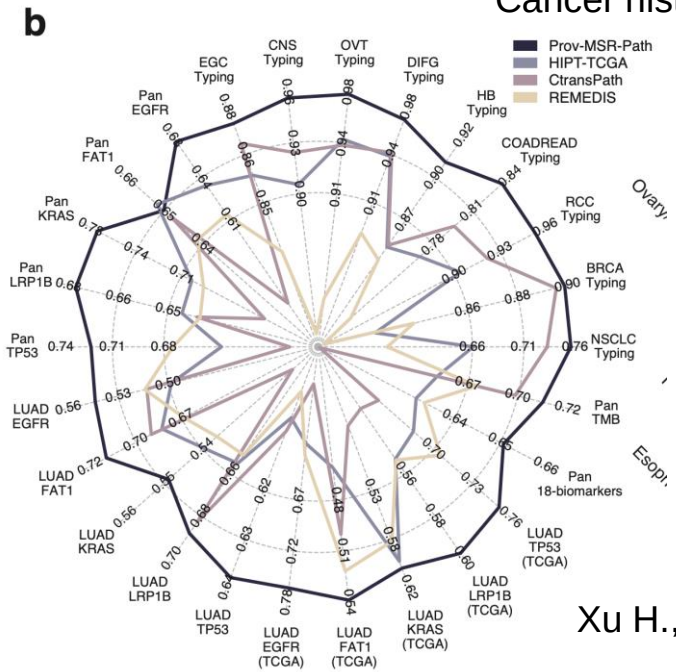
Application of ProvGigaPath, an open-weight billion-parameter foundation model based on a novel vision transformer architecture for cancer mutation prediction and TME analysis

C. Bifulco and colleagues

ProvGigaPath, digital pathology for cancer mutation prediction

C. Bifulco and colleagues

Cancer histology, molecular alterations



Self Supervised Transformer based Models

Model	Param. (M)	Algorithm	Training Data Source	Tiles (M)	Slides (K)	Organs
CTransPath [3]	28	SRCL	TCGA, PAIP	16	32	25
Phikon [7]	86	iBOT	TCGA	43	6	13
UNI [10]	303	DINOv2	MGB	100	100	20
Virchow [12]	631	DINOv2	MSKCC	2,000	1,488	17
Campanella et al. [13]	22	DINO	MSHS	1,600	423	42
Campanella et al. [13]	303	MAE	MSHS	3,200	423	42
Rudolf-V [16]	304	DINOv2	Multicenter	1,200	134	14
Prov-GigaPath [17]	1,135	DINOv2	PHS	1,300	171	31

arxiv.org/pdf/2407.06508v3

Xu H., et al., Nature 2024 Jun;630(8015):181-188.

Presented by Carlo Bifulco at ESMO 2024

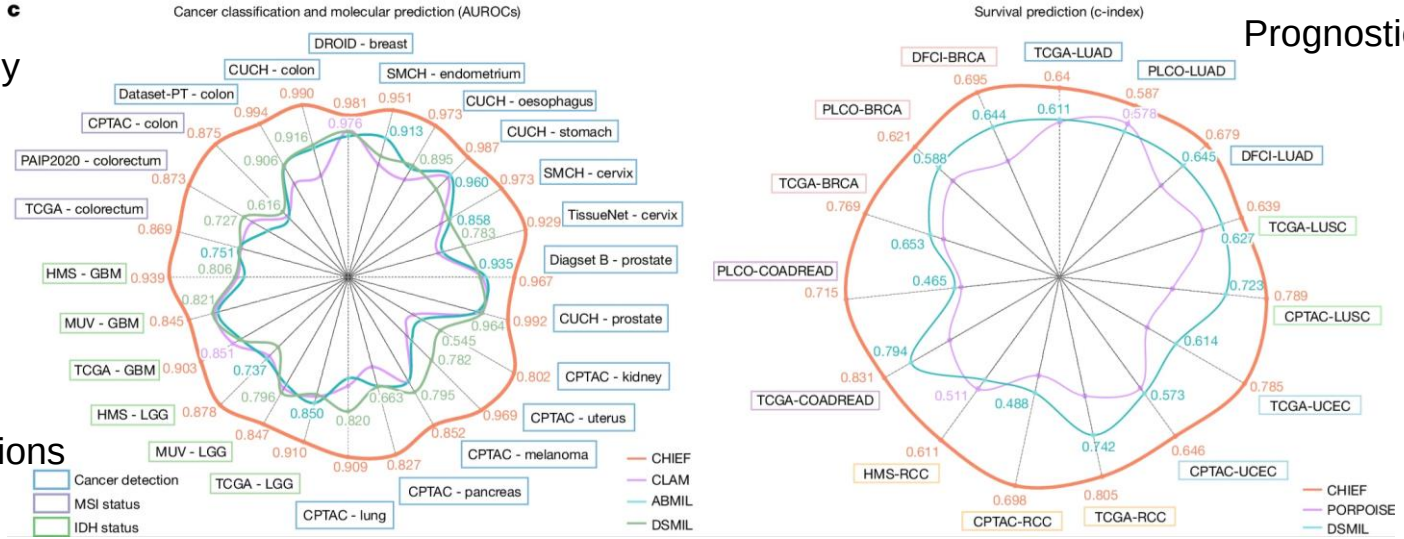
Predicting cancer diagnosis and prognosis by applying AI to pathology slides

Clinical Histopathology Imaging Evaluation Foundation (CHIEF) model: weakly supervised machine learning framework to extract pathology imaging features for systematic cancer evaluation

Cancer histology

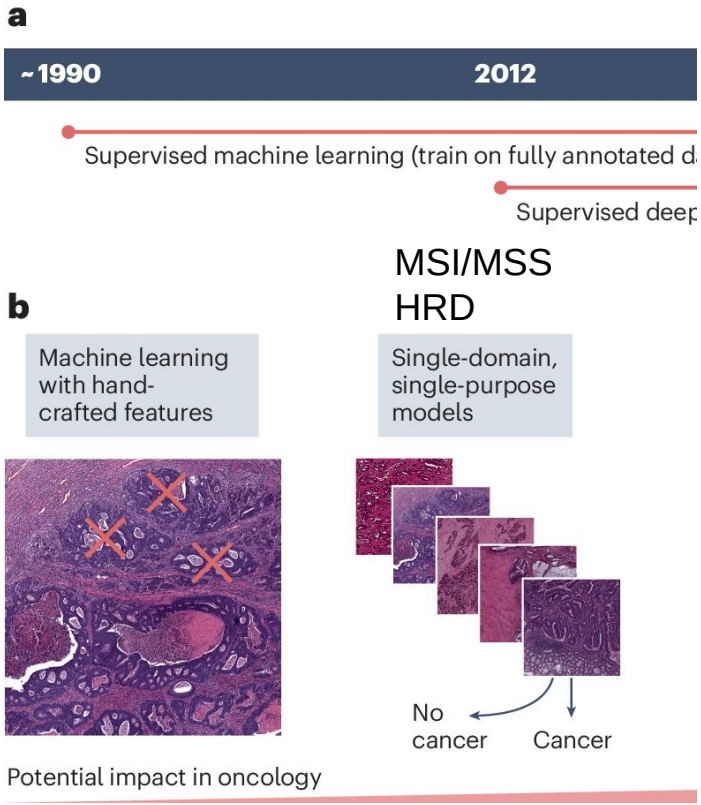
molecular alterations

Prognostic impact



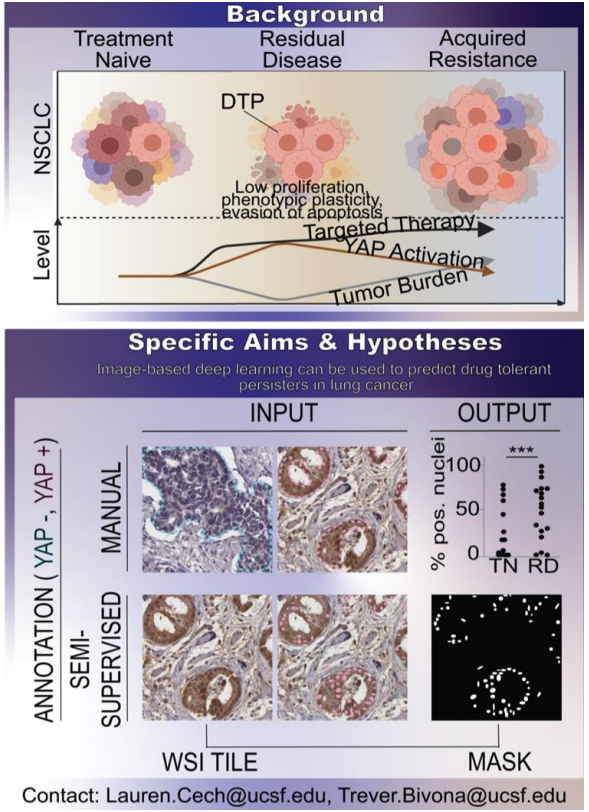
Wang, X., Zhao, J., Marostica, E. et al. A pathology foundation model for cancer diagnosis and prognosis prediction. Nature Sep 4, 2024. https://doi.org/10.1038/s41586-024-07894-z

Progress of AI in medical imaging



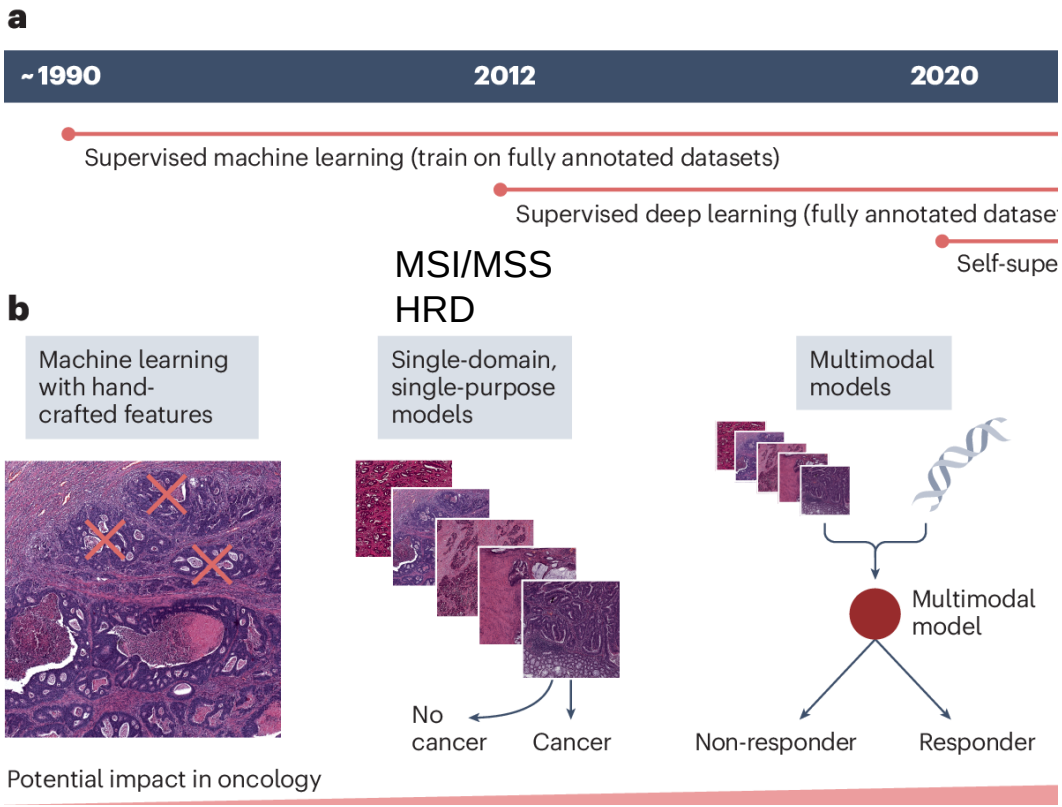
Perez-Lopez, et al., Nat Rev Cancer. 2024 Jun;24(6):427-441.

Predicting drug tolerant persister cells by AI

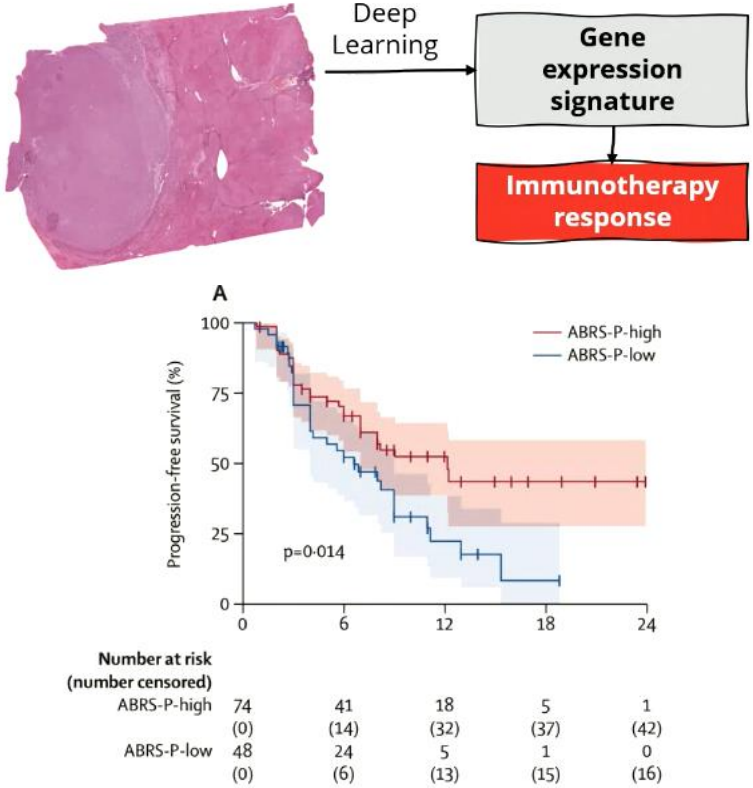


Lauren Cech, ESMO 2024, Poster Presentation Number 189P

Progress of AI in medical imaging

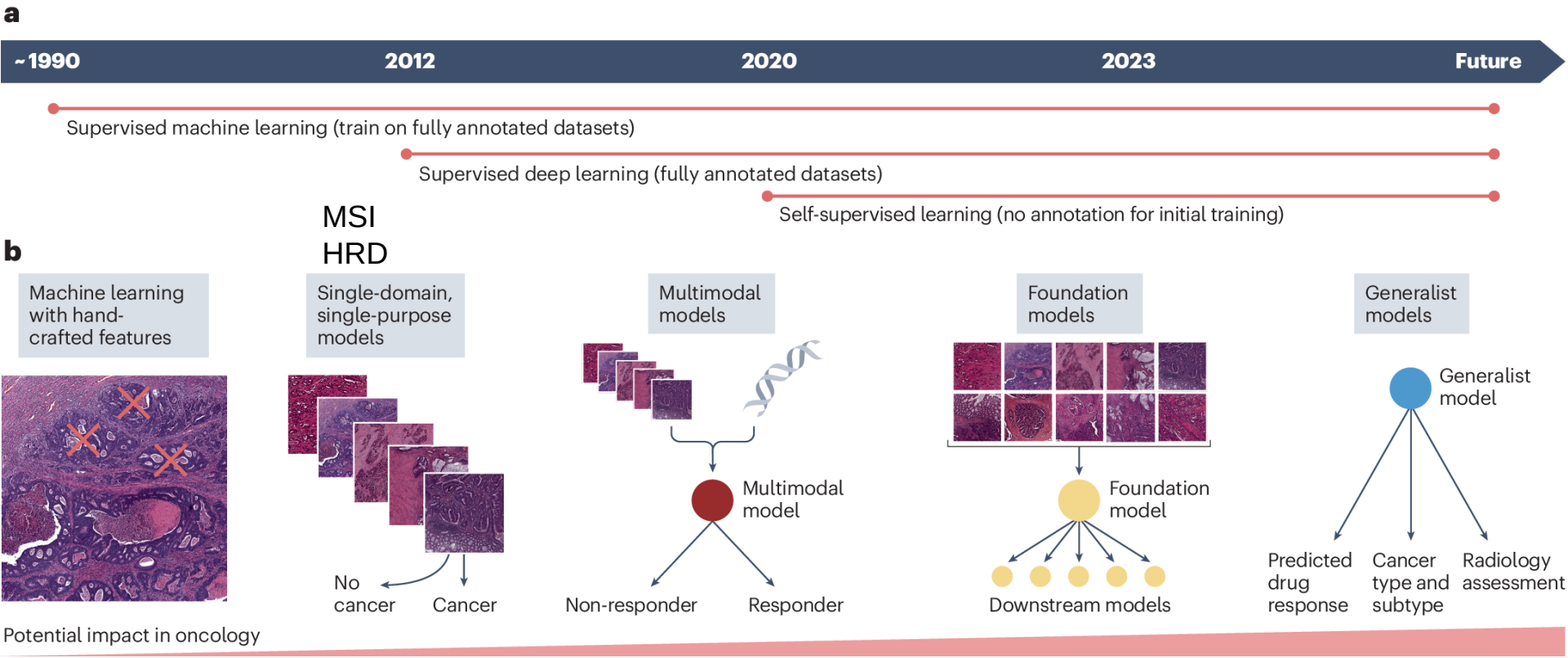


Perez-Lopez, et al., Nat Rev Cancer. 2024 Jun;24(6):427-441.



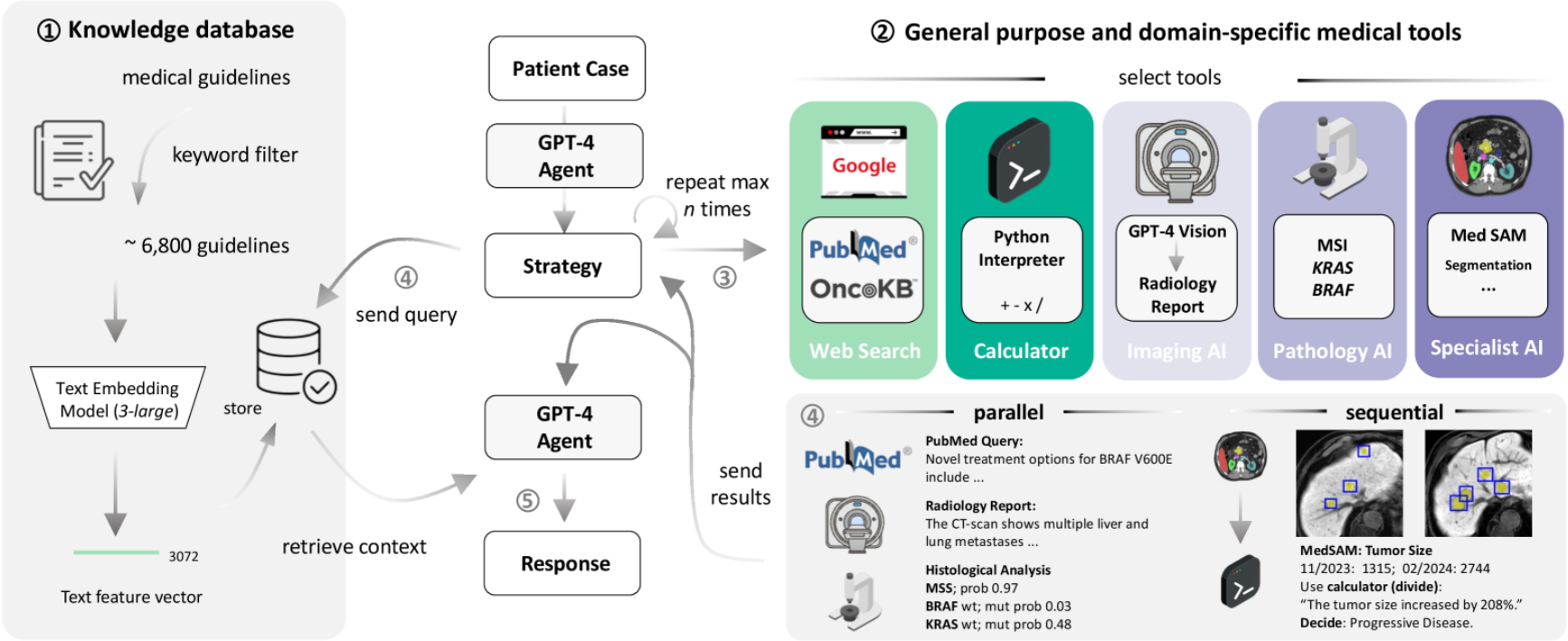
Zeng, et al., Lancet Oncol., 2023

Progress of AI in medical imaging



Perez-Lopez, et al., Nat Rev Cancer. 2024 Jun;24(6):427-441.

Autonomous Artificial Intelligence Agents for Clinical Decision Making in Oncology



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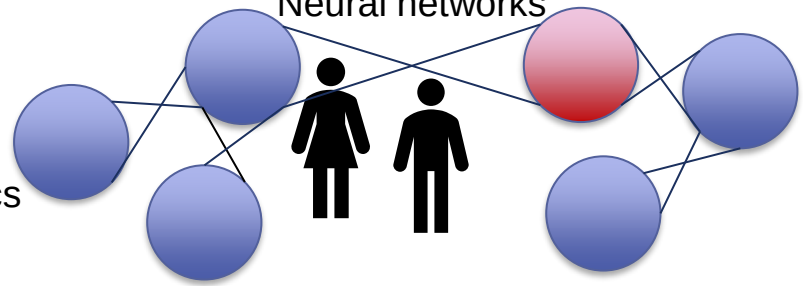
Ferber …. Kather J, pre-print, https://arxiv.org/pdf/2404.04667
Kather J, ESMO 2024 presentation 15 Sept 2024

Implementing tumor agnostic precision medicine through AI

Neural networks



Radiology (AI features)

Histopathology (AI features)

Spatial Pathology and -omics

Anatomical features

Plasma/serum protein markers

Tumour Molecular Profiling (DNA – WGS and 4D genome, RNA, protein)

Germ-line genomic testing

Liquid Biopsy (ctDNA and beyond)

Microbiome sequencing

Plasma (and tissue) metabolomics

Tissue resident and circulating immune cells (and markers)

Comorbidities
Smoking
Diet
Lifestyle
Physical Exercise
Vital sign monitoring (smart)
Education
Social/family interactions
Patient preference
Financial issues
(cost effectiveness)

(AI driven) approach

Surgery (if so, when?)
Radiotherapy (and dose)

Investigational and approved therapies

Drug combinations

Drug holidays

Dose reduction

Therapy switch

Acquired resistance

Surveillance duration and interval

Novel surrogate biomarkers for early drug development

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THANK YOU

Thanks to the presenters for making the slides available ahead of the ESMO meeting.

Prof. Federica Di Nicolantonio
@fdinicolantonio

federica.dinicolantonio@unito.it
https://www.aibh.unito.it/do/home.pl

European Society for Medical Oncology (ESMO)
Via Ginevra 4, CH-6900 Lugano
T. +41 (0)91 973 19 00
esmo@esmo.org

esmo.org