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# Increasing output & reducing waste of drug repurposing trials

## Thanks to strong drug candidates and efficient designs

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*Director of Clinical Research @ the Anticancer Fund, Brussels, Belgium*

*Morningside CIAM conference on drug repurposing – 15 Nov 2019*

# Why did the Anticancer Fund decide to invest in drug repurposing?

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# Rationale for **drug repurposing**

- The list of *secondary uses* is long
- 39 drugs repurposed in pediatric hemato-oncology (*Blatt 2013 Drug Discov Today*)
- 

*DeMonaco & Von Hippel 2006 Pharmacotherapy*
- Note to self (& others): quantifying the proportion of FDA/EMA approved drugs that found secondary uses after approval would give a great service.

# Rationale for **investing** in drug repurposing

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## *Introducing the drug toolbox*

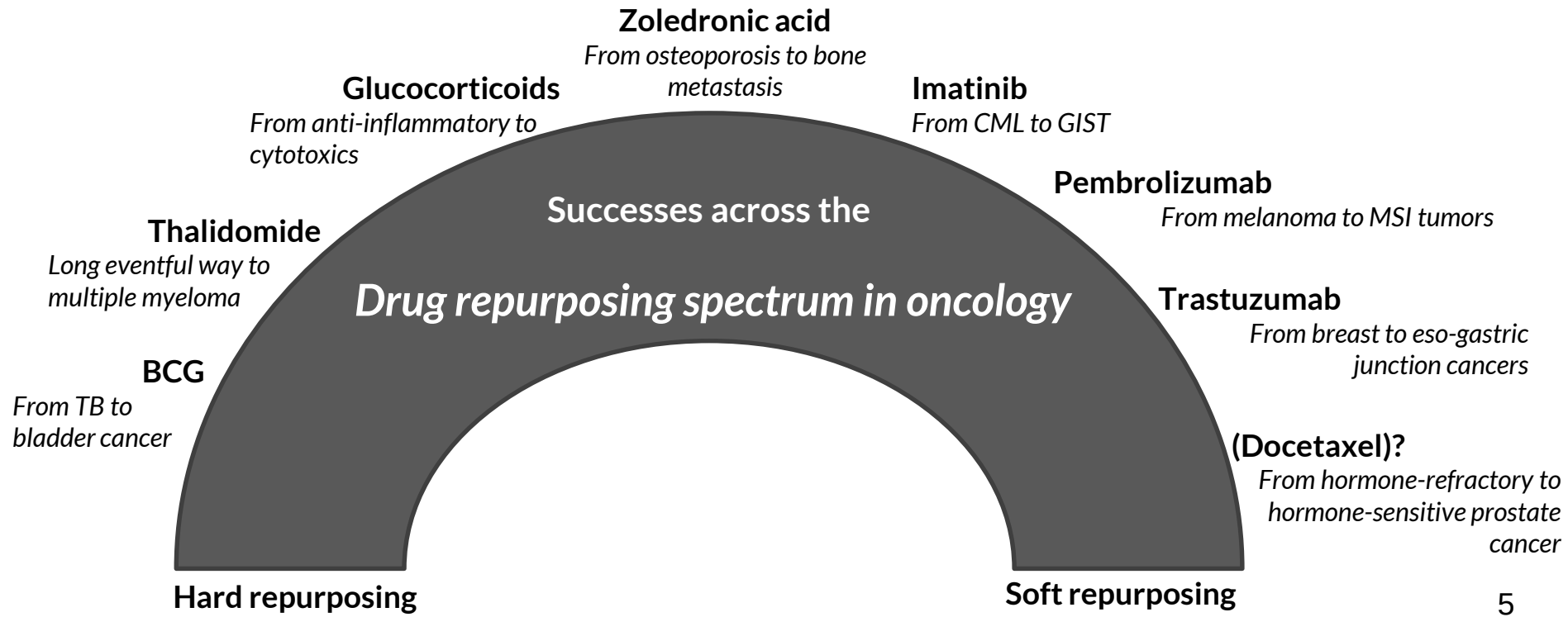
- Toolbox is large: > 2000 drugs approved (+ ≈ 30 new each year)
- Tools have multiple functions = polypharmacology (Mestres 2008 Nat Biotech, Klaeger 2018 Science), even for mAb (Fornoni 2011 STM, Bogdanovich 2015 Signal Transduct Target Ther)
- Science sheds new light on diseases & drugs → new ways of tinkering

**Drugs may not do what we think they do**

The majority of proposed anticancer treatments do not succeed in advancing to clinical use because of problems with efficacy or toxicity, often for unclear reasons. Lin *et al.* discovered that a drug candidate in clinical development was effective at killing cancer cells even when its target protein was knocked out, suggesting that its proposed mechanism of action was incorrect. The researchers then identified multiple drugs with similar problems and also

***Lin 2019 STM***
*Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials*

# Rationale for investing in drug repurposing **in oncology**



# Rationale for investing in drug repurposing in oncology **as a (rather small) foundation**

- As a rather small foundation, **off-patent drugs are interesting** as we need
  - **Affordable trials**
  - **Projects that are free of** (or easy for) **legal/IP issues**
- Off-patent drugs are ‘financial orphans looking for adoption’ *(Sukhatme 2014 Health Affairs Blog)*. Maybe, we can adopt some of them!
- Literature and conferences are full of stories of missed opportunities

# Randomized clinical trial - 120 RCC patients - IL-2 for 7 days preop
*(Klatte 2006 Br J Cancer)*

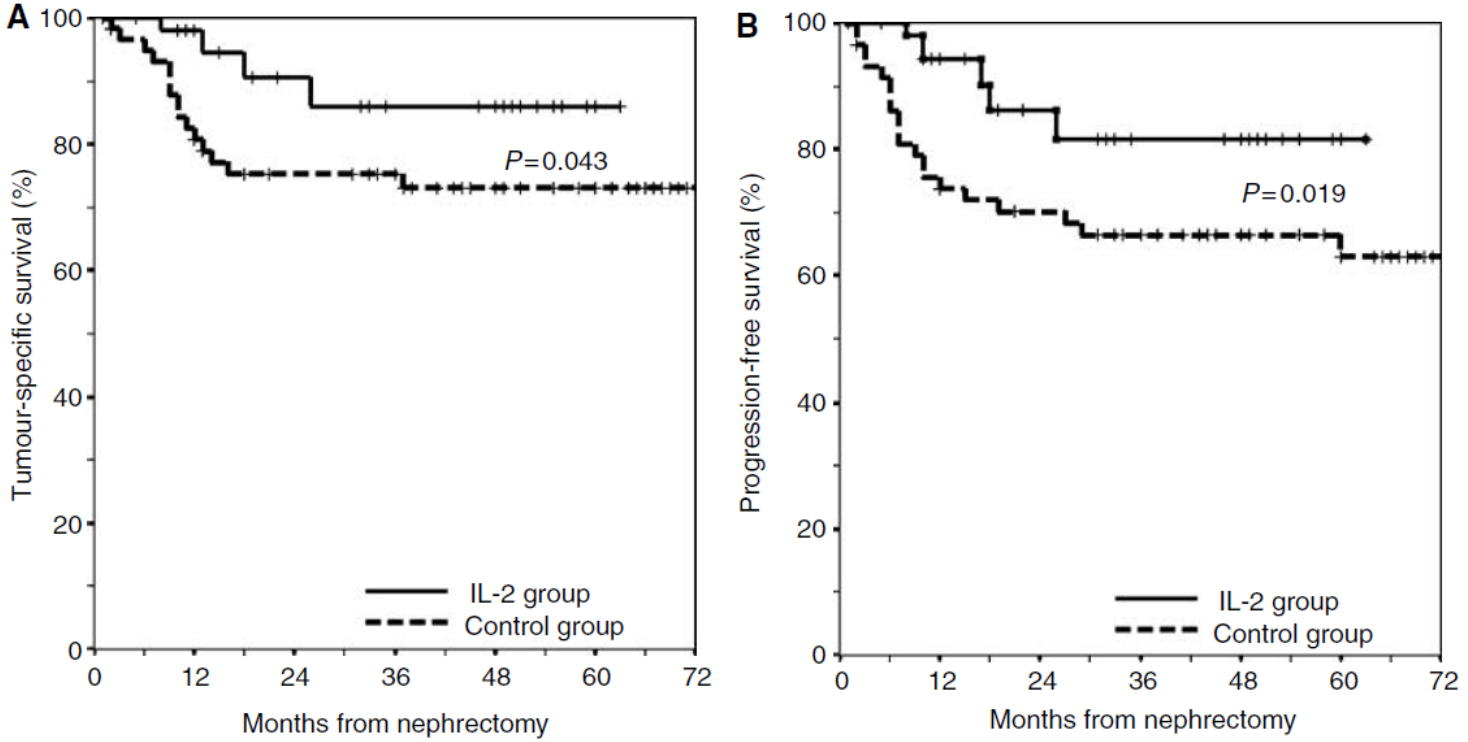



**Figure 3** Kaplan–Meier survival estimates of patients treated with IL-2 (——, IL-2 group) and without treatment (– – – –, control group) according to (**A**) tumour-specific survival and (**B**) progression-free survival.

# Building up a plan to be successful

**Success** = improving cancer patients' outcomes (thanks to drug repurposing here)

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# 1/ Mapping the potential – ReDO

- Collect data on **hard repurposing opportunities → 300 drugs now!**
- Review evidence for a **selection of promising candidates**
- Understand the **non-scientific reasons** of lack of success

http://www.redo-project.org/

http://www.redo-project.org/db

*(Pantziarka 2018 Ecancermedicalscience)*

# 2/ First trials – Exploring the field

| Drugs | Cancer | Phase |
|---|---|---|
| Dichloroacetate | Glioblastoma | 1 |
| Fluvastatin & celecoxib | Low-grade optic pathway glioma | 1 |
| Ketorolac | Breast cancer | 3 |
| Clarithromycin & pioglitazone | NSCLC | 2 |
| 9 drugs | Glioblastoma | 1 |
| Low-dose paclitaxel | Melanoma | Pilot |
| Nitroglycerin | NSCLC | 2 |
| ATRA & pioglitazone | AML | 1/2 |

# 2/ First trials – Failing (& learning)

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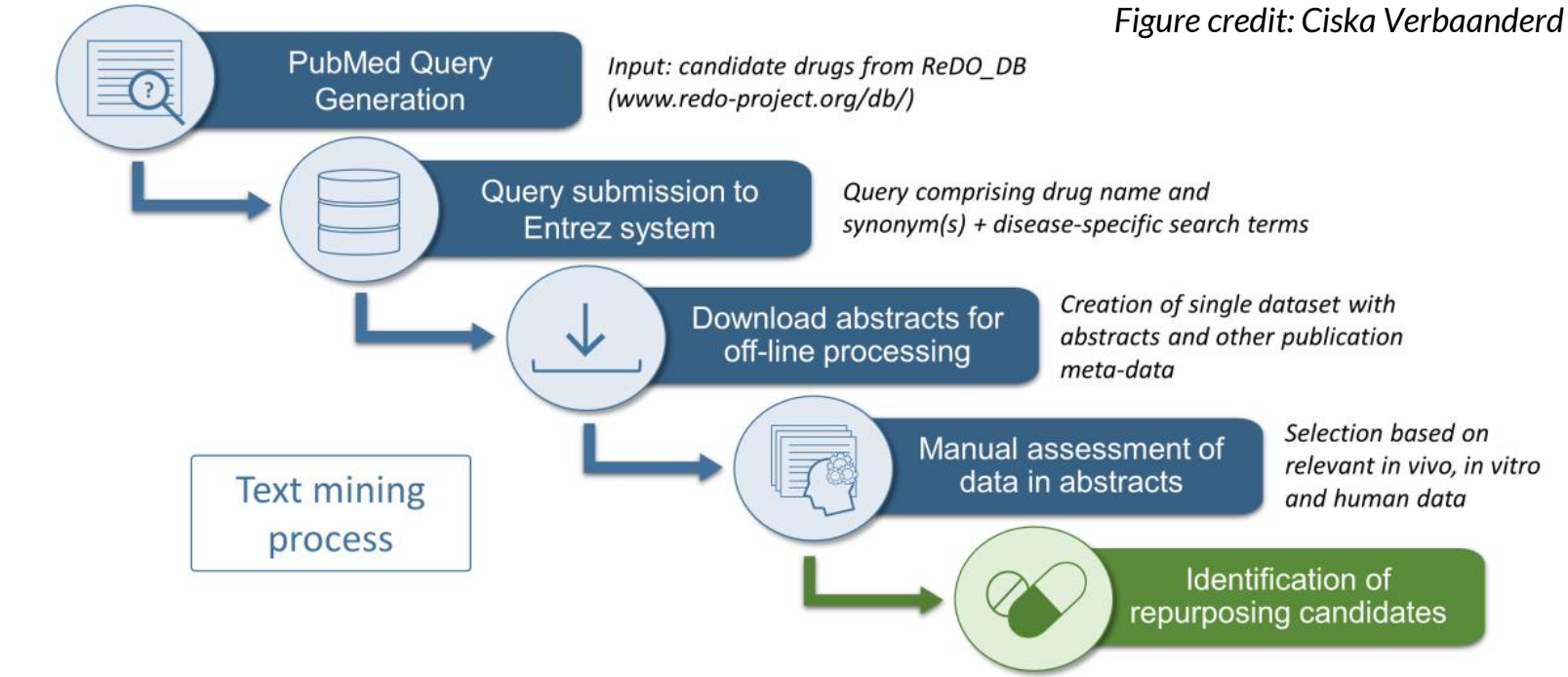
| Drugs | Cancer | Phase | Prim. endpoint met? | Results | FU trial |
|---|---|---|---|---|---|
| Dichloroacetate | Glioblastoma | 1 | Yes (safety) | Dunbar 2014 Invest New Drugs | No |
| Fluvastatin & celecoxib | Low-grade optic pathway glioma | 1 | Yes (Phase 2 dose) | SIOP 2019 | TBD |
| Ketorolac | Breast cancer | 3 | No (efficacy) | SABCS 2018 | No |
| Clarithromycin & pioglitazone | NSCLC | 2 | No (efficacy) | ESMO 2019 | No |
| 9 drugs | Glioblastoma | 1 | Yes (safety) | SNO 2018 | TBD |
| Low-dose paclitaxel | Melanoma | Pilot | Yes (biology) | German Skin Cancer Conf 2018 | No |
| Nitroglycerin | NSCLC | 2 | No (efficacy) | ESTRO 2018 | No |
| ATRA & pioglitazone | AML | 1/2 | Yes (safety) but… | ASH 2019 | No |

# 3/ A more rational approach – Drugs

*Pantziarka et al 2019, submitted*
*Figure credit: Ciska Verbaanderd*




**+ similar methods for trials registries**

Analysis

*Carlisle 2018 BMJ*

# Trials that say "maybe": the disconnect between exploratory and confirmatory testing after drug approval

*BMJ* 2018 ; 360 doi: https://doi.org/10.1136/bmj.k959 (Published 20 March 2018)

## Key messages

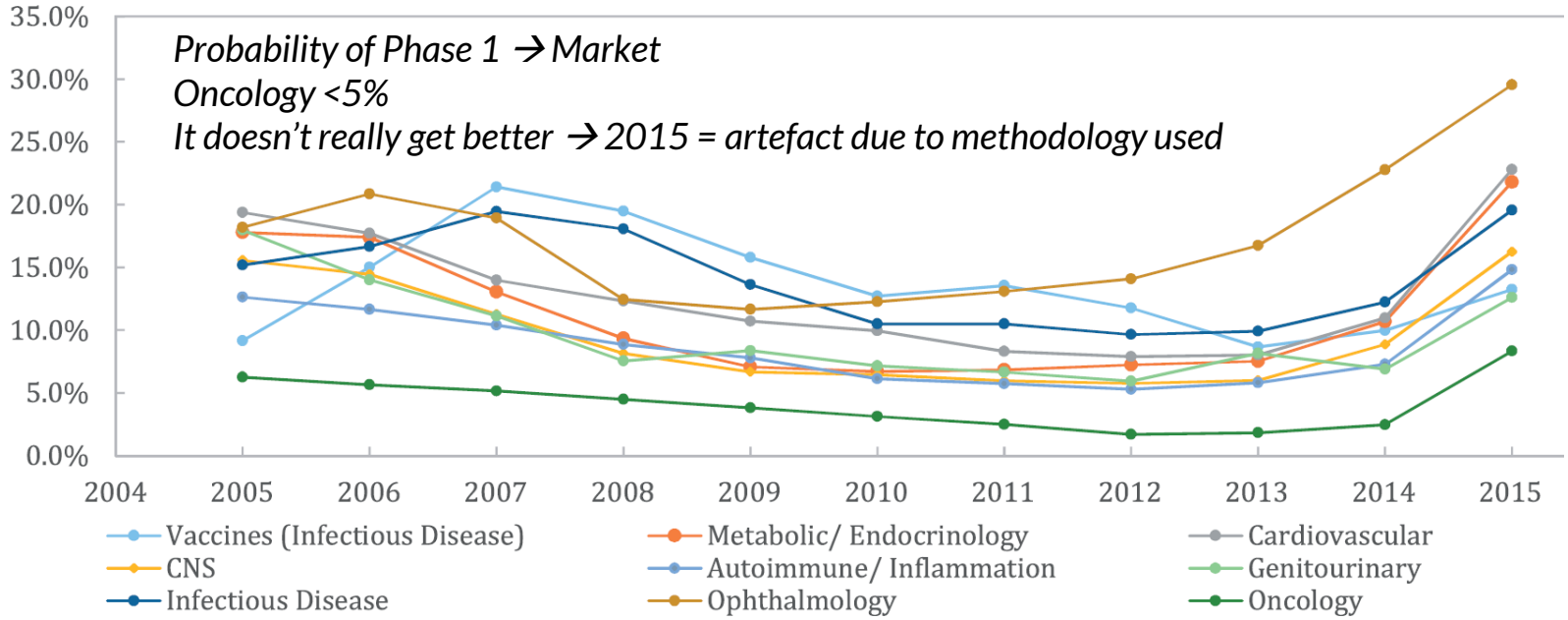
- After a new drug receives approval, companies and public sponsors often run numerous small trials exploring the drug's activity in different indications
- The level of evidence produced in such trials is usually low, and drug companies and public sponsors often fail to follow up on promising exploratory findings by running large, confirmatory trials

# 3/ A more rational approach – Trials (1)

- **Some financial orphans need help now**
- Let's help unsexy **confirmatory** trials
- 3 trials
  - **Vitamin D** supplementation as adjuvant treatment in early stage cutaneous malignant melanoma (NCT01748448)
  - A phase 3 double-blind placebo-controlled randomised trial of **aspirin** on recurrence and survival in colon cancer patients (NCT02301286)
  - Maintenance therapy with **aromatase inhibitor** in epithelial ovarian cancer: a randomised double-blinded placebo-controlled phase 3 trial (NCT04111978)

# 3/ A more rational approach – Trials (2)

## Probability of Success of Trials *(Wong & Lo Biostat 2019)*



# How to increase our success rate?

1. **Multiple arms in the same trial** *(Parmar 2014 Lancet)*
2.
3.

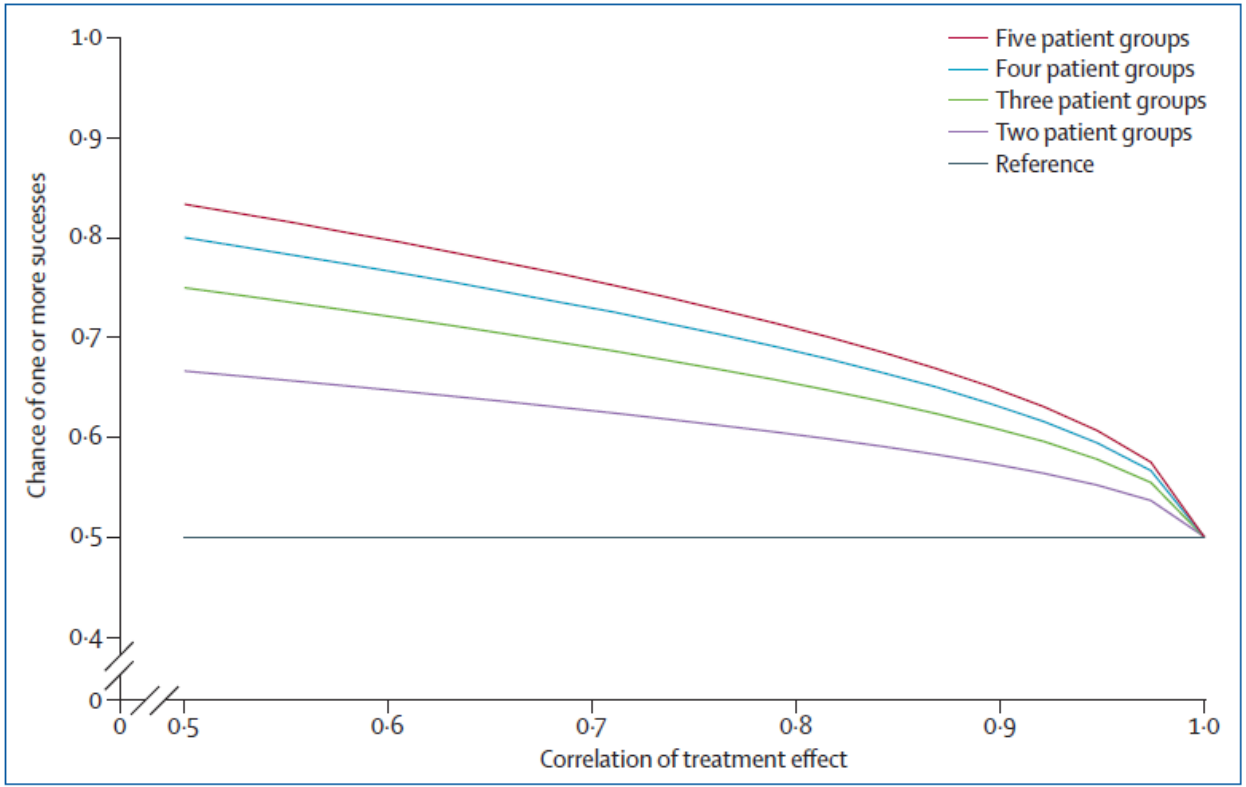



*Figure 1*: Probability of a patient group being found superior to control, as a function of the number of groups (assuming probability of a single group being found superior is 50%)[6]

# How to increase our success rate?

1. **Multiple arms in the same trial** *(Parmar 2014 Lancet)*
2. **Use of a biomarker for patients' selection → 5.5% to 10.3% -** FDA data *(Wong 2019 Biostatistics)*
3.

# How to increase our success rate?

1. **Multiple arms in the same trial** *(Parmar 2014 Lancet)*
2. **Use of a biomarker for patients' selection** (*Wong 2019 Biostat*)
3. **Ask for regulators' scientific advice & comply with it** *(Regnstrom 2010 Eur J Clin Pharmacol)*

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| | | | |
|---|---|---|---|
| Compliance[b] | | | <0.0001 |
| Non-compliant to SA | 6/20 (30%) | 0.166 [0.059; 0.465] | |
| Compliant to SA | 38/39 (97%) | 14.709 [1.946; 111.158] | |
| No-SA ($n$=119) or SA without a assessment of compliance ($n$=10) | 93/129 (72%) | 1 | |

# 3/ A more rational approach – Trials

- With so many drug repurposing candidates, **multi-arm trials are a no brainer**
- Use biomarker and ask for scientific advice upfront, whenever possible
- Plan we initiated in 2018

1. **Identify cancer trials that can accept new arms**
2. **Work out proposal of strong drug candidates** supported by good preclinical and early phase trial data
3. **Offer funding to plug in a new arm**

# Identify trials that accept new arms

| Name | Country | Disease and setting | Status |
|---|---|---|---|
| **STAMPEDE** | UK | Advanced and metastatic prostate cancer | Ongoing |
| **ACTIW** | France | Chronic myeloid leukemia in chronic phase | Ongoing |
| **I-SPY-2** | USA | Breast cancer, neo-adjuvant | Ongoing |
| **GBM AGILE** | USA | Newly-diagnosed and recurrent glioblastoma | Ongoing |
| **Precision Promise** | USA | Advanced pancreatic cancer | In preparation |
| **LEAP** | USA | Acute myeloid leukemia in patients >60 | Ongoing |
| **NRG GI-002** | USA | Rectal cancer, neo-adjuvant | Ongoing |
| **Brain Matrix** | UK | Newly-diagnosed adult and pediatric gliomas | In preparation |
| **MYDRUG** | USA | Multiple Myeloma, NOS | Ongoing |
| **UPSTREAM** | Belgium | Recurrent head & neck cancers | Ongoing |
| **FAR-RMS** | UK | Newly-diagnosed & recurrent rhabdomyosarcoma | In preparation |
| **MAGMA** | Australia | Newly-diagnosed glioblastoma | In preparation |
| **REECUR** | UK | Recurrent and refractory Ewing sarcoma | Ongoing |

# **Failing** (& learning) again

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| Cancer | Drug candidate proposed | Outcome of discussion | Reasons (my interpretation) |
|---|---|---|---|
| Prostate | Low-dose cyclophospamide | No | No additional arm needed |
| Breast | Propranolol (with trastuzumab) | No | Change in standard of care & financial model inadequate for off-patent drugs |
| CML | Clarithromycin, tigecycline | No | Weak evidence for candidates |
| AML | ATRA, pioglitazone, azacitidine | No | Trial in preparation, too early |
| Rectal | Nelfinavir | Ongoing | |
| Pancreas | None specific | No? | No interest & financial model inadequate for off-patent drugs |
| *Glioblastoma* | *Work ongoing* | *NA* | |
| *Ewing* | *Work ongoing* | *NA* | |

# Now what?

Trying harder while addressing non-scientific issues in parallel

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# Regulatory issues

- Learning by doing: **Orphan Drug Designation** (ODD)

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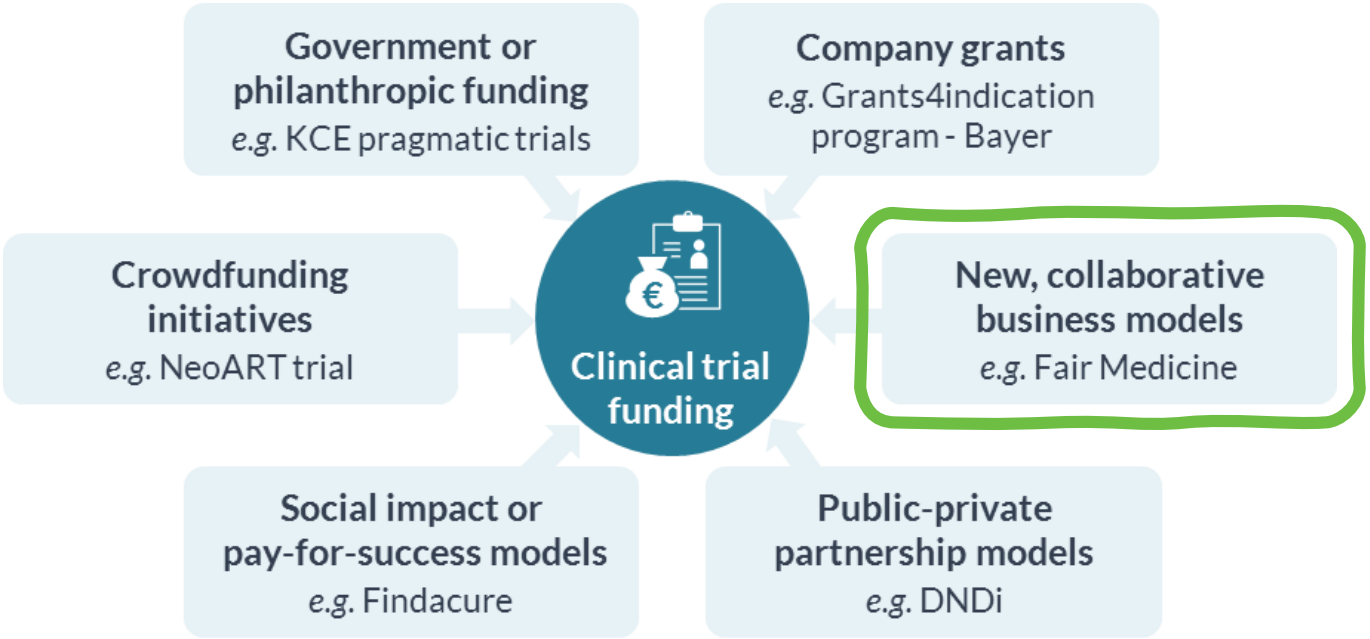
On 12 December 2016, orphan designation (EU/3/16/1805) was granted by the European Commission to The Anticancer Fund, Belgium, for propranolol for the treatment of soft tissue sarcoma.

- Adapting the **regulatory framework** in Europe (*Verbaanderd 2017 Trends in Cancer*)

# *Financial* orphan – Alternative models?

*Unpublished*
*Figure credit: Ciska Verbaanderd*



# The Fair Medicine model

Fair Medicine
first co-operative medicine collective

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## Together we invest knowledge, time and money to produce better, safe and affordable medicines

Fair Medicine takes it differently than the classic pharmaceutical industry. We work with the coalition model. Patients, doctors, hospitals and pharmacists develop new resources together. Together we invest knowledge, time and money. And we're transparent about the costs and what's left at the end of the ride at acceptable profit. This enables us to access safe, effective and affordable medicines for everyone.

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