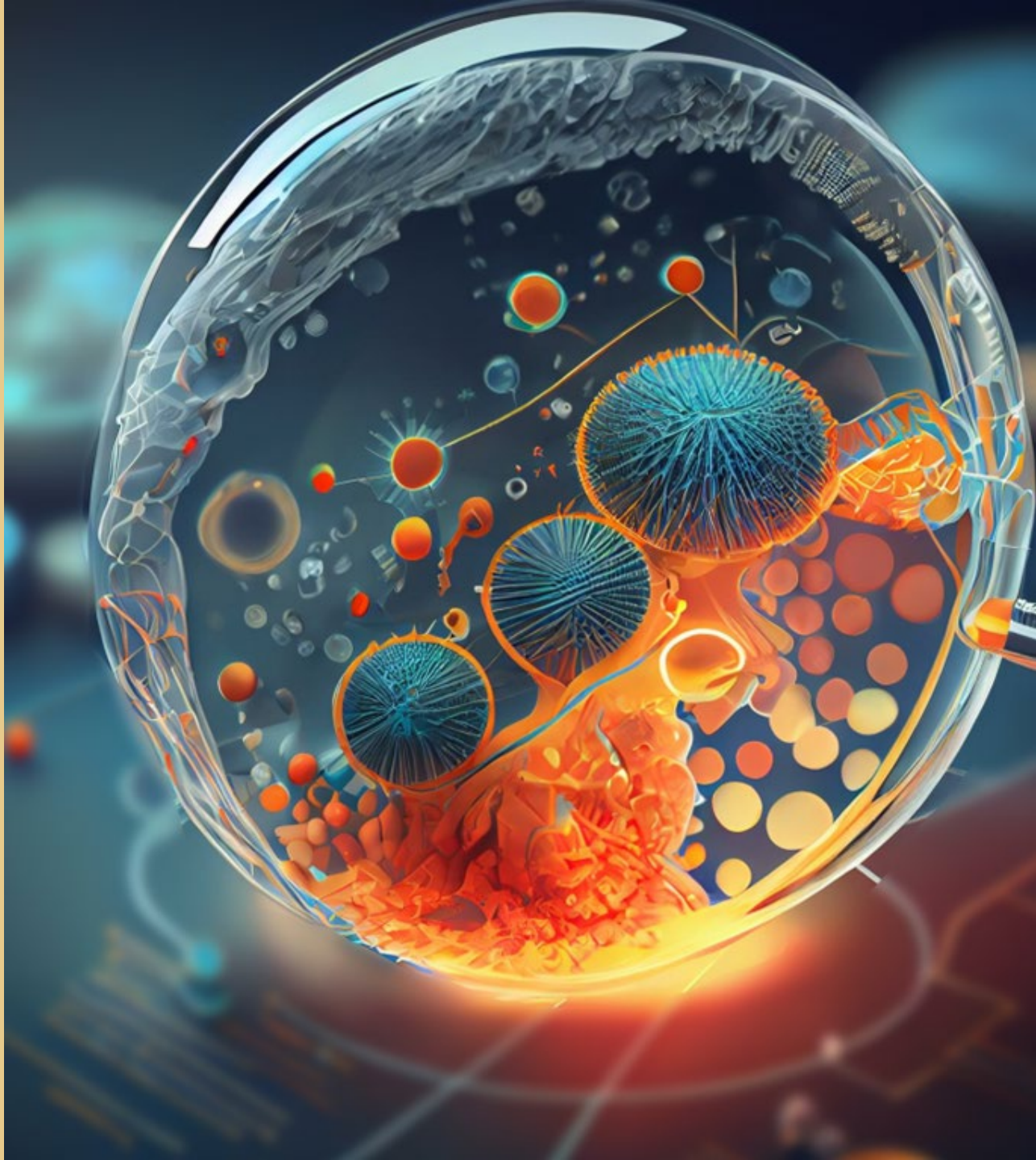
eha Sf(PM)

EXALT1 and 2 trials



September 25 2024 Philipp Staber

Challenges of genetic driver

Driver of clonal expansions

- Target 1 specific gene in cancer cells;
  pos. examples: Herceptin, Glivec

But:

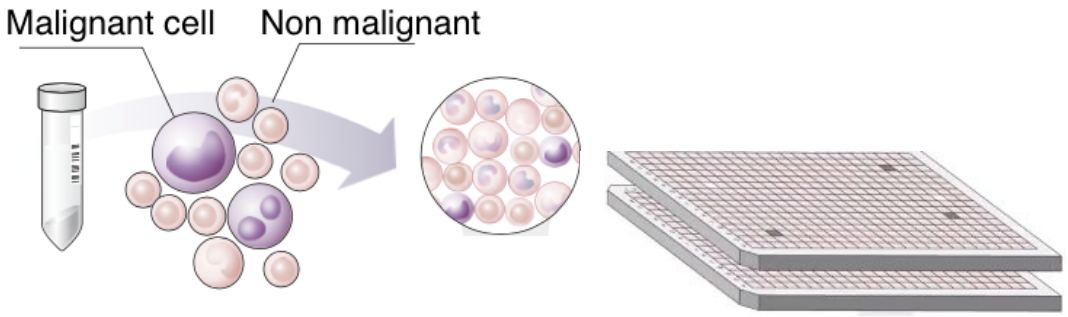
Genetic therapy matching

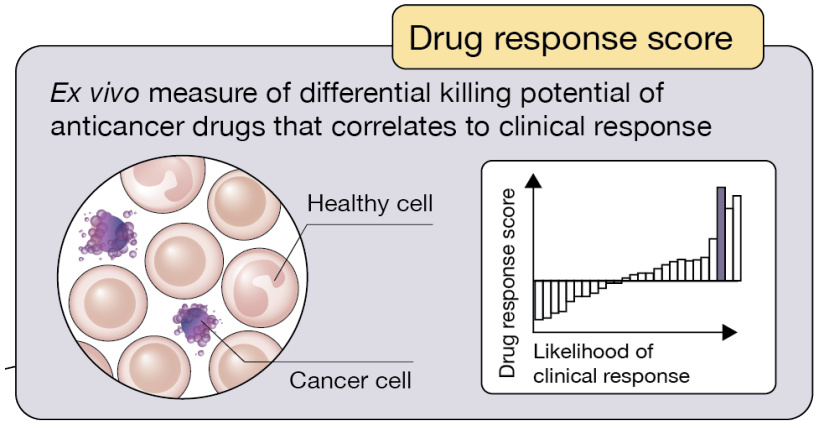
- Matched therapies 4-25% (most <10%)
- Responses/ benefit about 5% of ITT population

- many cancer driver mutations in healthies
- inter-& intra-tumor heterogeneity
- dynamic

Functional assays

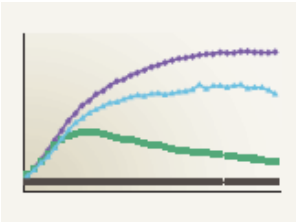
Tea Pemovska



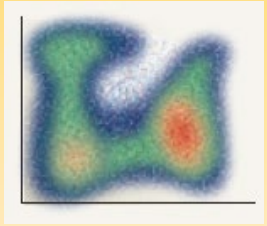


Read-out

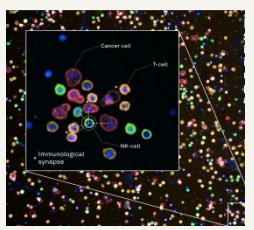
Ex vivo drug cytotoxicity (ATP levels, MTT, proliferation)



DBP (apoptotic priming)



Automated flow profiling ((phosphor)-antibody FACS)



Automated microscopy profiling (image analysis)

Tea Pemovska et al. *Curr Opin. Pharm.* 2018

eha SIG(PM)

Functional Precision Medicine (FPM)

Superti-Furga Vladimer Staber

EHA president: Elizabeth Macintyre, 6/2023

EHA EUROPEAN HEMATOLOGY ASSOCIATION
Topic-in-Focus

EHA | SWG
SPECIALIZED WORKING GROUPS
Precision Hematology

1st	meeting March 12-13 2019	Vienna
2nd	meeting: March 25-26 2021	Zurich
3rd	meeting: Sept. 5-7 2022	Helsinki
4th	meeting: Sept. 24-26 2024	Copenhagen
5th	meeting: March 2025	Boston
	...	

1. Foster research in precision hematology
2. Foster the development of diagnostic tests
3. Foster clinical PM trials
4. Foster access to drugs

Current action task:
MI-FPM criteria
... minimal information on reporting of FPM results

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How to apply FPM to patients?

- Classic: drug discovery as rationale for a clinical trial

- Personalization of treatment („ n-of-one therapy“)

How to apply FPM to patients?

- Classic: drug discovery as rationale for a clinical trial

- Personalization of treatment („ n-of-one therapy“)

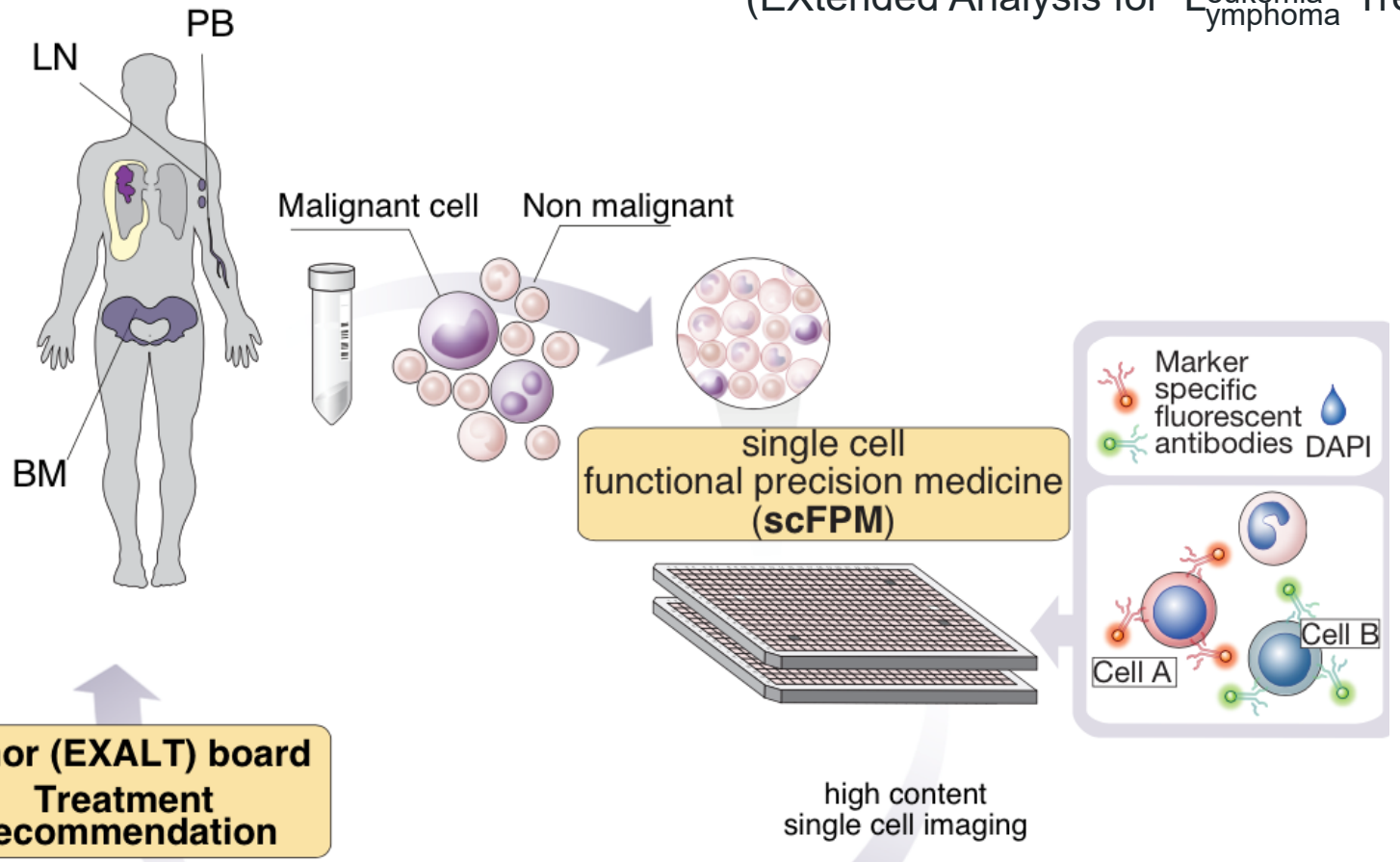
scFPM trial: EXALT

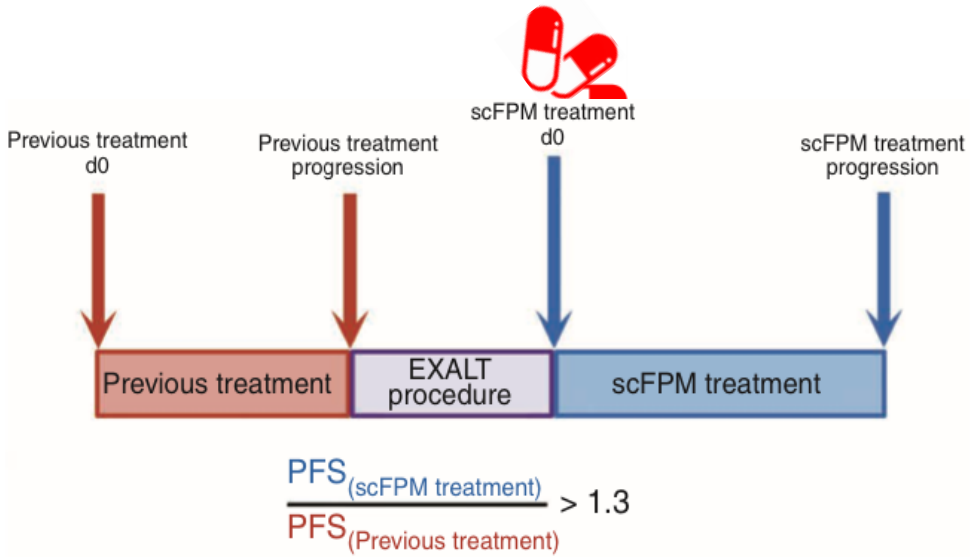
(EXtended Analysis for Leukemia Lymphoma Treatment)


Christoph Kornauth


Tea Pemovska


Gregory Vladimer

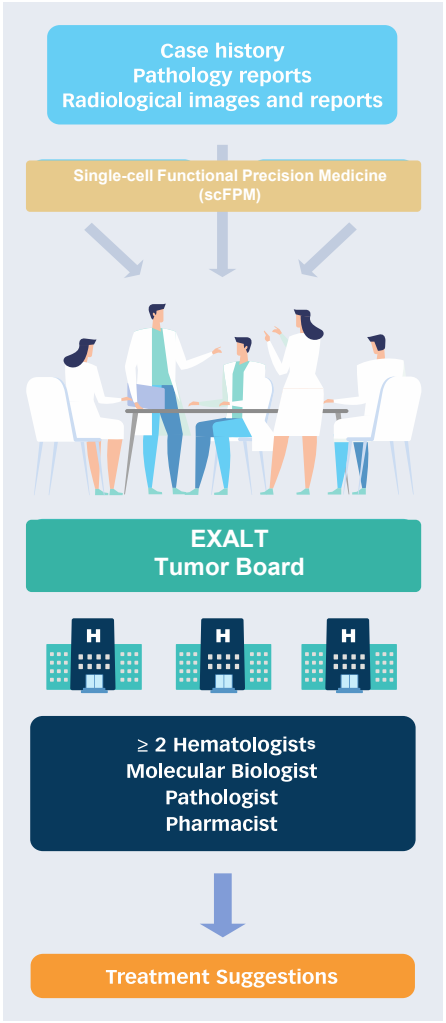




Clinicaltrials.gov: NCT03096821

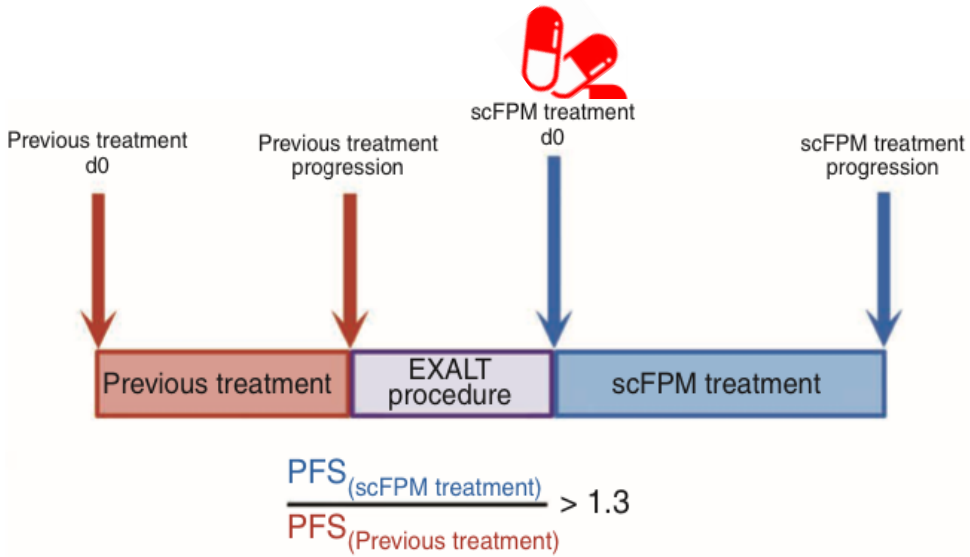
eha Sf(PM)

EXALT Tumor Board



www.mol-onko.at

Pocket-Guide Molekulare Hämatologie
Staber P., Prager G. Spectrum 2024




Christoph Kornauth


Tea Pemovska


Gregory Vladimer

Clinicaltrials.gov: NCT03096821

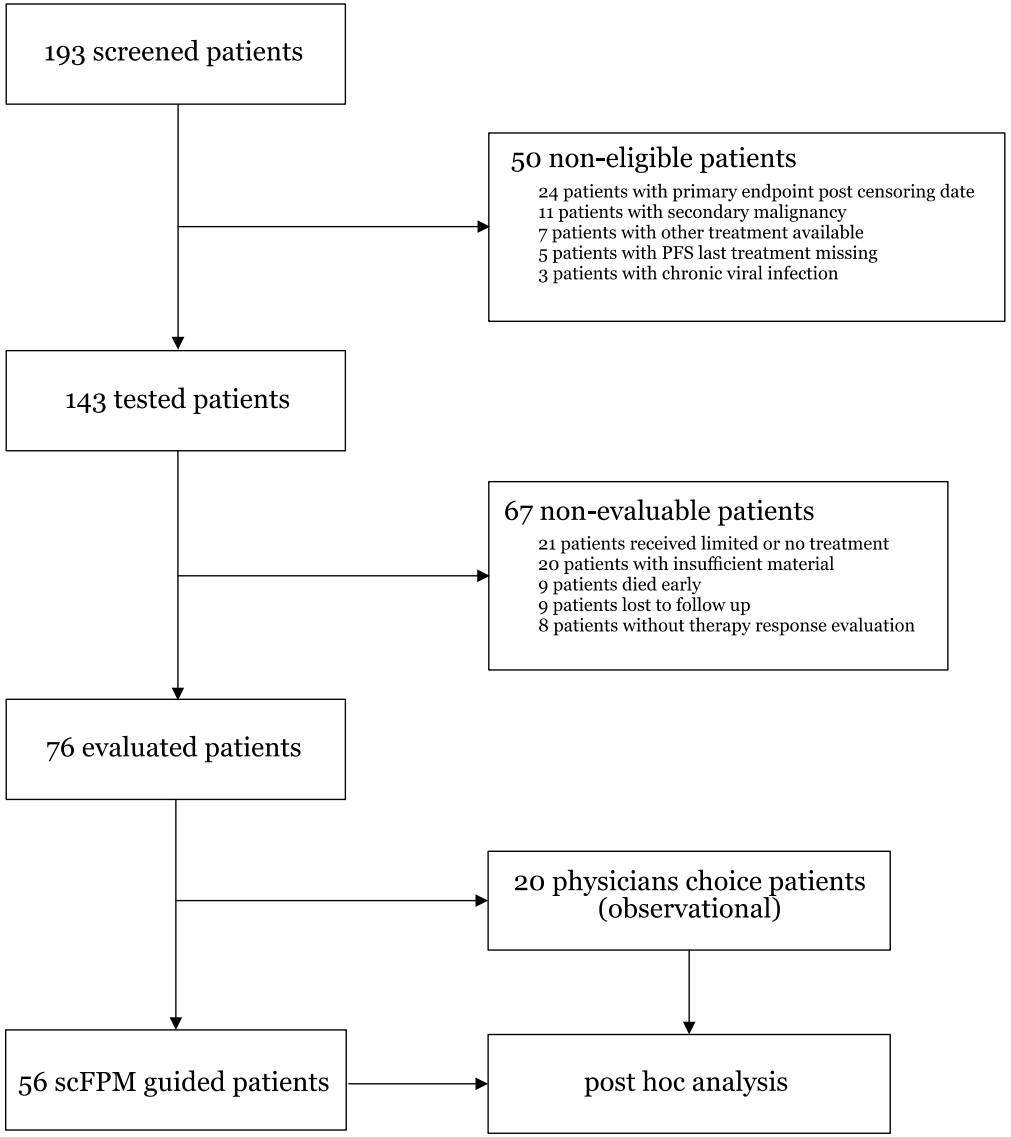
eha Sf(PM)

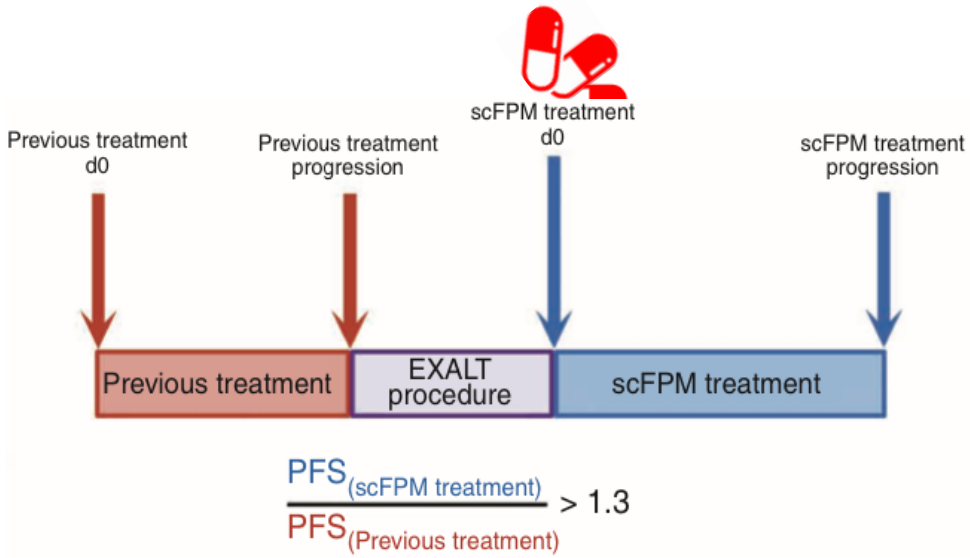
EXALT1 consort diagram


Christoph Kornauth


Tea Pemovska


Gregory Vladimer





Clinicaltrials.gov: NCT03096821

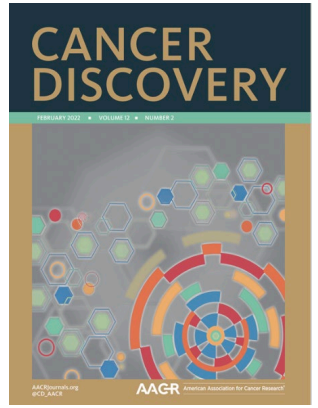
eha Sf(PM)

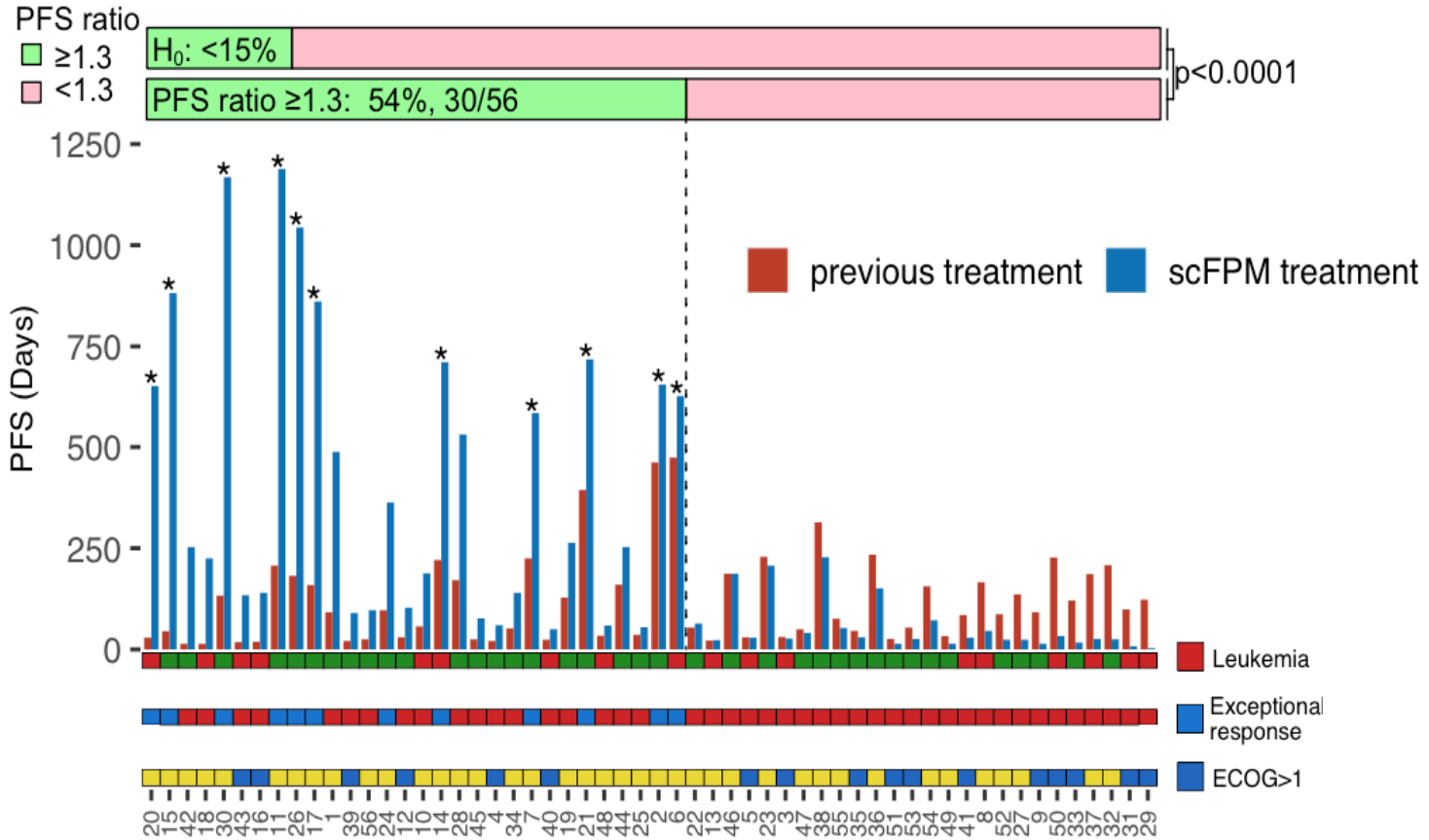
EXALT1: 54% improved their PFS ratio > 1.3


Christoph Kornauth


Tea Pemovska


Gregory Vladimer





Kornauth, Pemovska, Vladimer et al. *Cancer Discovery 2022*

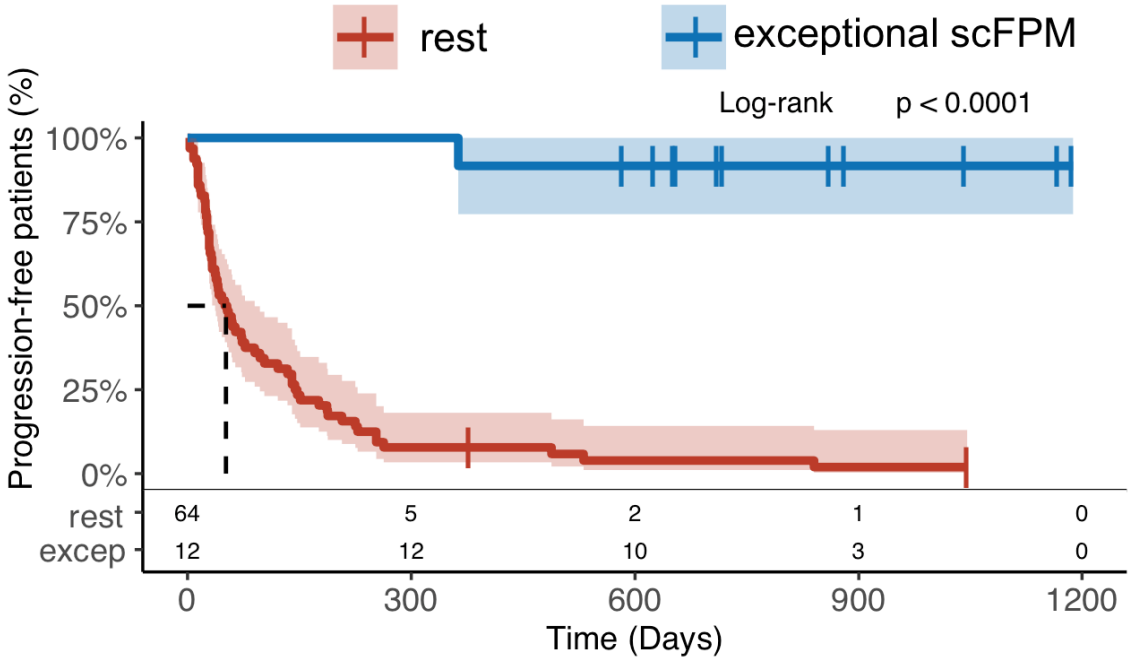
eha Sf(PM)

EXALT1: 40% of responders “exceptional responses”

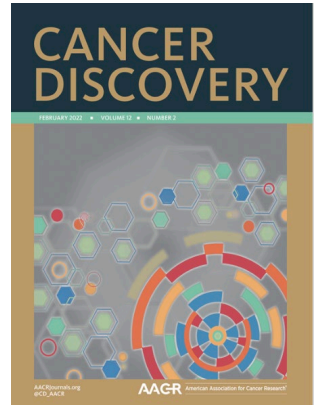

Christoph Kornauth


Tea Pemovska


Gregory Vladimer



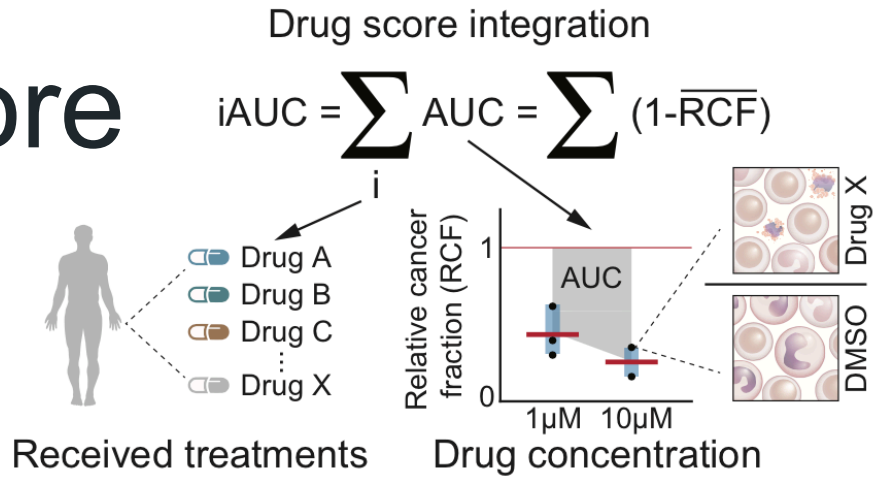
		Count	%
Exceptional Responders		12	21
Sex			
	Male	6	50
	Female	6	50
Median Age (range)		60 (29-86)	
Disease Group			
	Lymphoma	9	75
	Leukemia	3	25
	B-NHL	2	17
	AML	3	25
	T-NHL	7	58
	ALL/LBL	0	0
Median number of previous treatments		2(2-9)	
Response - Last Treatment			
	CR	7	58
	PR	3	25
	SD	1	8
	PD	1	8
Sampling - Treatment in days		28 (4-56)	
ECOG at treatment start			
	ECOG 0	8	67
	ECOG 1	4	33
	ECOG 2	0	0
	ECOG 3	0	0

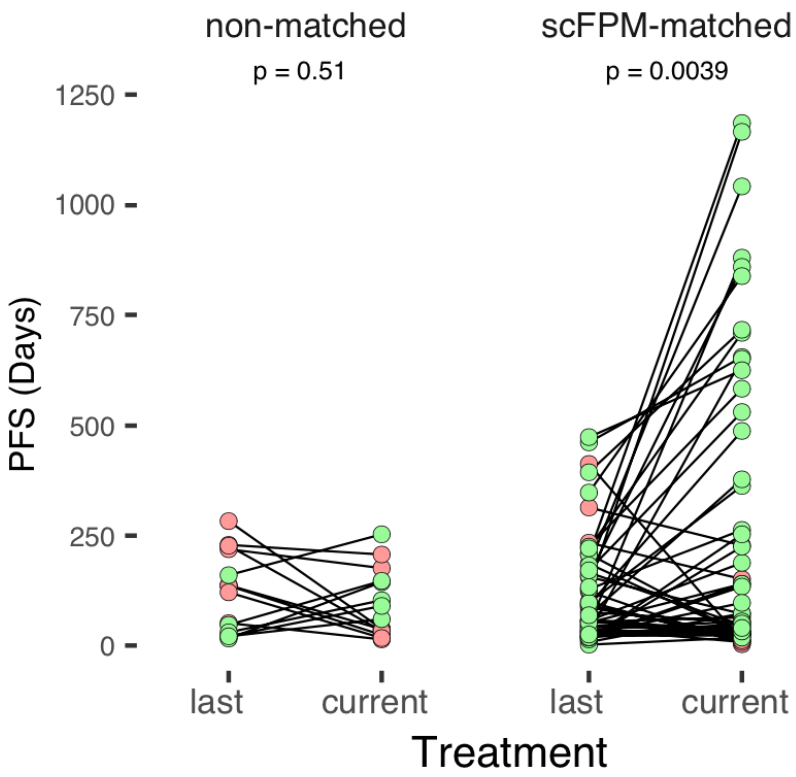


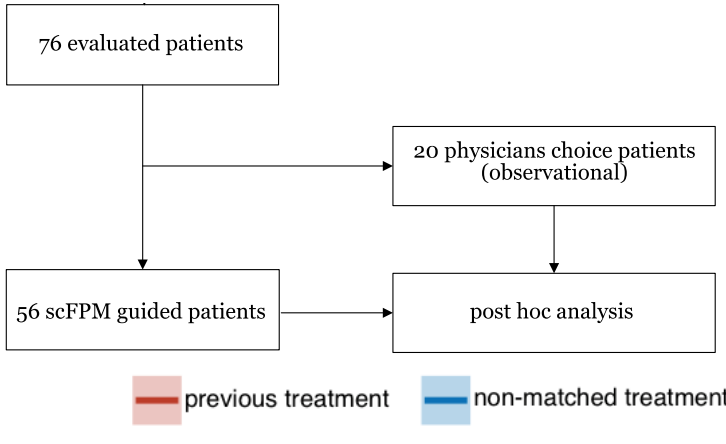
Kornauth, Pemovska, Vladimer et al. *Cancer Discovery 2022*

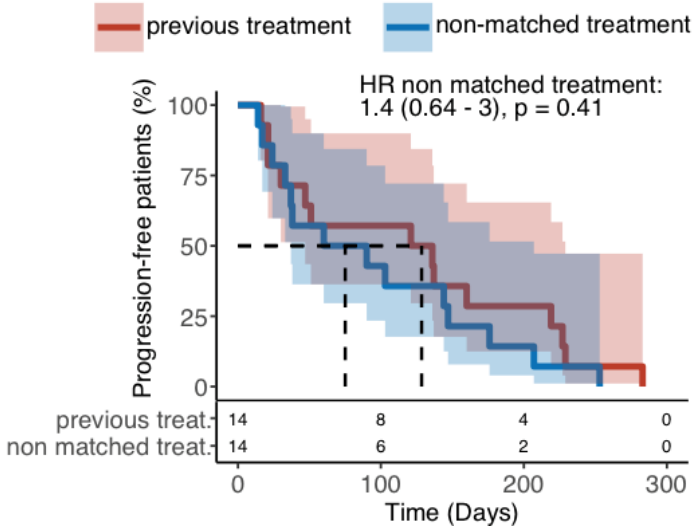
Data integration: matching score

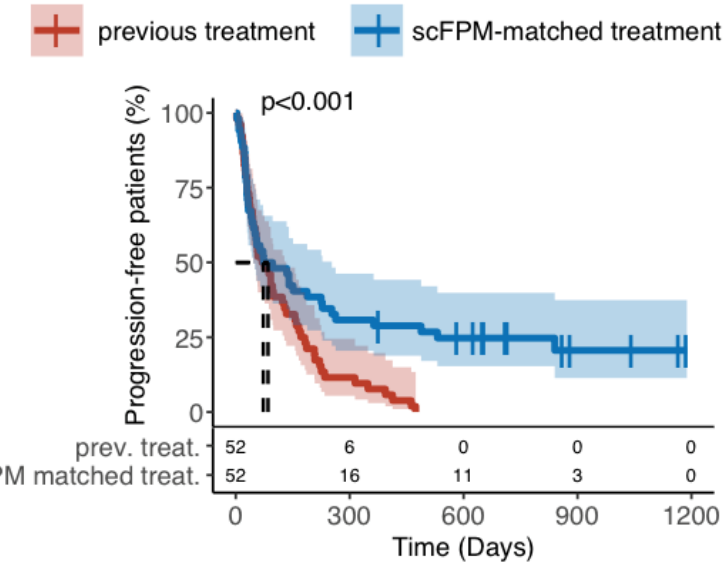
... (a posthoc analysis)
Therapy matching score relates to clinical outcome









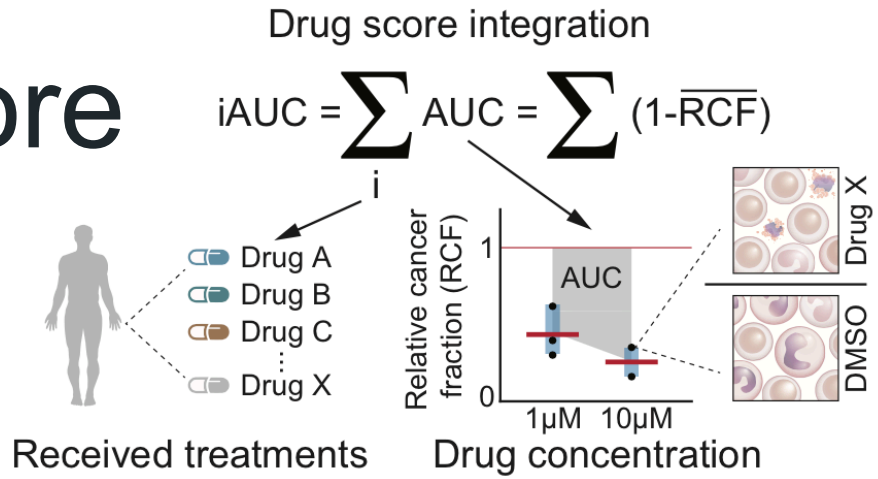


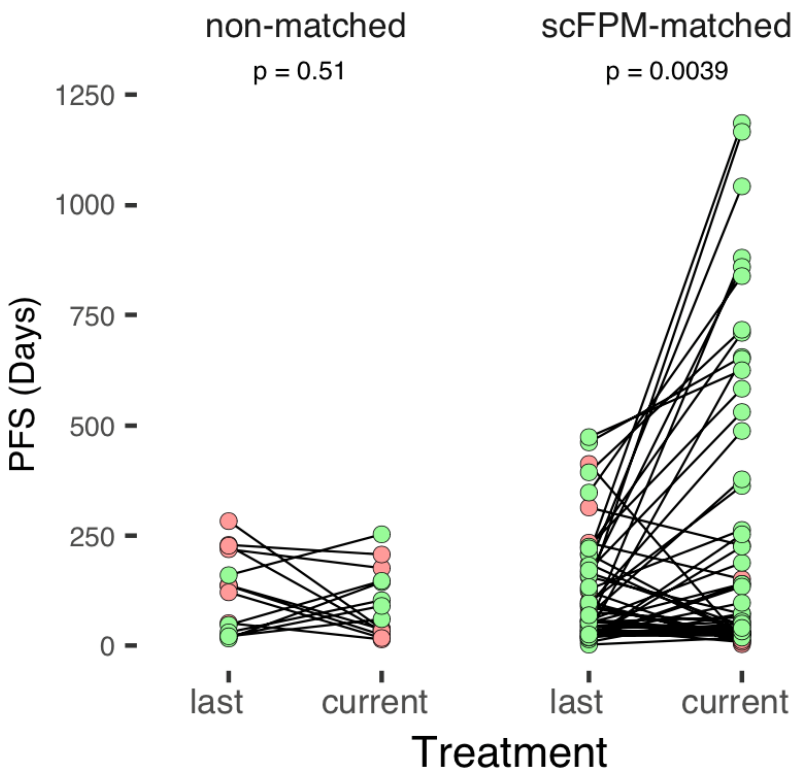
Kornauth, Pemovska, Vladimer et al. *Cancer Discovery 2022*

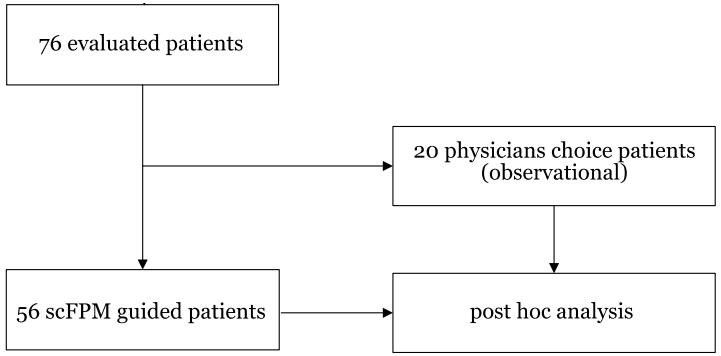
eha SƒPM

Data integration: matching score

... (a posthoc analysis)
Therapy matching score relates to clinical outcome

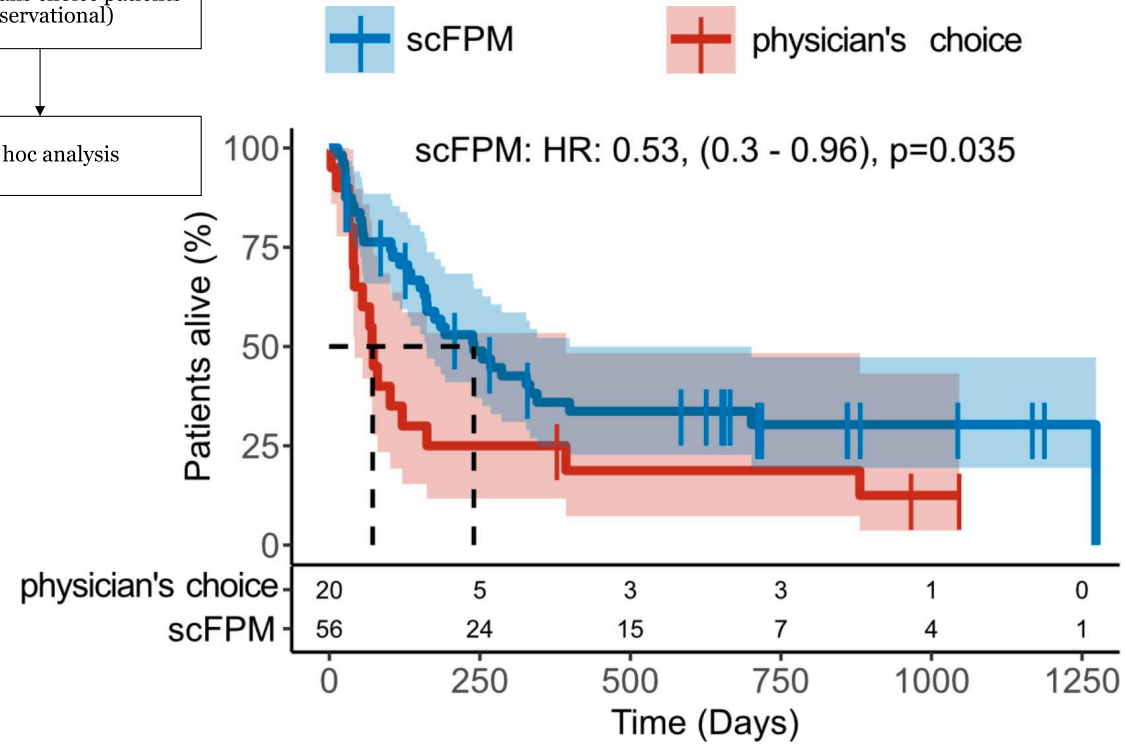






PFS ratio < 1.3

PFS ratio ≥ 1.3



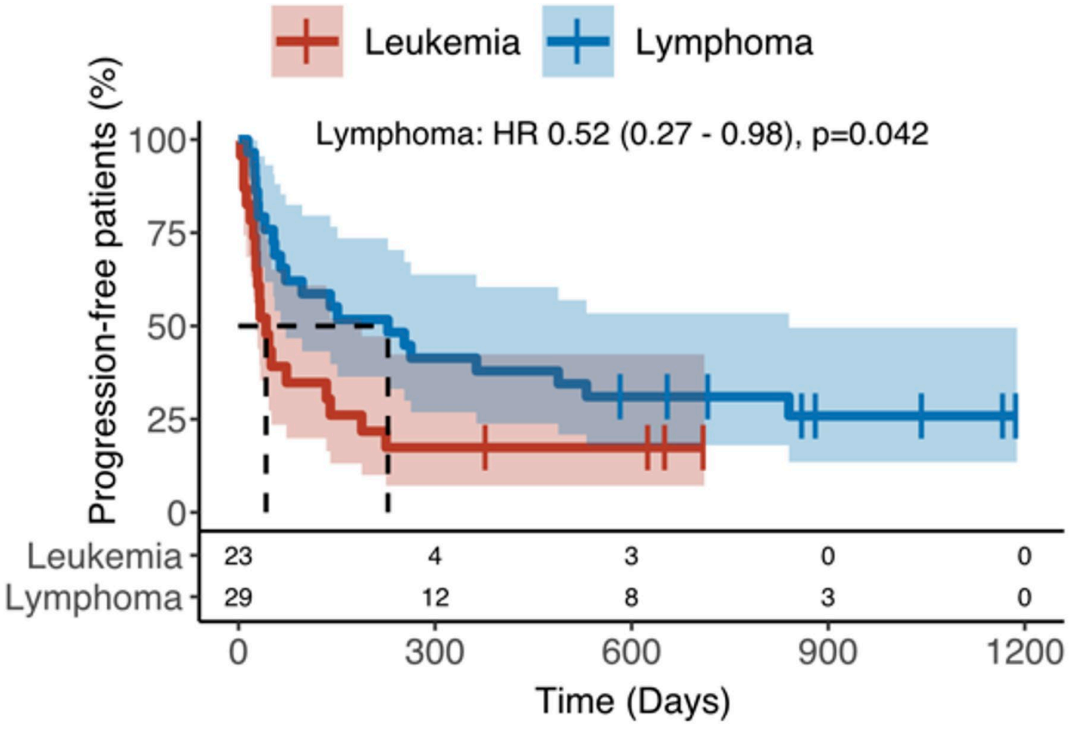
Kornauth, Pemovska, Vladimer et al. *Cancer Discovery 2022*

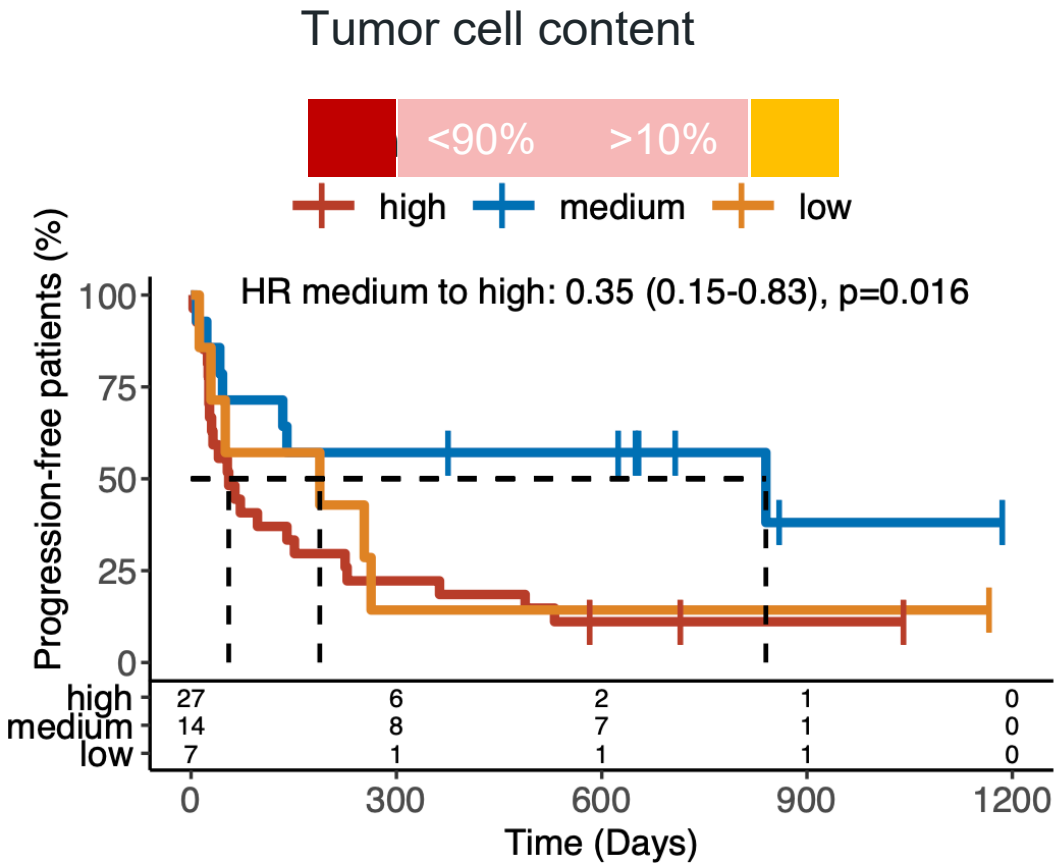
eha Sf(PM)

scFPM response prediction relies on tumor cell content


Christoph Kornauth


Tea Pemovska





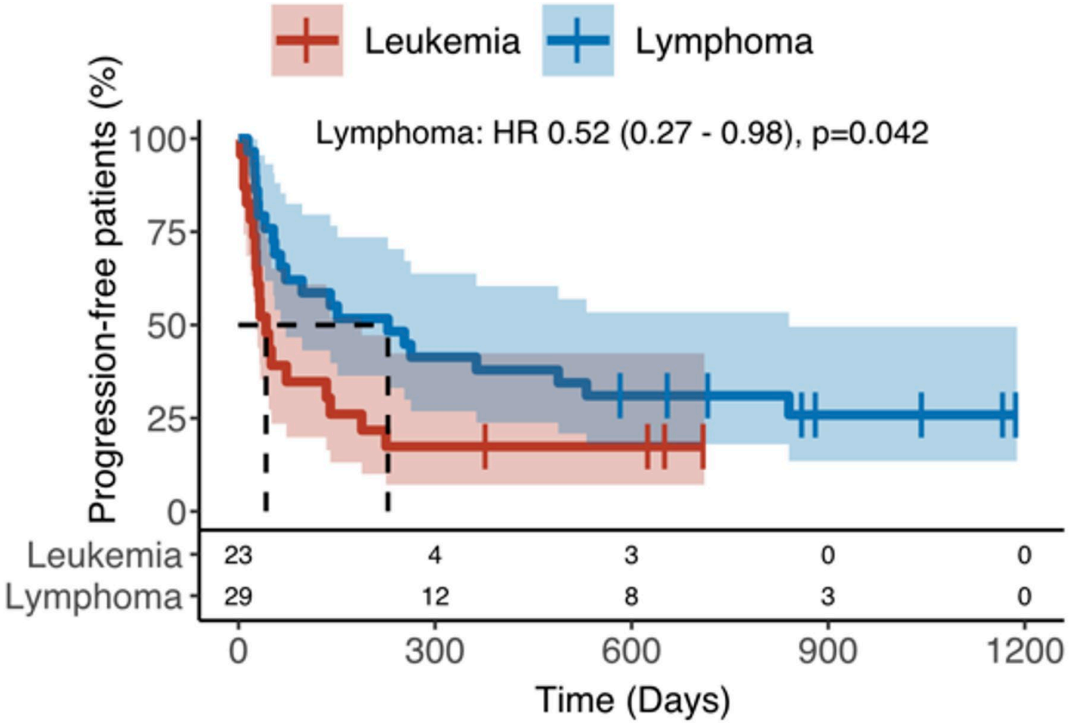
Kornauth, Pemovska, Vladimer et al. *Cancer Discovery 2022*

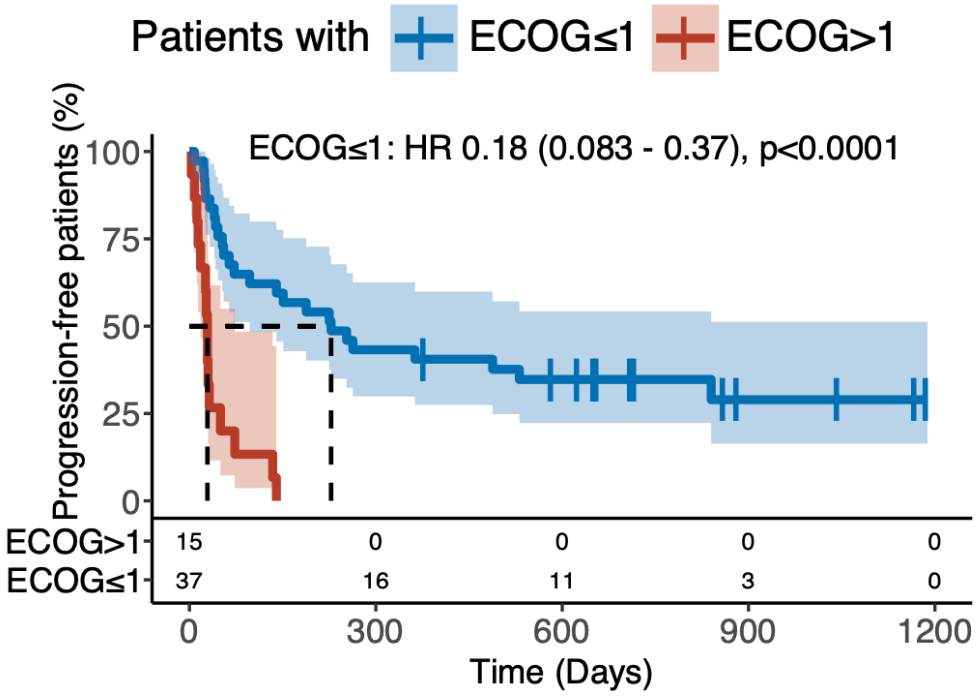
eha Sf(PM)

scFPM response prediction relies on tumor type and fitness


Christoph Kornauth


Tea Pemovska





Kornauth, Pemovska, Vladimer et al. *Cancer Discovery 2022*

How to apply FPM to patients?

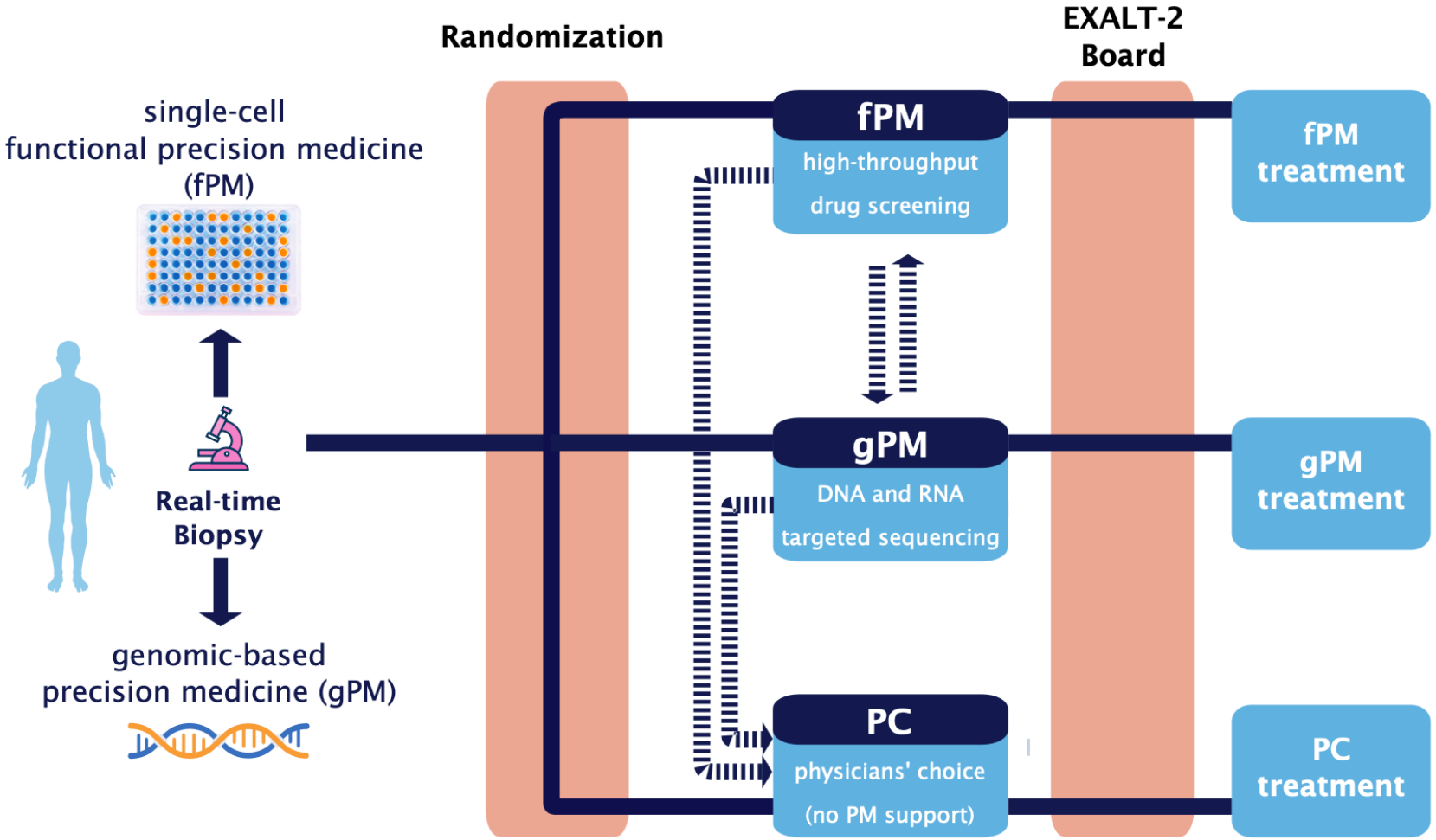
- Classic: drug discovery as rationale for a clinical trial

- Personalization of treatment („ n-of-one therapy“)

EXALT2: scFPM vs CGP vs physicians'choice


Lukas Kazianka


Tea Pemovska



Centers
- Medical University Vienna
- Innsbruck University Hospital
- Medical University Graz
- Keppler University Linz
- Medical University Salzburg

Start Q2 2020

Sponsor MUW, Roche

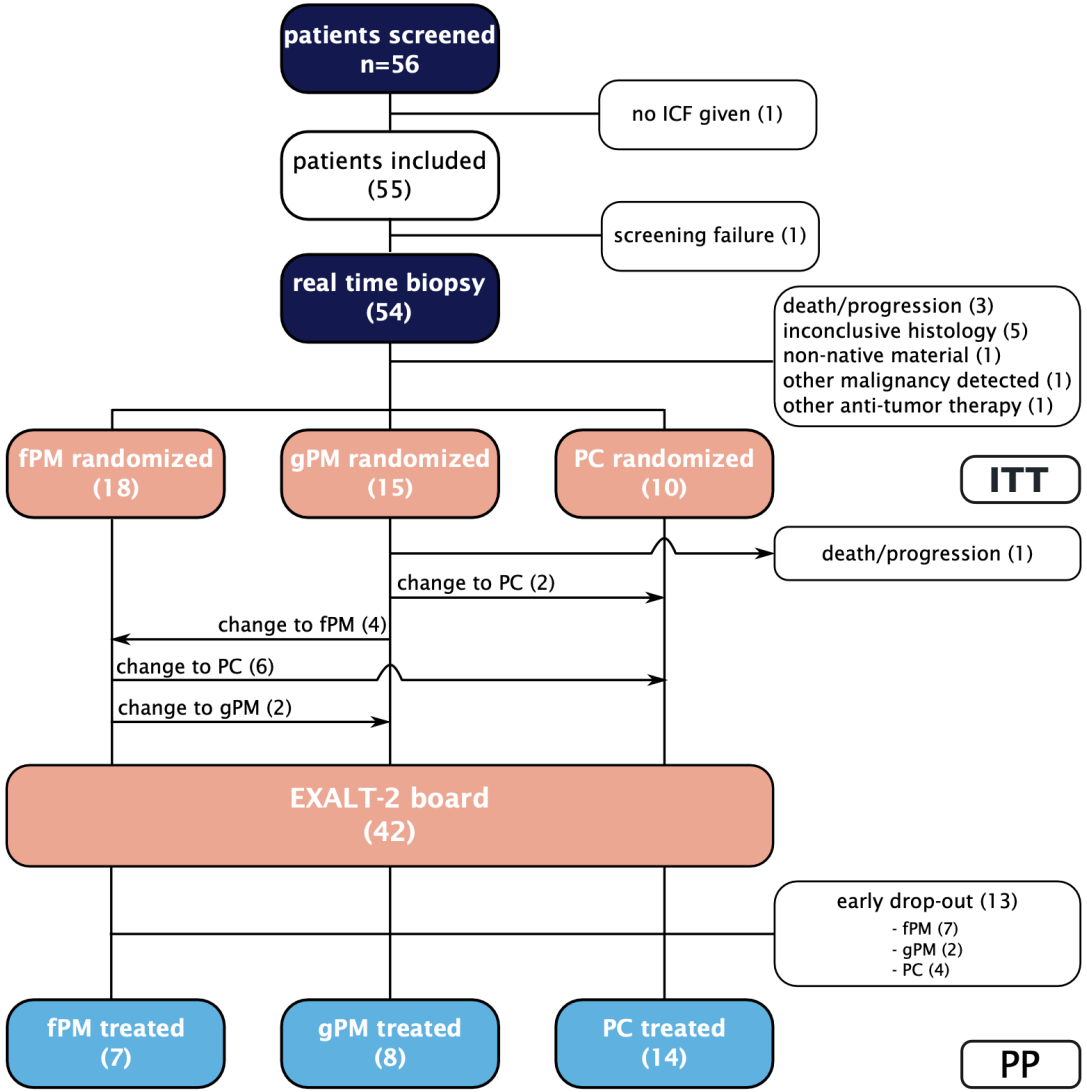
Clinicaltrials.gov: NCT04470947

Kazianka, Pemovska, et al. in rev

EXALT2: consort diagram


Lukas Kazianka


Tea Pemovska



Clinicaltrials.gov: NCT04470947

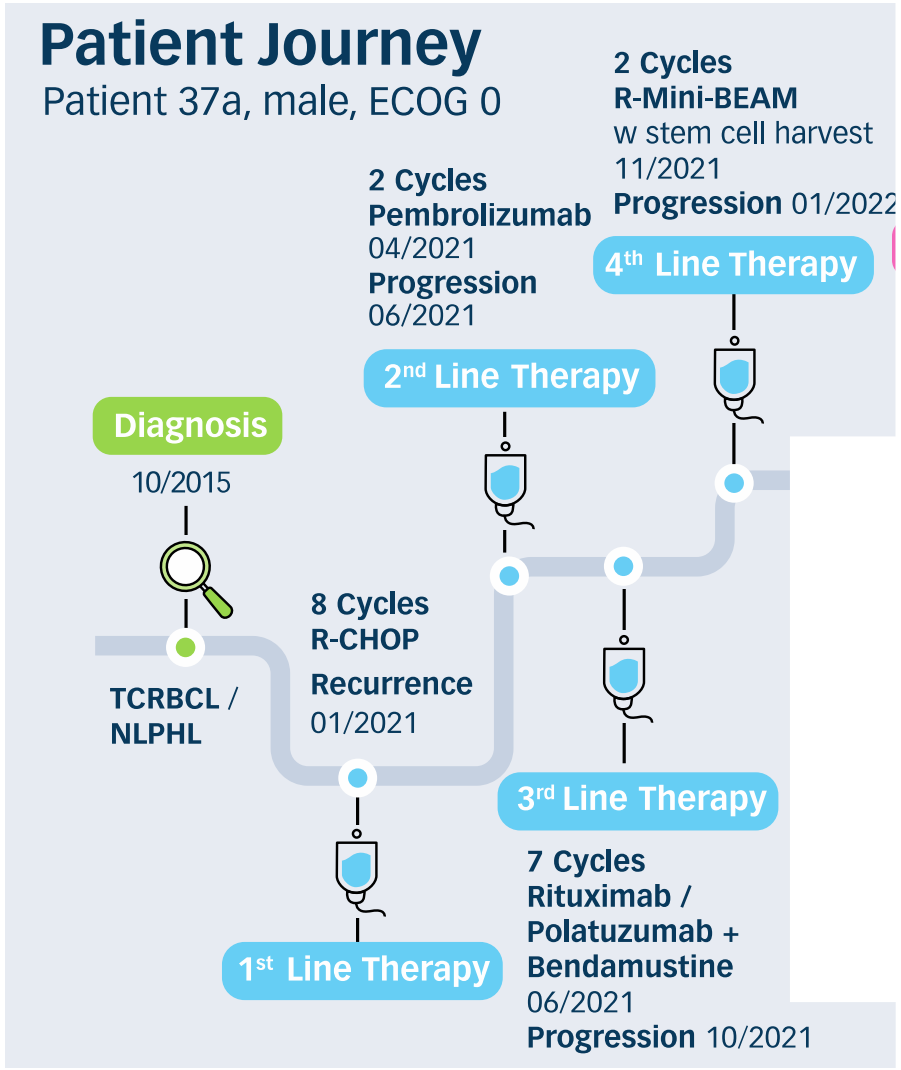
Kazianka, Pemovska, et al. in rev

eha SIF(PM)

EXALT2: scFPM vs CGP vs physicians'choice


Lukas Kazianka


Tea Pemovska



Clinicaltrials.gov: NCT04470947

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EXALT2: scFPM vs CGP vs physicians'choice


Lukas Kazianka


Tea Pemovska

FOUNDATIONONE®HEME

PATIENT
01-033, 01-033

TUMOR TYPE
Lymph node lymphoma Hodgkins disease

REPORT DATE
07 Feb 2022

Report Highlights

- There are no highlights associated with this patient's genomic findings.

For more information on potential biological and clinical significance, see the Biomarker and Genomic Findings sections.

THERAPY AND CLINICAL TRIAL IMPLICATIONS

No therapies or clinical trials. see Biomarker Findings section

No therapies or clinical trials. see Biomarker Findings section

Diagnosis
10/2015

TCRBCL / NLPHL

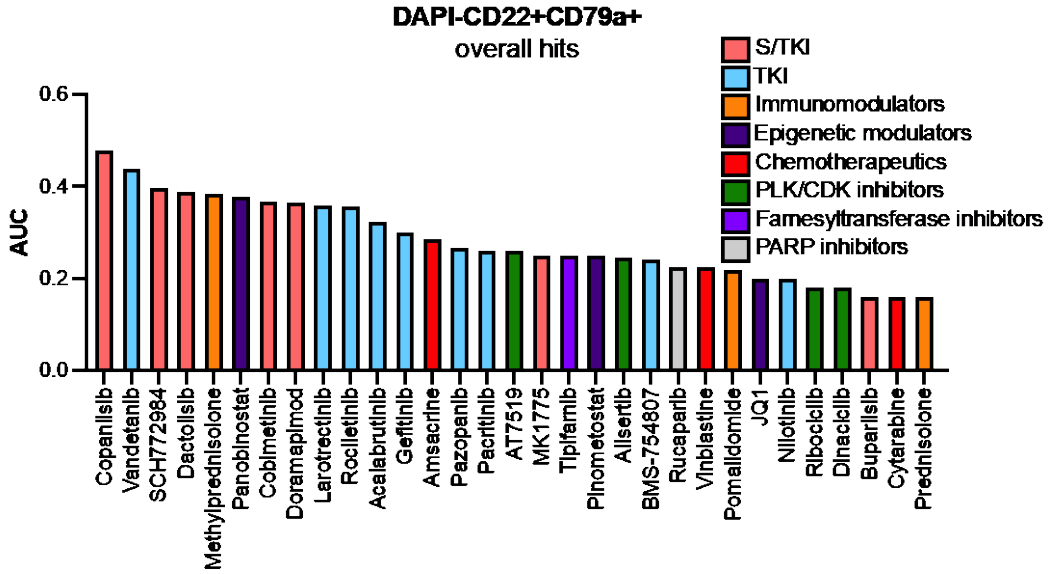
8 Cycle
R-CHOP

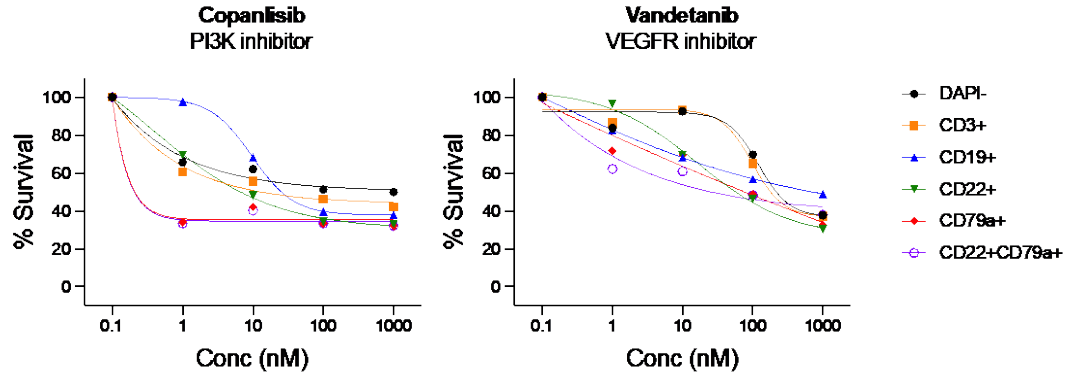
Recurre
01/2021

1st Line Therapy

Rituximab / Polatuzumab + Bendamustine
06/2021
Progression 10/2021

inhibitors:
Vandetanib, Larotrectinib, Rociletinib and Gefitinib





EXALT1 and 2 trials

Clinicaltrials.gov: NCT04470947

Kazianka, Pemovska, et al. in rev

eha SfPM

EXALT2: scFPM vs CGP vs physicians'choice


Lukas Kazianka


Tea Pemovska

Patient Journey

Patient 37a, male, ECOG 0

Diagnosis
10/2015
TCRBCL / NLPHL

1st Line Therapy
8 Cycles R-CHOP
Recurrence 01/2021

2nd Line Therapy
2 Cycles Pembrolizumab
04/2021
Progression
06/2021

3rd Line Therapy
7 Cycles Rituximab / Polatuzumab + Bendamustine
06/2021
Progression 10/2021

4th Line Therapy
2 Cycles R-Mini-BEAM
w stem cell harvest
11/2021
Progression 01/2022

EXALT-2
01/2022
Real-time biopsy
Randomization to Arm A (scFPM)

scFPM: potential treatment options
- **PI3K inhibitors:** Copanlisib and Dactolisib
- **VEGFR/EGFR/Trk inhibitors:** Vandetanib, Larotrectinib, Rociletinib and Gefitinib

Molecular Tumorboard
02/2022
Tafasitamab + Copanlisib or Vandetanib

scFPM supported Therapy
Tafasitamab + Vandetanib
02/2022

Partial response (PET-CT 04/2022), Evaluation for **autologous HSCT**

Response

Clinicaltrials.gov: NCT04470947

Kazianka, Pemovska, et al. in rev

EXALT2: scFPM vs CGP vs physicians'choice

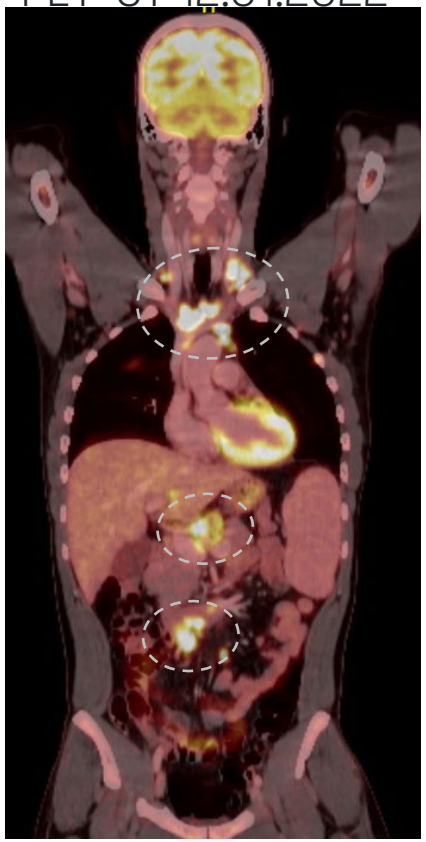

Lukas Kazianka


Tea Pemovska

Patient Journey

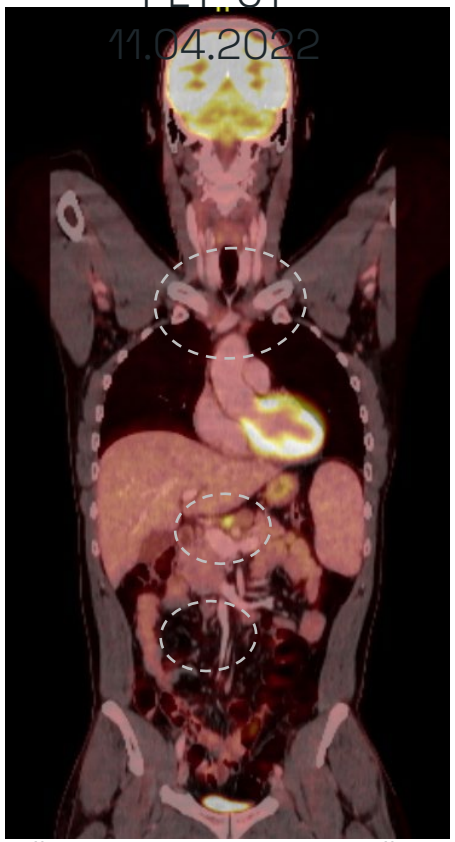
Patient 37a, male, ECOG 0

PET-CT 12.01.2022



after 2 months
(04/2022)

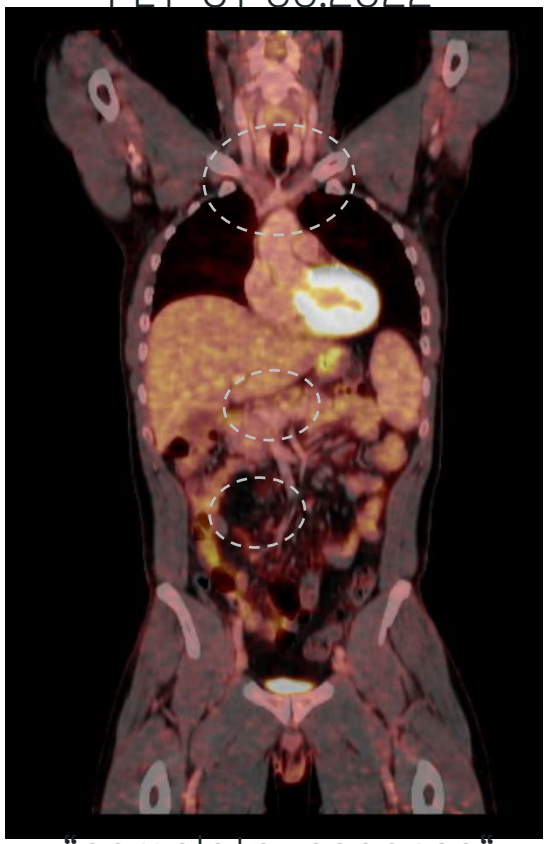
PET-CT
11.04.2022



"partial response"

after 4 months
(06/2021)

PET-CT 06.2022



"complete response"

allo-HSCT
29.07 2022

Clinicaltrials.gov: NCT04470947

Kazianka, Pemovska, et al. in rev

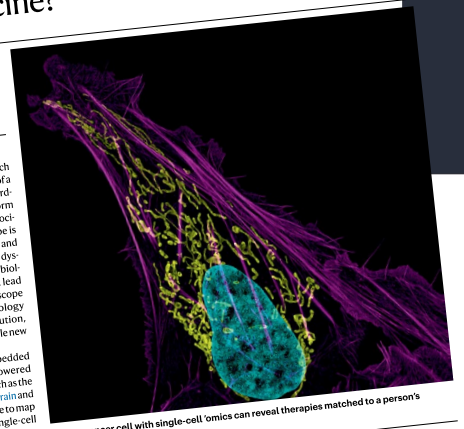
Functional Precision Medicine in the news

News

Can single-cell biology realize the promise of precision medicine?

Biology's quiet revolution is underway, as single-cell tools fuel the next-wave of drug discoveries and promise to match therapies to the individual.

By Cormac Sheridan



A bone cancer cell with single-cell 'omics can reveal therapies matched to a person's tumor type.

Cellarity's single-cell-based approach to drug discovery is at the heart of a recent agreement with Novo Nordisk to develop new drugs for a form of chronic fatty liver disease associated with metabolic dysfunction. The hope is that this shift away from molecular targets and toward identifying the underlying cellular dysfunction will offer deep insights into the biology of the condition, which will, in turn, lead to improved therapies. Just as the microscope enabled the development of microbiology in the seventeenth century, high-resolution, single-cell methods are opening up whole new biological vistas (Table 1).

Single-cell methods are already embedded in basic research, where they have powered agenda-setting research initiatives, such as the recently published map of the human brain and the Human Cell Atlas, a global initiative to map every cell in the human body. But single-cell 'omics and imaging techniques are not confined to basic research. Because of the exquisite sensitivity of single-cell analysis in detecting biological signals, its potential is likely to spill over into myriad areas of medicine too. At this point, single-cell analysis is nowhere near routine clinical practice, but a handful of pioneering studies points to its potential in realizing the largely unattained goal of precision medicine — that is, accurately matching an individual patient to the therapies from which they are most likely to benefit. "Clinically, I would say, we're at the very early stages," says Joseph Powell, of the Garvan Institute of Medical Research in Darlinghurst, Australia.

The cell has been a central focus of biological research for almost 200 years, following its recognition in the 1830s as the fundamental structural and functional unit of life. But until recently, genomic, epigenomic, proteomic and other 'omic analyses could only be conducted on cells isolated in bulk. The resulting data provided an average view of a given biological sample, but glossed over rare cells, infrequently expressed transcripts, and metabolites present in low concentrations.

The widespread adoption of next-generation sequencing over the last two decades has ushered in the present era of single-cell biology. A whole-transcriptome analysis of a single mouse blastomere, published in 2009 by a team of scientists from the University of Cambridge and Applied Biosystems (now part of Thermo Fisher Scientific), is generally held to represent the first example of single-cell transcriptomics in action. The term 'single cell' applied literally in this case: the group used micropipetting techniques to handle the individual cells, which are present in very low numbers during early embryonic development.

But the whole value of single-cell biology lies in the ability to conduct parallel analyses of individual cells at massive scale. This relies on automated cell-handling platforms based on microfluidic and cytometric technologies, coupled with powerful computational platforms for managing and interpreting the data.

The migration of single-cell techniques from research labs to the clinic still requires test developers to build an evidence base to support their diagnostic or prognostic claims. That effort remains early stage. Mission Bio, for example, recently launched a single-cell assay for detecting measurable residual disease in patients with acute myeloid leukemia. It evaluates a panel of 40 genes and 19 protein markers, as defined in European LeukemiaNet guidelines, and one recent academic study suggests it may be ten

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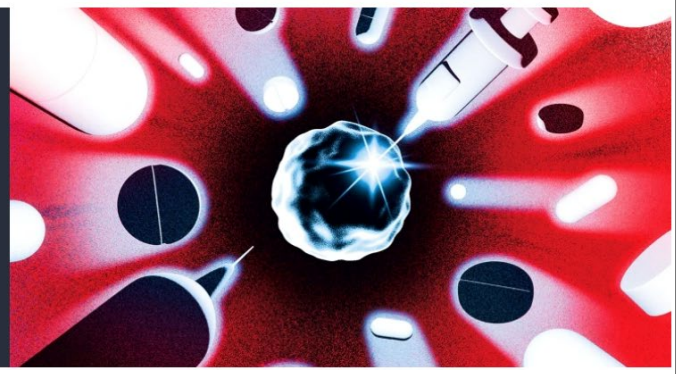
The future of precision cancer therapy might be to try everything

Researchers are blasting patients' cancer cells with dozens of drugs in the hope of finding the right treatment.



Many cancer researchers feel the same way, and now they just need to prove it to the wider medical community. All eyes are therefore on Staber and his randomized trial, which researchers anticipate will go a long way towards convincing clinicians that genomics is not the be-all and end-all of personalized care. "Paradigm shifts can be very threatening to people," says Howard, the University of Mississippi radiologist, "but it shouldn't be threatening. It's just another tool in our arsenal against disease."

Elie Dolgin is a science journalist in Somerville, Massachusetts.

The blood cancer had returned, and Kevin Sander was running out of treatment options. A stem-cell transplant would offer the best chance for long-term survival, but to qualify for the procedure he would first need to reduce the extent of his tumour — a seemingly insurmountable goal, because successive treatments had all failed to keep the disease in check.

As a last throw of the dice, he joined a landmark clinical trial. Led by haematologist Philipp Staber at the Medical University of Vienna, the study is exploring an innovative treatment strategy in which drugs are tested on the patient's own cancer cells, cultured outside the body.

In February 2022, researchers tried 130 compounds on cells grown from Sander's cancer — essentially trying everything at their disposal to see what might work.

One option looked promising. It was a type of kinase inhibitor that is approved to treat thyroid cancer, but it is seldom, if ever, used for the rare subtype of lymphoma that Sander had. Physicians prescribed him a treatment regimen that included the drug, and it worked. The cancer receded, enabling him to undergo the stem-cell transplant. He has been in remission ever since. "I'm a bit more free now," says Sander, a 38-year-old procurement manager living in Podersdorf am See, Austria. "I do not fear death any more," he adds. "I try to enjoy my life."

His story is a testament to this kind of intensive and highly personalized drug-screening method, referred to as functional precision medicine. Like all precision medicine, it aims to match treatments to patients, but it differs from the genomics-guided paradigm that has come to dominate the field. Instead of relying on genetic data and the best available understanding of tumour biology to select a treatment, clinicians throw everything they've got at cancer cells in the laboratory and see what sticks.

But what it sometimes lacks in elegance, it could make up for in results: in pilot studies, Staber and his colleagues found that more than half of people with blood cancer whose treatment was guided by functional drug testing enjoyed longer periods of remission compared with their experiences of standard treatments[1,2]. Large-scale testing of genome-directed approaches suggests that the techniques are very effective against some cancers, yet they benefit, at most, only around 10% of patients overall[3]. Staber and his group's latest trial is the first to compare functional- and genome-guided approaches head-to-head alongside treatments directed by standard pathology and physician intuition.

"That'll be a very powerful study, and it will probably vindicate the utility of these functional assays," says Anthony Letai, a haematologist at the Dana-Farber Cancer Institute in Boston, Massachusetts, and president of the Society for Functional Precision Medicine, a professional organization founded in 2017 to advance the field. And, if anecdotal reports serve as any indication, the try-everything tactic seems to bring about meaningful improvements, even when the genetic sequence of a tumour provides no actionable information, as was the case for Sander.

Companies around the world are already offering these kinds of personalized drug testing service. But proponents of the strategy still have much to prove. Although the concept

"THIS IS A REVOLUTION. PATIENTS ARE DEMANDING THIS APPROACH."

of screening a bunch of drugs seems simple, the methods used to culture cancer cells outside the body can be technically demanding, time-consuming and costly.

The challenges are particularly acute for solid tumours, which live in complex environments inside the body; replicating those conditions is no easy feat. Researchers are trying wildly differing methods that range from growing tumour samples in mice and chicken embryos to cultivating carefully engineered organoids, and even the delivering infinitesimal amounts of various medicines to a tumour while it's still in a patient.

Figuring out what works and what is practical, with regard to cost and scale, won't be easy. But momentum is growing, says Christopher Kemp, a cancer biologist at the Fred Hutchinson Cancer Center in Seattle, Washington. "This is a revolution. Patients are demanding this approach."

Behind the screen

Down a long corridor, beyond a set of tangerine-coloured doors, lies the Vivi-Bank at the Medical University of Vienna. Short for 'Viable Biobank', the room is brimming with liquid-nitrogen dewars, each containing frozen lymphoma samples.

When surgeons extract biopsies from cancerous lymph nodes, they usually immerse the tissue in formaldehyde to prepare for standard pathology analyses. That kills the cells, however, rendering them useless for functional testing. So, to enable drug screens, Staber and haematopathologist Ingrid Simonitsch-Klupp, who jointly oversee the Vivi-Bank, had to convince their surgical colleagues to change their ways, keeping the tissue alive and sending it quickly for processing and storage. "Fresh tissue is the most important thing," Simonitsch-Klupp says.

Some of that tissue arrives in Staber's lab, where researchers break up the cells using a knife, forceps and a nylon strainer, creating a slurry to distribute across a 386-well plate. In each well, they test a different drug compound — chemotherapy agents, enzyme-targeted drugs, immune-modulating therapies and more. After a night of incubation, lab testing reveals which drugs are active against the cancer and which ones are not.

A team of clinicians, known as a molecular tumour board, then uses this information to determine the most appropriate course of treatment for each patient.

Several groups have reported success with this general approach. In a trial from the University of Helsinki, for example, researchers found that individualized drug screening of leukaemia cells provided informative results substantially faster than did genomic profiling, yielding impressive clinical responses as well[4]. Of 29 people with treatment-resistant acute myeloid leukaemia (AML), 17 responded to drug-screening-informed therapies and entered remission.

Likewise, Candace Howard, a radiologist at the University of Mississippi Medical Center in Jackson, and her colleagues published a study last year showing that people with aggressive brain tumours live longer when their chemotherapy regimens are guided by lab testing than when their treatment is directed by a physician's intuition alone[5] — with lower annual health-care costs to boot[6].

"It's cheaper and it's more effective," says Jagan Valluri, a cell biologist at Marshall University in Huntington, West Virginia, who co-founded a company called Cordgenics, also based in Huntington, to commercialize the assay used in Howard's trial.

Functional drug testing is not a new idea. It was embraced by cancer researchers in the late twentieth century, but soon fell out of favour — largely owing to the limitations of assays at the time and a restricted repertoire of anti-cancer drugs. Technological improvements and an expanded pharmacopoeia have changed the picture. Yet, as with most lab-based testing systems, the necessary equipment can be expensive and requires trained personnel to operate it.

That's a big limitation according to Joan Montero, a biochemist at the University of Barcelona in Spain, because it hinders the broad implementation of functional precision drug testing, especially in low-resource settings. To address these challenges, Montero and his colleagues have been developing inexpensive and portable microfluidic devices for rapid, on-site testing of cancer cells[7].

2323 EXALT1 and 2 trials

Clinicaltrials.gov: NCT04470947

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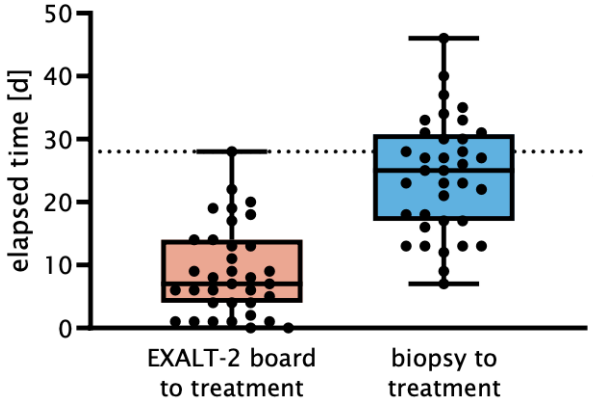
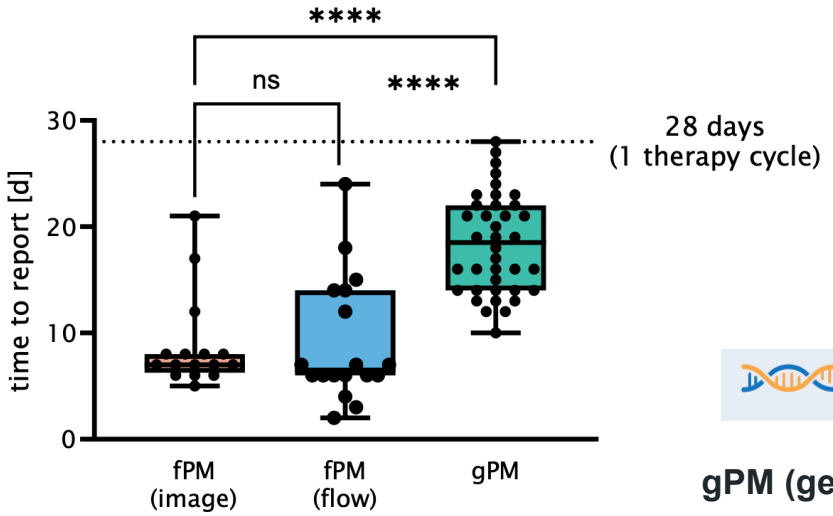
eha Sf(PM)

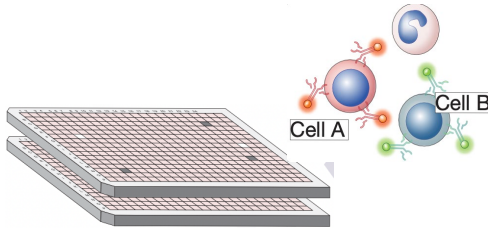
EXALT2: assay performance


Lukas Kazianka

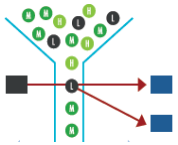

Tea Pemovska

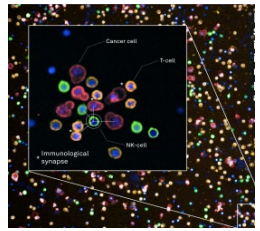






gPM (genomic)


fPM (flow)


fPM (image)

assay	report available [%]	targets identified [%]	PM therapy feasible [%]	median time to report
fPM (image)	64	100	64	7 (5 - 21)
fPM (flow cytometry)	86	100	86	6.5 (2 - 24)
gPM	86	76	65	19 (10 - 28)

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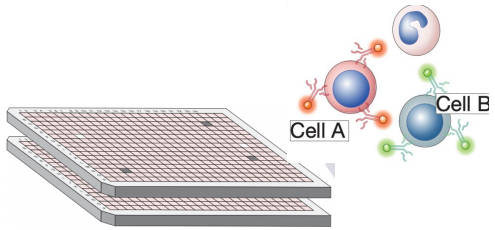
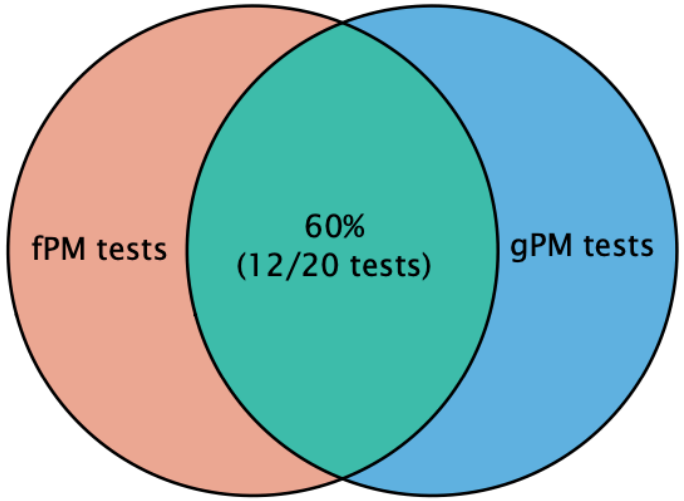
EXALT2: PM assay comparison


Lukas Kazianka


Tea Pemovska



fPM (functional)



gPM (genomic)

Clinicaltrials.gov: NCT04470947

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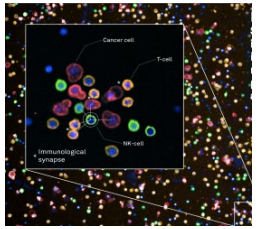
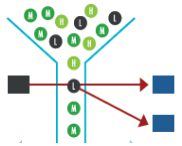
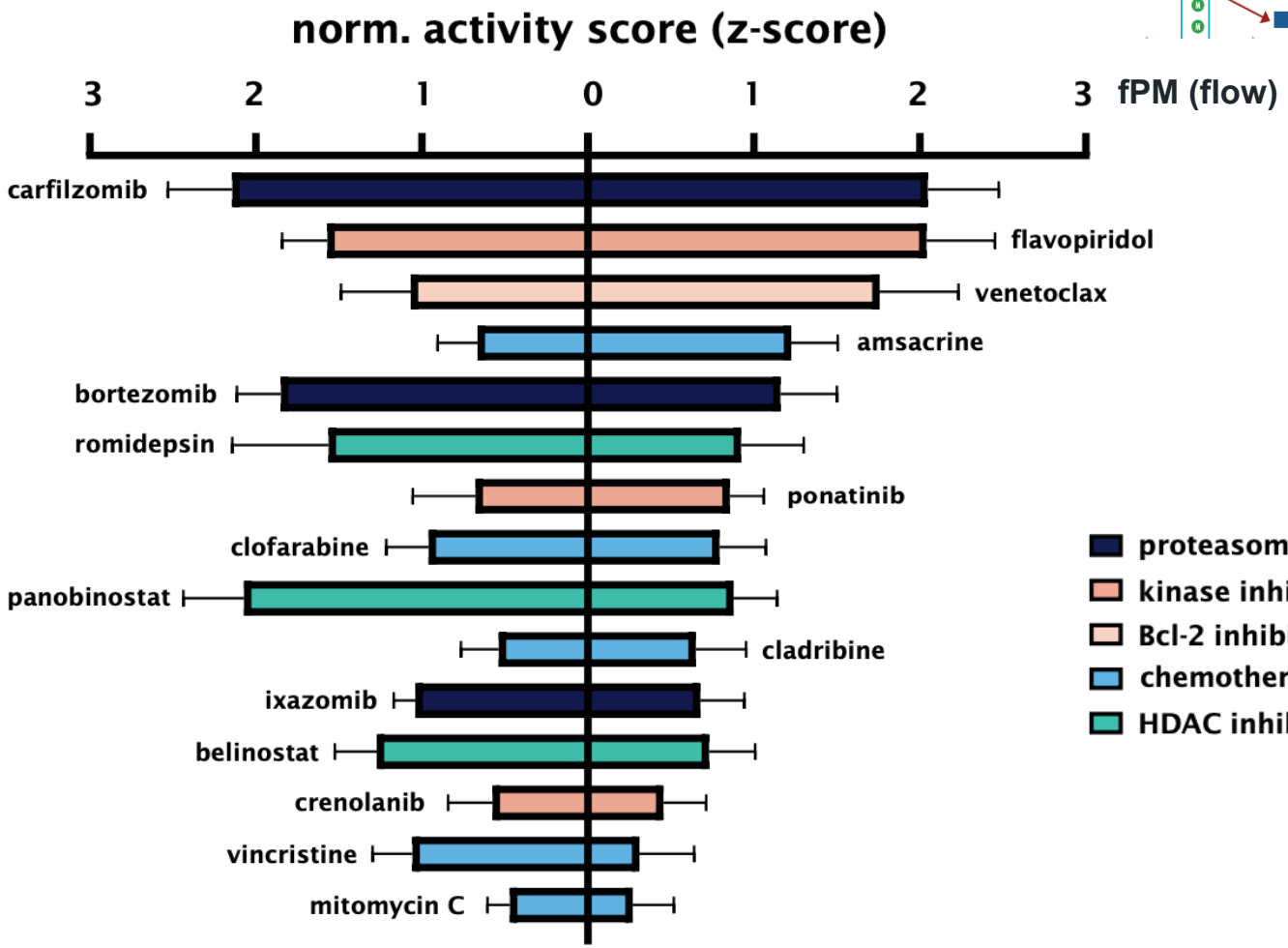
EXALT2: fPM assay comparison



fPM (image)

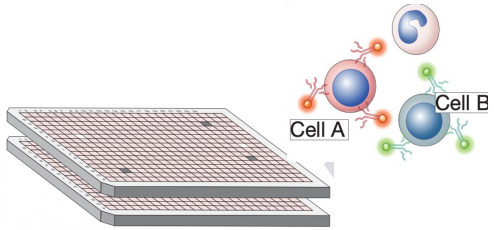


fPM (flow)



Lukas Kazianka

Tea Pemovska



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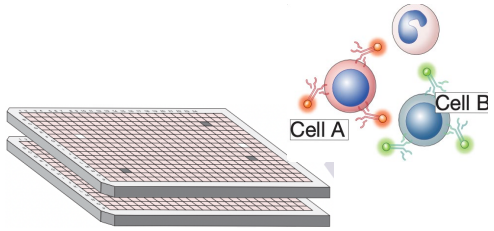
EXALT2: fPM assay comparison


Lukas Kazianka

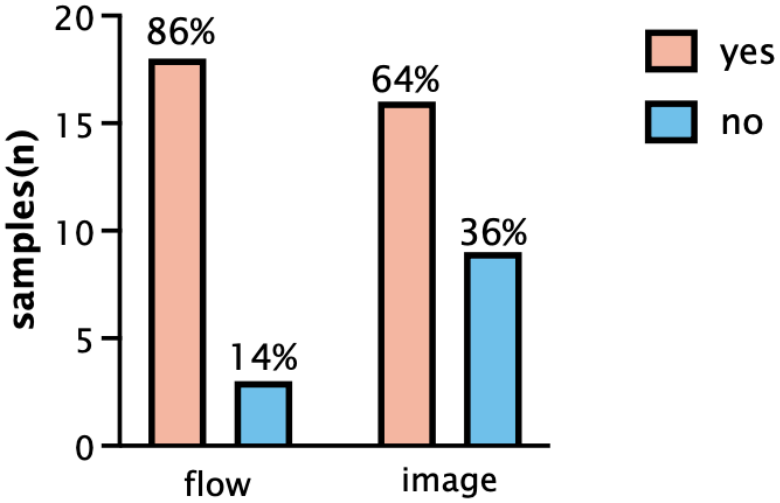

Tea Pemovska

Efficacy:

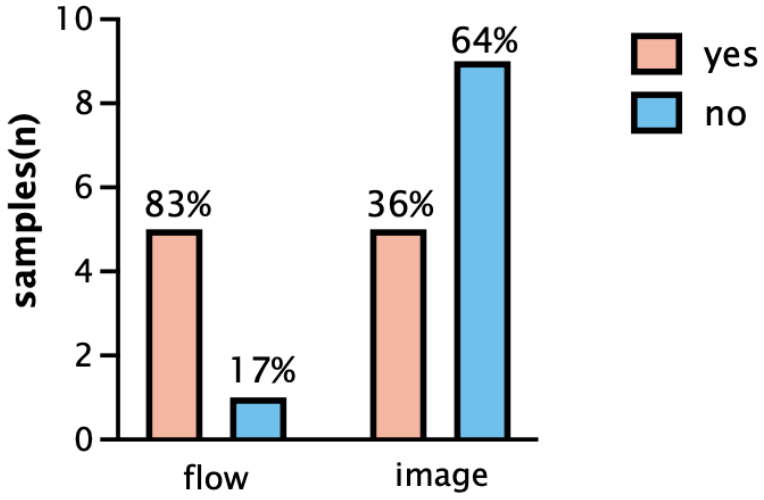
to deliver a robust result from patient samples



fPM assay worked



fPM assay worked
< $10x10^6$ cells



Clinicaltrials.gov: NCT04470947

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EXALT1 and 2: conclusion

- scFPM implementation rates 39% (EXALT1) to 80% (EXALT2)

  related to patients' clinical performance status (ECOG)

- scFPM guided tx demonstrated meaningful clinical responses, 40% exceptional

- Randomized 3-arm PM study, EXALT2, feasible and currently ongoing

- Different single-cell functional platforms deliver comparable results

- EHA-SWG Precision Hematology: Apply today!

Patients and their families

Thank you!

ÖAW AUSTRIAN ACADEMY OF SCIENCES

PEOPLE MARIE CURIE ACTIONS

FWF Der Wissenschaftsfonds.

FOUNDATION MEDICINE

WWTF

TRANSCAN-2 ERA-NET: Aligning national/regional translational cancer research programmes and activities

EHA SWG SCIENTIFIC WORKING GROUPS Precision Hematology

Sf(PM)

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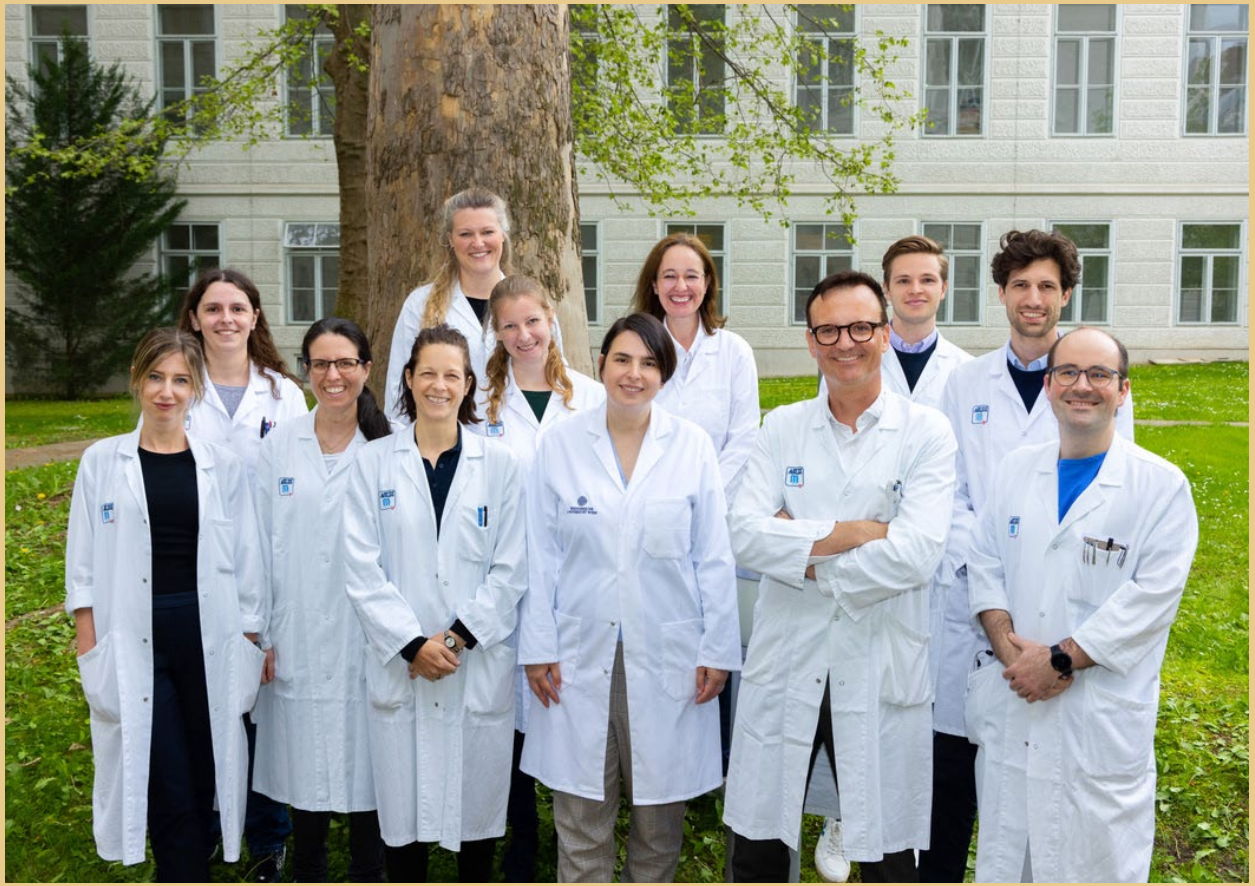

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