SYGNATURE DISCOVERY

Re-thinking oncology drug discovery

Where are we heading next…?

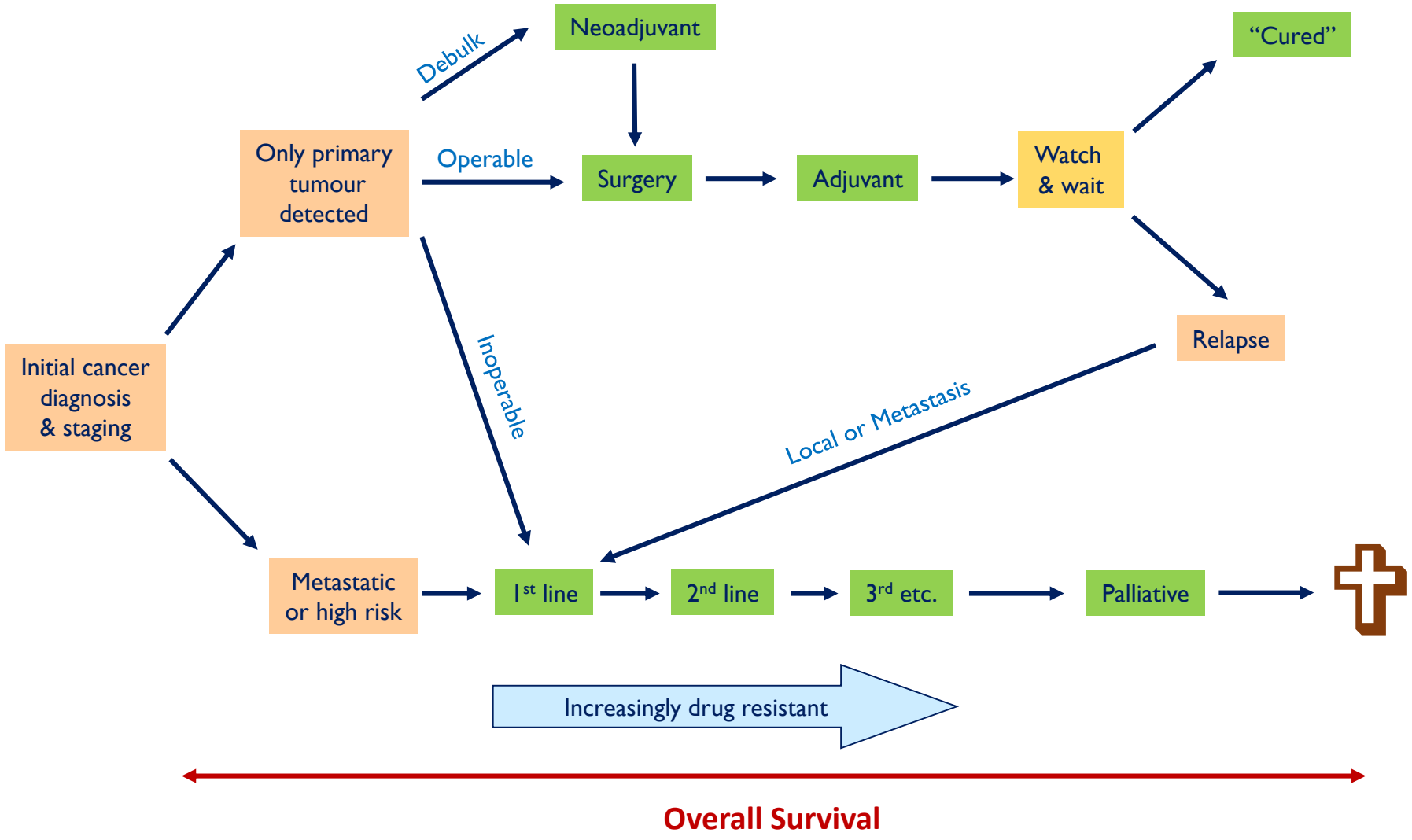
Allan Jordan

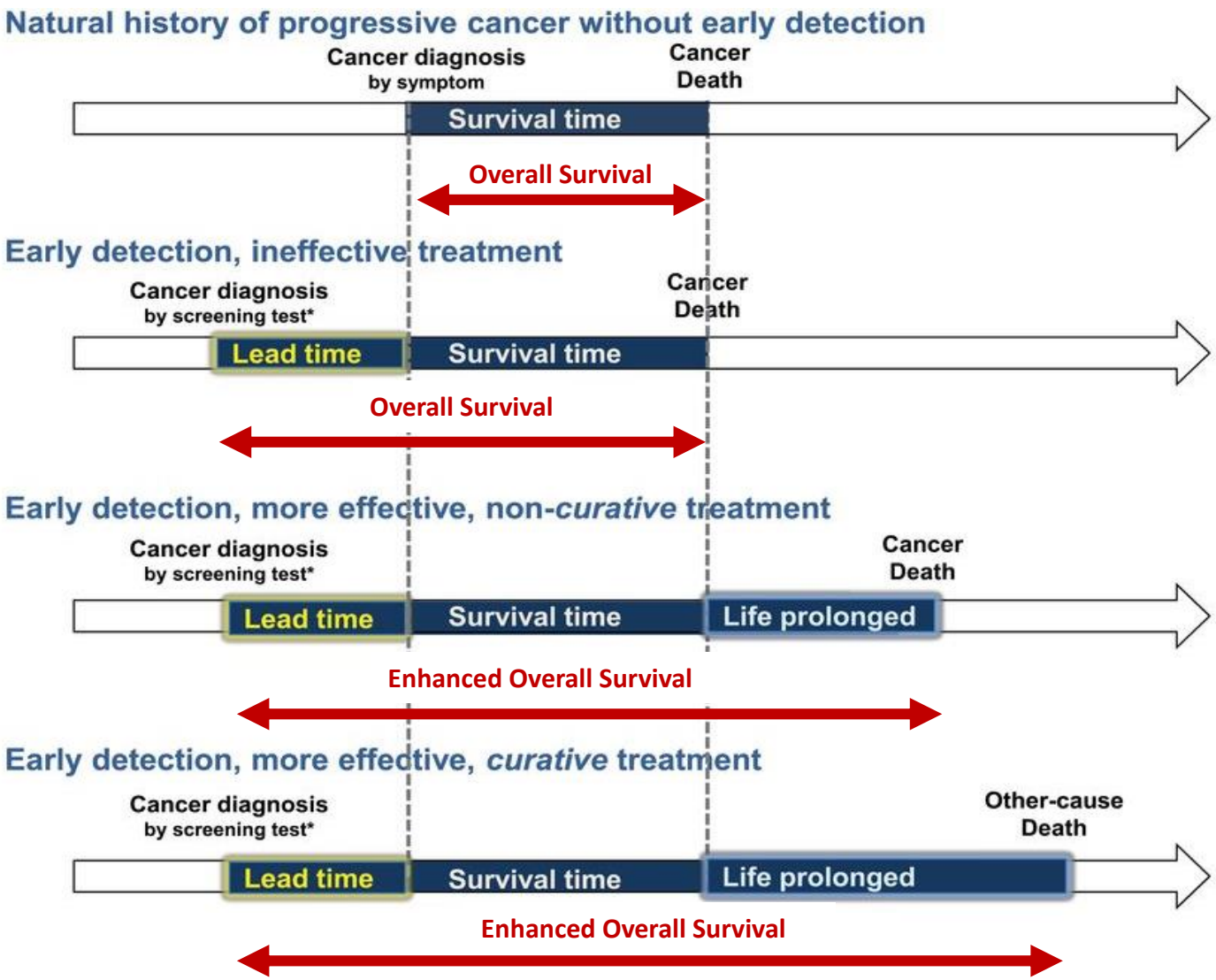
Director of Oncology Drug Discovery

Enabling Success

www.sygnaturediscovery.com

Solid Tumours:- The patient journey





JNCI Monographs (2014) 49:187

What defines a good cancer drug?

- Potency
- Selectivity
- Pharmacokinetics
- Pharmacodynamics
- Safety
- Stability
- Novelty
- Ease of synthesis
- Formulation
- Commercially viable

- Cure vs control
- Secondary disease limitation / eradication
- Safer
- More effective
- Fewer side effects
- Better Quality of Life
- Convenience

Delivering better drugs

- CNS oncology
- Better combination therapies
- Better delivery systems
- Alternate drug targets

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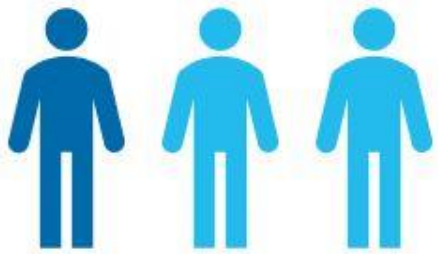
CNS oncology



1 of 3 people who die of cancer…

…have evidence of brain metastasis at autopsy

- Most of the recent oncology drugs are poorly CNS-penetrant
- Significant need in, *e.g.* breast cancer, lung cancer…

- Demands we think more about brain-penetrant compounds in drug discovery

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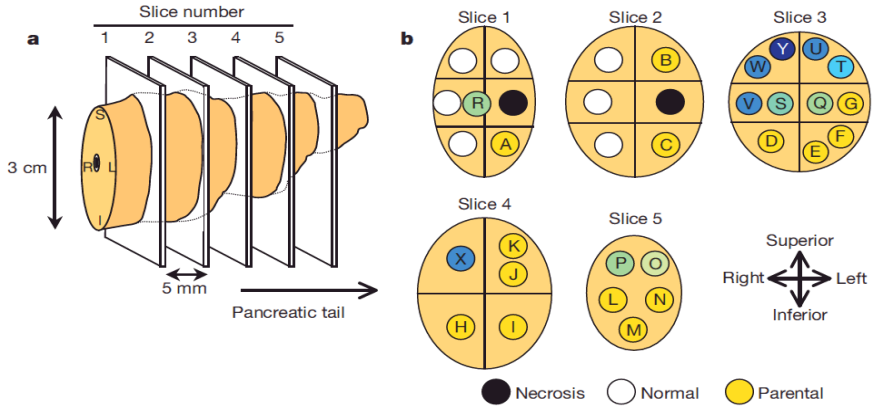
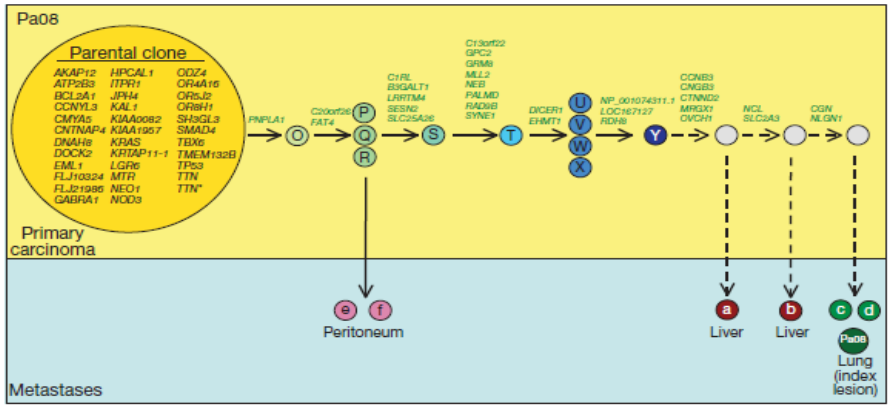
Why do single-agent therapies fail?

- Our cancer discovery model has been focussed upon single genetic drivers
  - Identify a single mutation that “drives” cancer progression
  - Enzyme, cell and *in vivo* assays use systems to represent these monogenic alterations
  - Monocultures of homogeneous, consistent cell populations

- How representative is this of the human condition?

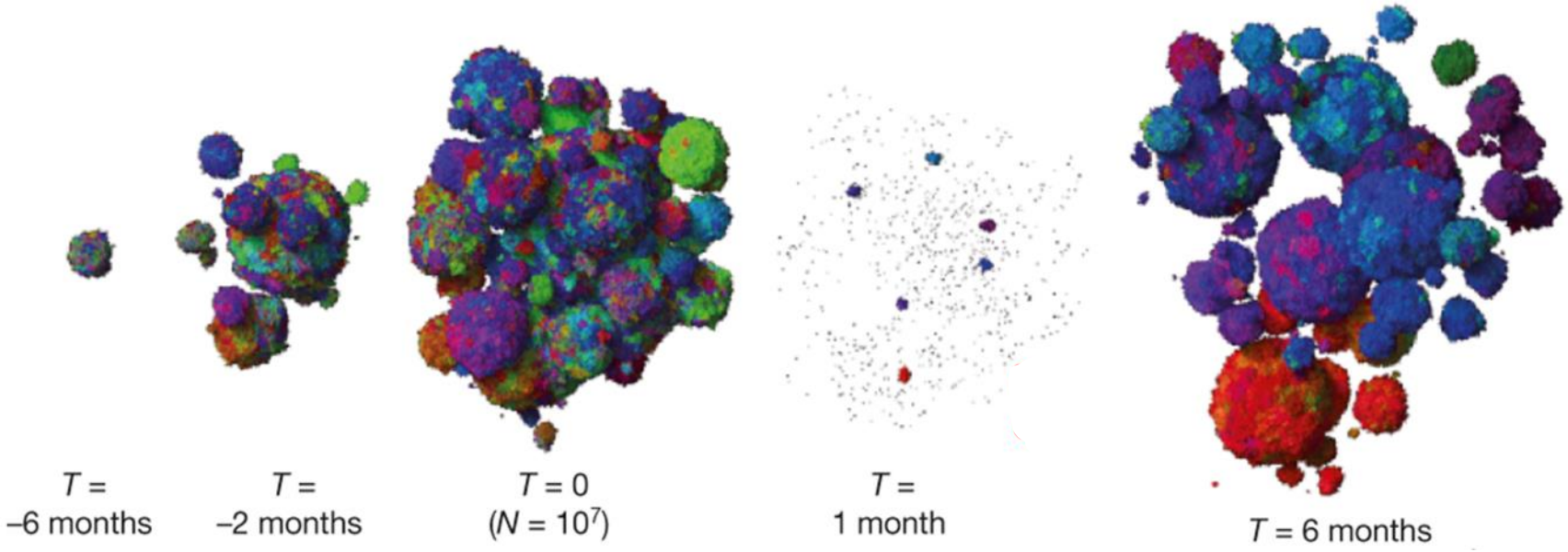
An example - Pancreatic cancer





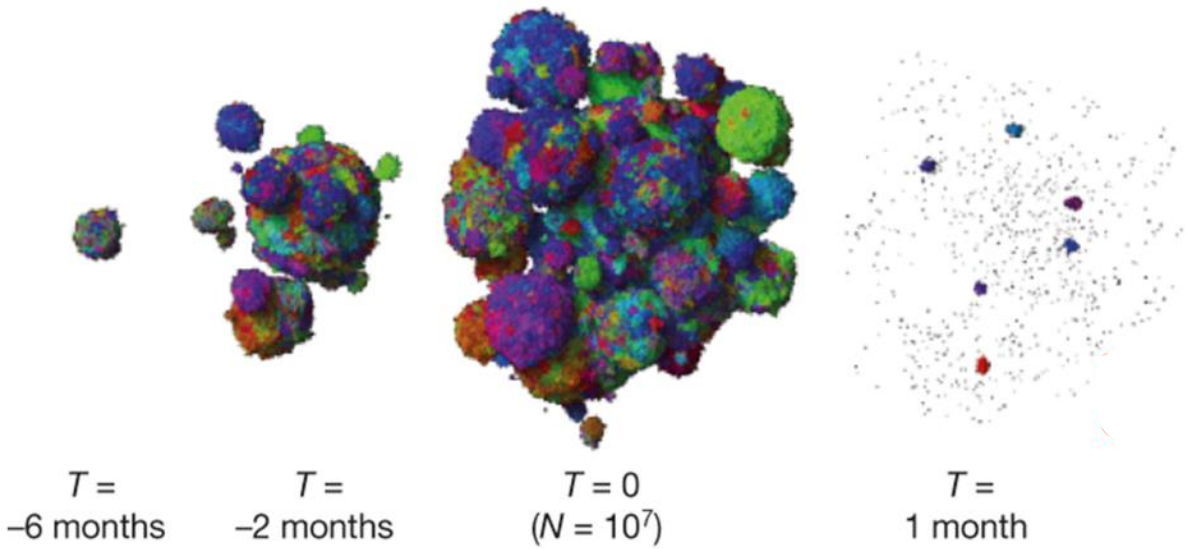
Nature (2010) 467: 1114

Implications for treatment…



Nature (2015) **525:** 261

Drug 1 **Drug 2 (3, 4,..)**



Overcoming intrinsic resistance

- Combination of agents inhibiting multiple pathways can deliver prolonged clinical response
  - *e.g.* dabrafenib / trametinib in melanoma

- But:
  - Cancer drugs have always been designed to push the limits of tolerability as single agents to deliver maximum therapeutic benefit
  - Dose-limiting toxicity often leads to dose reductions, to potentially sub-therapeutic levels

- **Demands better tolerated agents where side effect profiles allow co-dosing at biologically effective doses**

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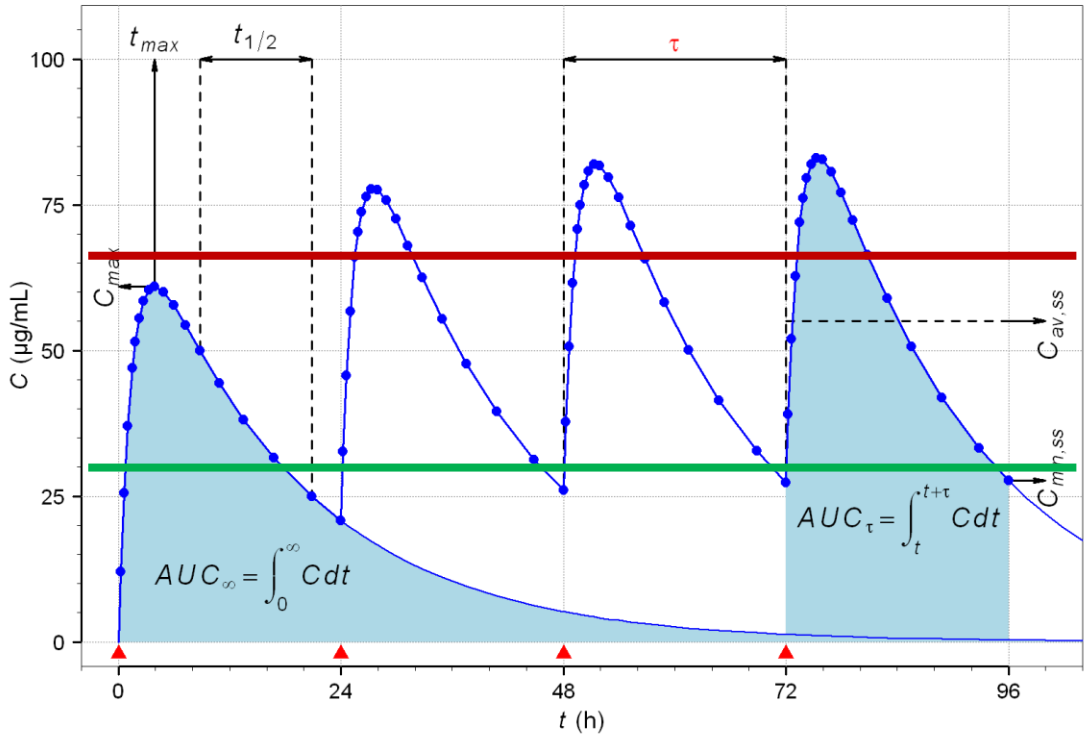
Drug delivery

- Drug exposure in humans can be unpredictable
  - Fine line between effective concentration and side effects…



Maximum Tolerated Dose (TD)

Minimum Biologically Effective Dose (BED)

Improving drug delivery?

- Can we develop better delivery techniques for more linear drug delivery?
- Efficacious, sustained, consistent and predicable exposure?
  - *e.g.* bicalutamde (Casodex) implants
  - Trans-dermal patches
  - Alternate medical devices?
- May deliver more uniform dosing, above Biologically Effective Dose but below Maximum Tolerated Dose for better tolerability?
- Demands engagement with formulation, medical device and delivery expertise

Delivering better drugs

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Better drug targets?

- Are there more effective ways of killing cancer cells?
- How do we find better points of intervention?
- How do we deliver more diverse treatment options?

The PD-(L)1 syndrome

- > 2,250 PD(L)-1 trials ongoing, requiring over 400,000 patients
- Likelihood of delivering further, *significant*, patient benefit?

- Or is this approach unsustainable, for only minor benefit?

Where do new treatment ideas come from?

nature International weekly journal of science

Mutations in CookieMonster Kinase drive oncogenic transformation and lead to aggressive pancreatic ductal adenocarcinoma

Oscar T. Grouch[1], Count V. Count[1] & Bunsen Honeydew[2]
[1]Sesame Street Medical Center, Kaufman, New York, USA and [2]MuppetLabs Oncology Inc., Kaufman, New York, USA

Nature, 547, 1-10. April 1, 2019
doi: 10.1038/nature10128

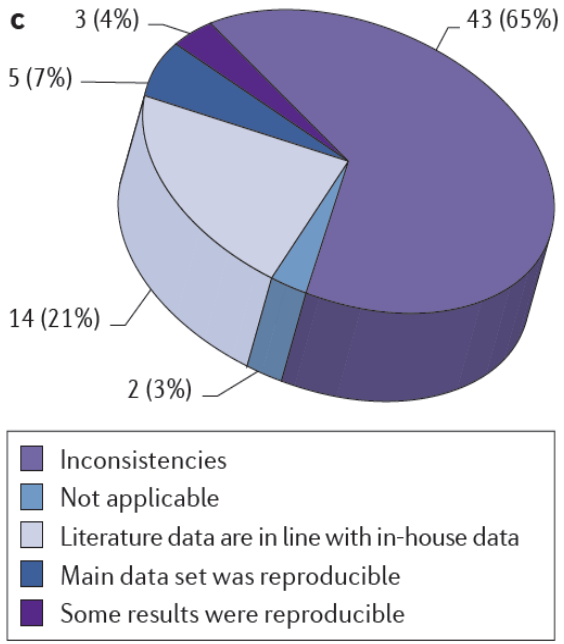
Repeating novel biology.

- For “exciting, novel” targets, most early information is derived from the literature

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

Industry studies suggest only 20-25% of all published biological data are truly and fully repeatable…



Better target validation…

- New targets should stand up to significant scrutiny:
  - Can the original hypothesis be robustly reproduced in the lab?
  - Is there an identifiable patient population who will benefit?
  - Can we confidently, reliably, and repeatedly, measure the change of activity of the target?
    - In a screening plate?
    - In cells?
    - In an *in vivo* model?
    - In a patient?
  - Will inhibition stop cancer growth?
    - And what will the systemic toxicity be?
    - Genetic knock-out ≠ target inhibition – use with care!
  - Is there a tool compound that can validate the pharmacology?
    - Is the activity genuine and on-target?

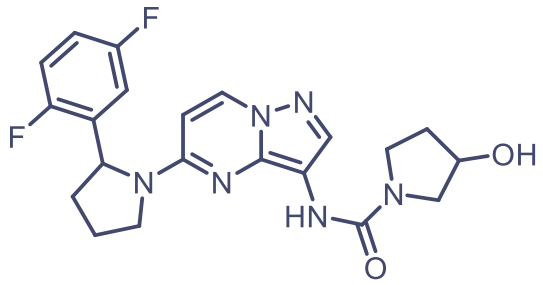
Target validation is an on-going process until the drug is approved, marketed and is successfully treating patients…

But the effort can be worth it…

- Cholangiosarcoma
- Salivary gland cancers
- Infantile febrile sarcoma

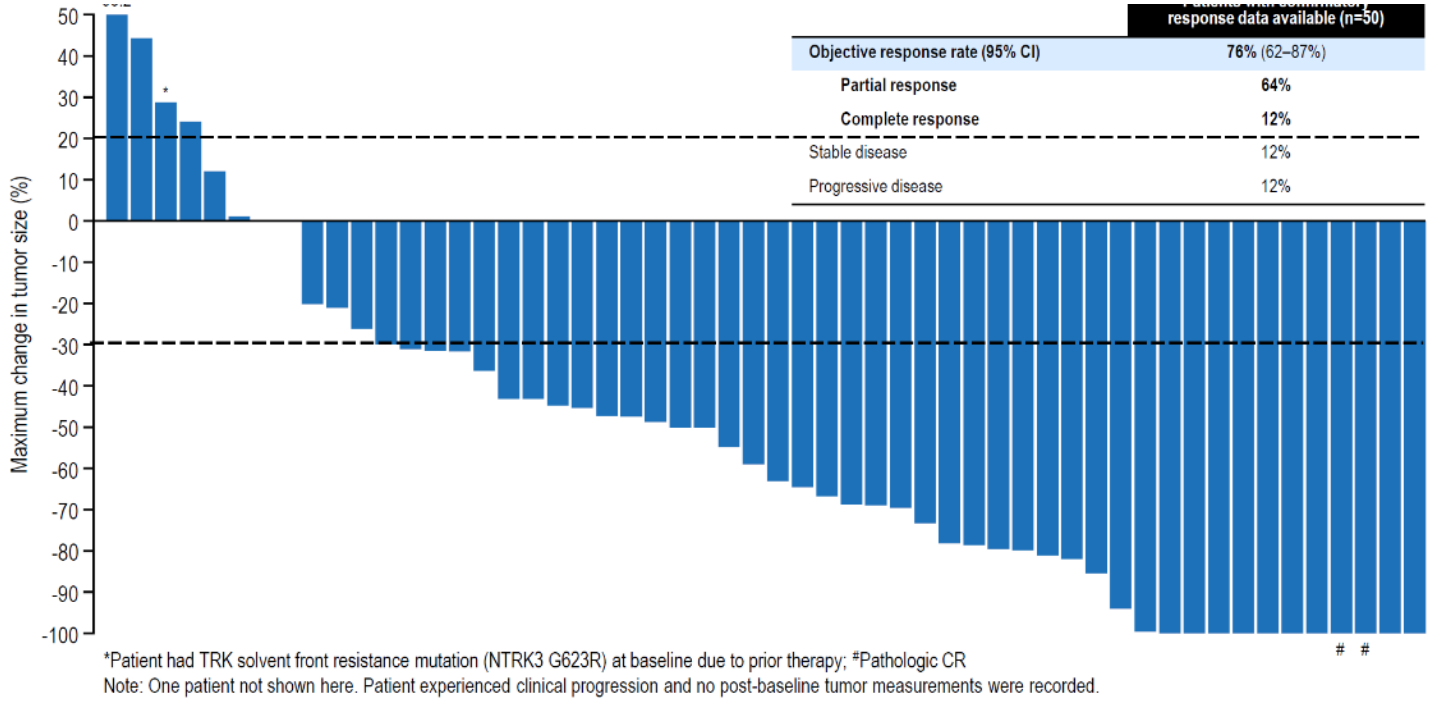
- Common feature - NTRK kinase fusions – identified across a diversity of tumour types
  - Three related kinases, TRK A, B and C

TRK inhibitors



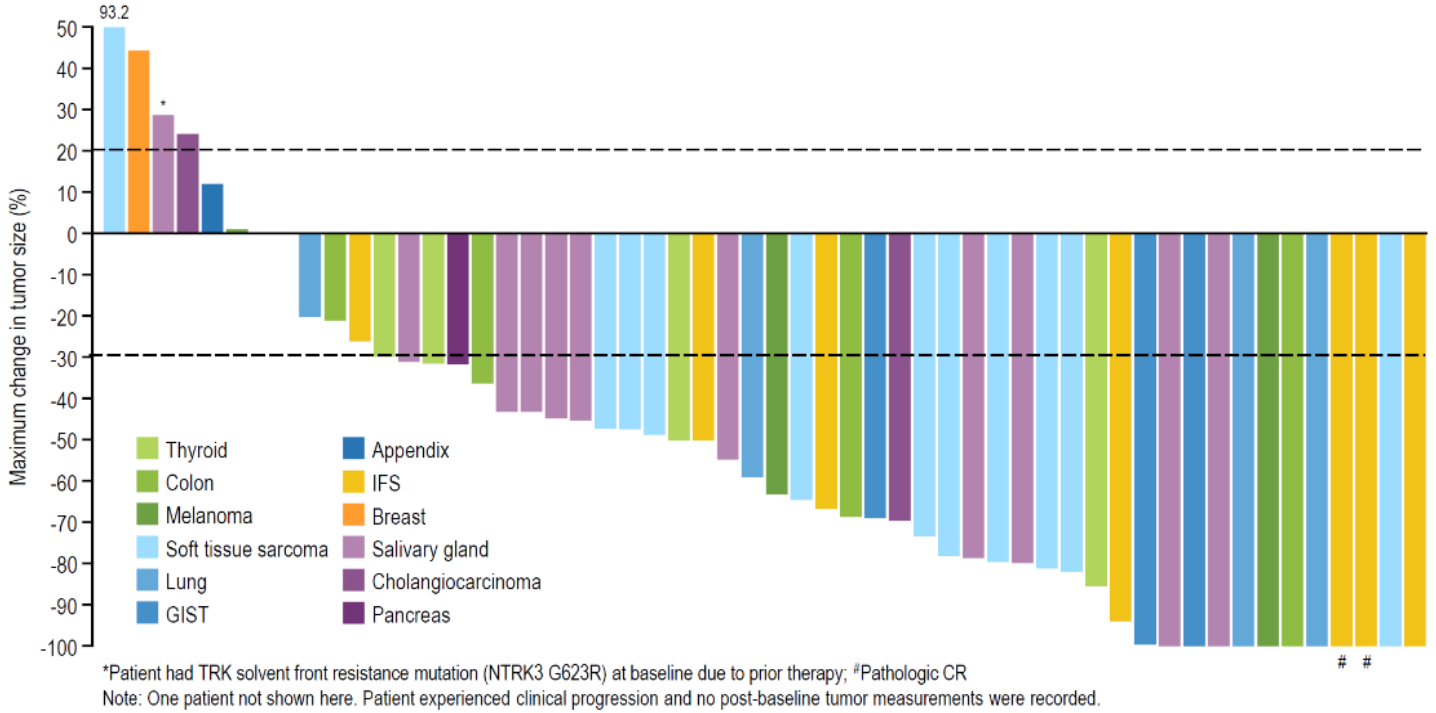
- Inhibitors of TRK identified, e.g. Larotrectinib (above)

- Inhibits all three members of the family
- Formulated as a tablet (adults) and a syrup (children)
- Few significant side effects, <1% discontinuation



*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR
Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

- Data presented at ASCO, 2017 and ESMO, 2018



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Setting a new standard in cancer drug discovery?

- These agents:
  - Are well-tolerated and have bearable side effects
  - Are orally bio-available
  - Are CNS penetrant and deliver clinical benefit against CNS metastatic disease
  - Are designed to combat likely resistance mechanisms
  - Work across multiple disease types, genders, ethnic backgrounds and ages

  - Offer significant increase in overall survival
    - Some patients remain on study >> 4 years after starting dosing
    - Usual kinase inhibitor responses are 6-9 months

Take home messages

- The patients we seek to treat deserve a *true* increase in their overall survival
- The drug discovery community will play an essential role in delivering this benefit
  - We can choose which molecular properties we “lock in” during the discovery phase
- Through better clinical insight, we can better understand where we need to improve our experimental drugs
- We need to engage with a wider community to deliver real step-changes in cancer care
- **We can, and should, be delivering better therapies into clinical trials**