Genomic-driven selection of systemic therapy in metastatic prostate cancer- The ProBio trial

Professor Henrik Grönberg, Karolinska Institutet, Sweden

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Why ProBio ?

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- Academic study
- Novel and powerful study design
- Prospective evaluation of biomarkers
- Safe for patients
- Rapid results
- Collaboration with industry

Traditional RCT in oncology

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- One experimental treatment
- One fixed standard arm
- 1000-1500 patients
- 100+ centres
- No prior selection of patients based on biomarkers
- Running for many years
- Driven by pharmaceutical companies

- Takes TIME and cost MONEY

- **We need academic studies with novel designs !!!**

Do we really need biomarkers ?

- Why not treat everyone the same ?
  - Not sustainable in the long run
  - Side-effects in patients that does not benefit from the treatment
  - Breast cancer, lung cancer as examples

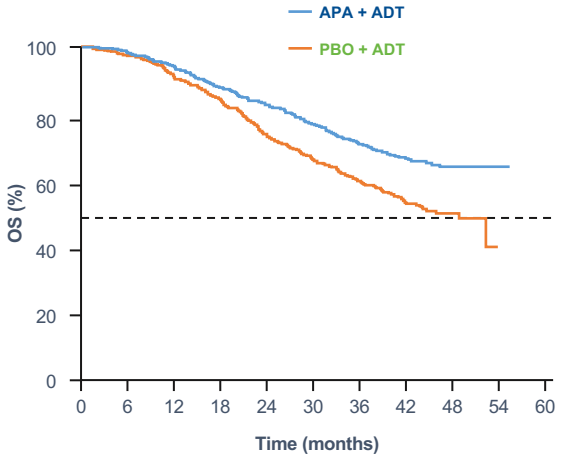
- BUT look at the results from
  - ARASENS and PEACE-1 in mHSPC
  - PROpel in mCRPC

Discussion: Triplet vs doublet OS data

ARASENS[1,2] DARO
ADT + docetaxel

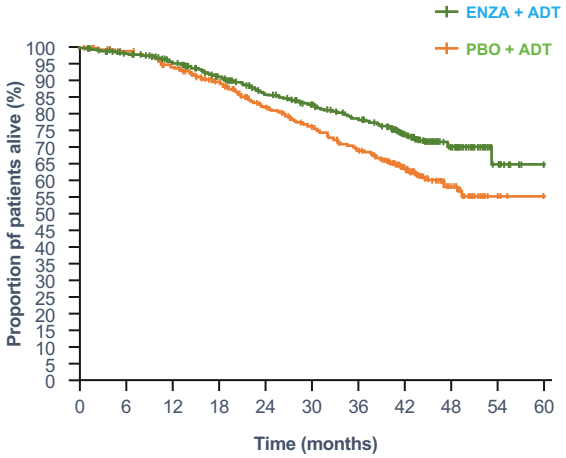
	DARO + ADT + DOC (n = 651)	PBO + ADT + DOC (n = 654)
Median, mo (95% CI)	NE (NE, NE)	48.9 (44.4, NE)
Events	229	304
HR (95% CI)	**0.68** (0.57, 0.80)	
p value	<0.001	

TITAN[3] APA



	APA + ADT (n = 525)	PBO + ADT (n = 527)
Median, y (95% CI)	NE	52.2
Events	170	235
HR (95% CI)	**0.65** (0.53, 0.79)	
p value	<0.0001	

ARCHES[4] ENZA



	ENZA + ADT (n = 574)	PBO + ADT (n = 576)
Median, y (95% CI)	NE (NE, NE)	NE (49.74, NE)
Events	154	202
HR (95% CI)	**0.66** (0.53, 0.81)	
p value	<0.0001	

These are not head-to-head comparisons; the trials cannot be directly compared.

*One patient randomised to placebo but who received darolutamide was included in the placebo group for the full analysis set.
ADT, androgen deprivation therapy; APA, apalutamide; CI, confidence interval; DARO, darolutamide; DOC, docetaxel; ENZA, enzalutamide; HR hazard ratio; NE, not estimable; OS, overall survival; PBO, placebo.

1. Smith MR, et al. Presented at ASCO GU 2022. Abstract 13; 2. Smith MR, et al. NEJM 2022 DOI: 10.1056/NEJMoa2119115. 3. Chi KN, et al. J Clin Oncol 2021;39:2294-2303; 4. Armstrong AJ, et al. Oral presentation at ESMO 2021; abstract LBA25.

Prospective use of biomarkers

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In 2020 ongoing or published RCT in mHSPC

ADT	+	Docetaxel	*GETUG-AFU15, CHAARTED E3805, STAMPEDE A/C/E*
		Abiraterone	*LATITUDE, STAMPEDE A/G*
		Enzalutamide	*ENZAMET (ANZUP1304), ARCHES*
		Apalutamide	*TITAN*
		Docetaxel + Darolutamide	*ARASENS*
		Abiraterone + Enzalutamide	*STAMPEDE A/J*
		Orteronel	*SWOG1216*
		SOC + local RT	*HORRAD, STAMPEDE A/H, SWOG1802*
		SOC + Radical Px	*G-RAMPP, SWOG1802*
		Docetaxel + Abiraterone Docetaxel + local RT Docetaxel + local RT + Abiraterone	*PEACE1*
		SOC + SBRT all lesions	*STAMPEDE A/M*
		Docetaxel + Nivolumab Docetaxel + Ipilimumab/docetaxel → nivolumab	*PROSTRATEGY*
		Docetaxel + REGN2810	*REGN2810*
		Carboplatin+Cabazitaxel (6cycles) → ADT+Abiraterone	*NCT03934840*
		Ra223 + SBRT	*NCT03361735*
		Rucaparib	*TRIUMPH*

Only one trial had patient selection based on biomarkers

Outcome adaptive design?

Example

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Initial probability to be randomized to LM_n

Drug	Biomarkör BM_1	BM_2	BM_3	BM_4
Abi/ Enza	0.7	0.1	0	0.1
Carbo	0.1	0.7	0.33	0.1
Doxe	0.1	0.1	0.33	0.7
Caba	0.1	0.1	0.33	0.1

400-500 patients

Updated probability to be randomized to LM_n

Drug	Biomarkör BM_1	BM_2	BM_3	BM_4
Abi/ Enza	0.8	0.4	0.2	0.25
Carbo	0.2	0.6	0.2	0.25
Doxe	0	0	0.6	0.25
Caba	0	0	0.2	0.25

Safe for the patient

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- Control arm – Standard of Care
  - Change over time when new treatments are available
  - Each physician decides what is the best treatment for the patient

- Adaptive design
  - Improve over time in the experimental arms

Rapid results

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Rapid results

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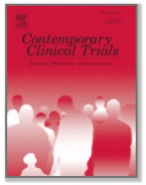
ELSEVIER

Contemporary Clinical Trials
Volume 112, January 2022, 106625



Research Article

Implementation of platform trials in the COVID-19 pandemic: A rapid review

Alyssa M. Vanderbeek, Judith M. Bliss, Zhulin Yin, Christina Yap

Results

We identified 58 COVID-19 platform trials globally registered between January 2020 and May 2021. According to trial registries, 16 trials have added new therapies (median 3, IQR 4) and 11 have dropped arms (median 3, IQR 2.5). About 50% of trials publicly share their protocol, and 31 trials (53%) intend to share trial data. Forty-nine trials (84%) explicitly report adaptive features, and 21 trials (36%) state Bayesian methods.

Collaboration with industry

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- Important that academia and pharmaceutical companies can work together in trials like ProBio
  - Knowledge
  - New drugs
  - Funding

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ProBio Today

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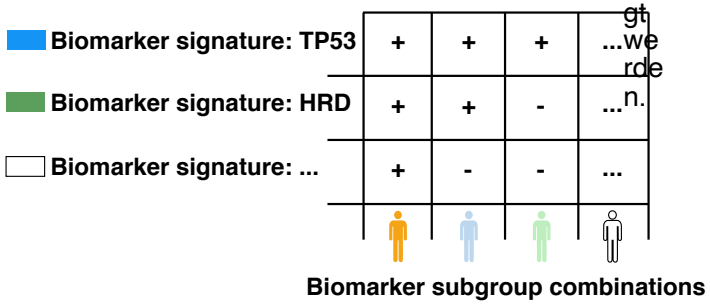
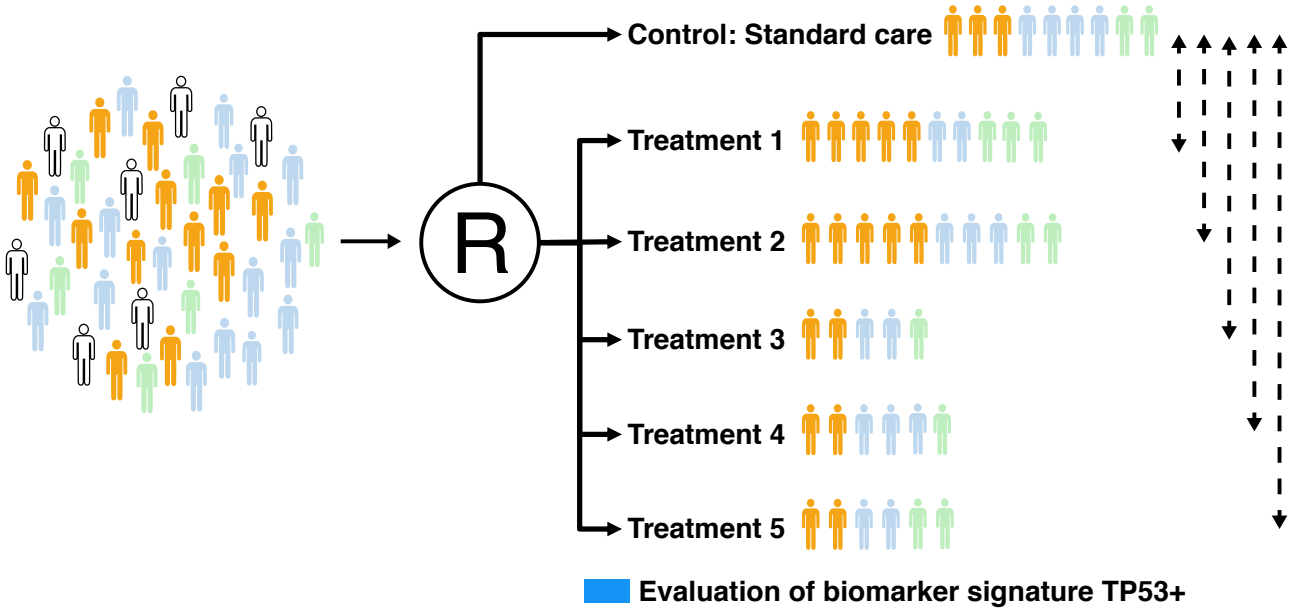
- In metastatic prostate cancer
  - Multiple therapies
  - Multiple molecular biomarkers with predictive potential
- ProBio = 1st biomarker-driven outcome-adaptive platform trial to evaluate these simulteanously





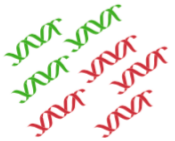
Circulating tumor DNA profiling

1 Draw blood

2 x 10 ml blood

2 Extract cfDNA from plasma and germline DNA from WBC

Normal cell-free DNA

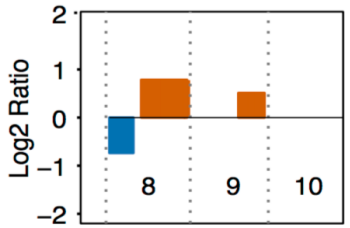


Circulating tumor DNA

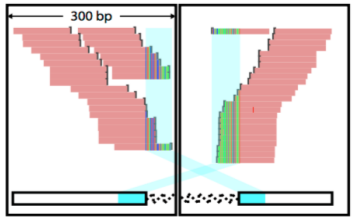
White blood cell DNA

3 Perform targeted sequencing of cfDNA and germline DNA

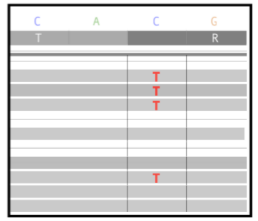
Copy-number alterations



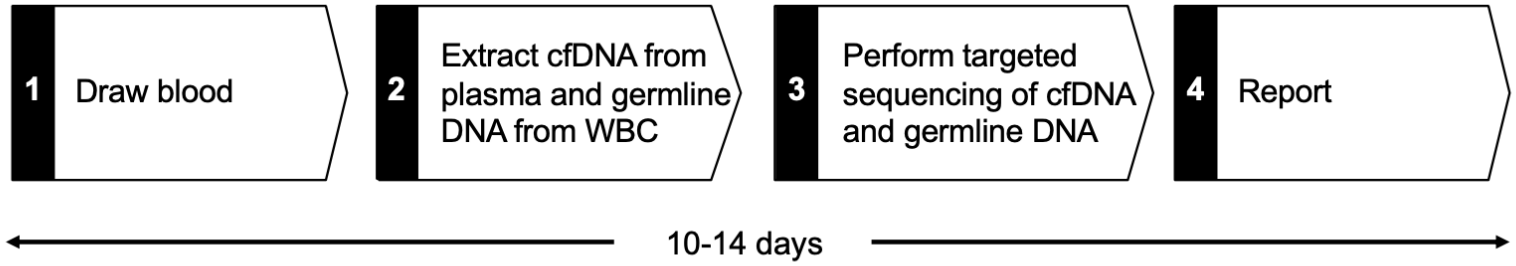
Structural variants



Point mutations



ProBio trial
- the assay



Custom ctDNA panel for metastatic prostate cancer (1.48 Mb)

- Mutations in 78 genes
- Structural rearrangements in 10 genes
- Genome-wide copy number alternations
- 63 microsatellites to infer MSI
- Tumor Mutational Burden (TMB)
- Estimation of circulating tumor burden (i.e. circulating tumor DNA fraction)

Initial biomarker signatures

- A gene or combinations of genes associated with response to a certain therapy
  - Somatic alteration in TP53 ($TP53_{mut}$)
    - hypothesis: poor prognosis overall
    - ~37% prevalence
  - DNA repair deficiency (DRD)
    - hypothesis: good response to
      - ARSi plus PARP and
      - Carboplatin
    - ~18% prevalence
  - TP53 wild type and AR wild type ($TP53_{wt}/AR_{gsr\text{-}wt}/AR_{mut\text{-}wt}$)
    - hypothesis: good response to abiraterone/enzalutamide
    - ~50% prevalence
  - TMPRSS2-ERG gene fusion ($T\text{-}E_{fusion}$)
    - hypothesis: good response to docetaxel
    - ~32% prevalence

- Retrospective analysis will generate new BS

ClinicalTrials.gov Identifier: NCT03903835

ProBio 2023

- Included patients:
  - 418 patients (358 in mCRPC and 61 in mHSPC)
- Randomised patients :
  - 281 in mCRPC (200+81)
  - 40 in mHSPC
- Including patients in 29 centres
  - Hope to open new centres in Switzerland
- New version of the protocol 5.0
  - Including a new arm in mCRPC
    - Capivasertib + Docetaxel (AKT inhibitor from AZ) in PIK mutated patients