Ottawa Hospital Research Institute

OHRI IRHO

Institut de recherche de l'Hôpital d'Ottawa

Focusing on clinical results

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Disclosures 01/01/14-11/11/16: DJ Stewart

- Consulting/Advisory Boards:
  - Roche Canada 2014, 2016
  - Pfizer Canada 2014
  - Boehringer Ingelheim Canada 2015
  - Amgen/Amgen Canada 2014
  - Novartis Canada 2015
- Speaker:
  - Pfizer Canada 2015
- Scientific writing support (review on angiogenesis): Boehringer Ingelheim 2015
- Clinical trials support:
  - Boehringer Ingelheim
  - AstraZeneca
  - Novartis
  - Bristol-Myers Squibb
  - Celgene







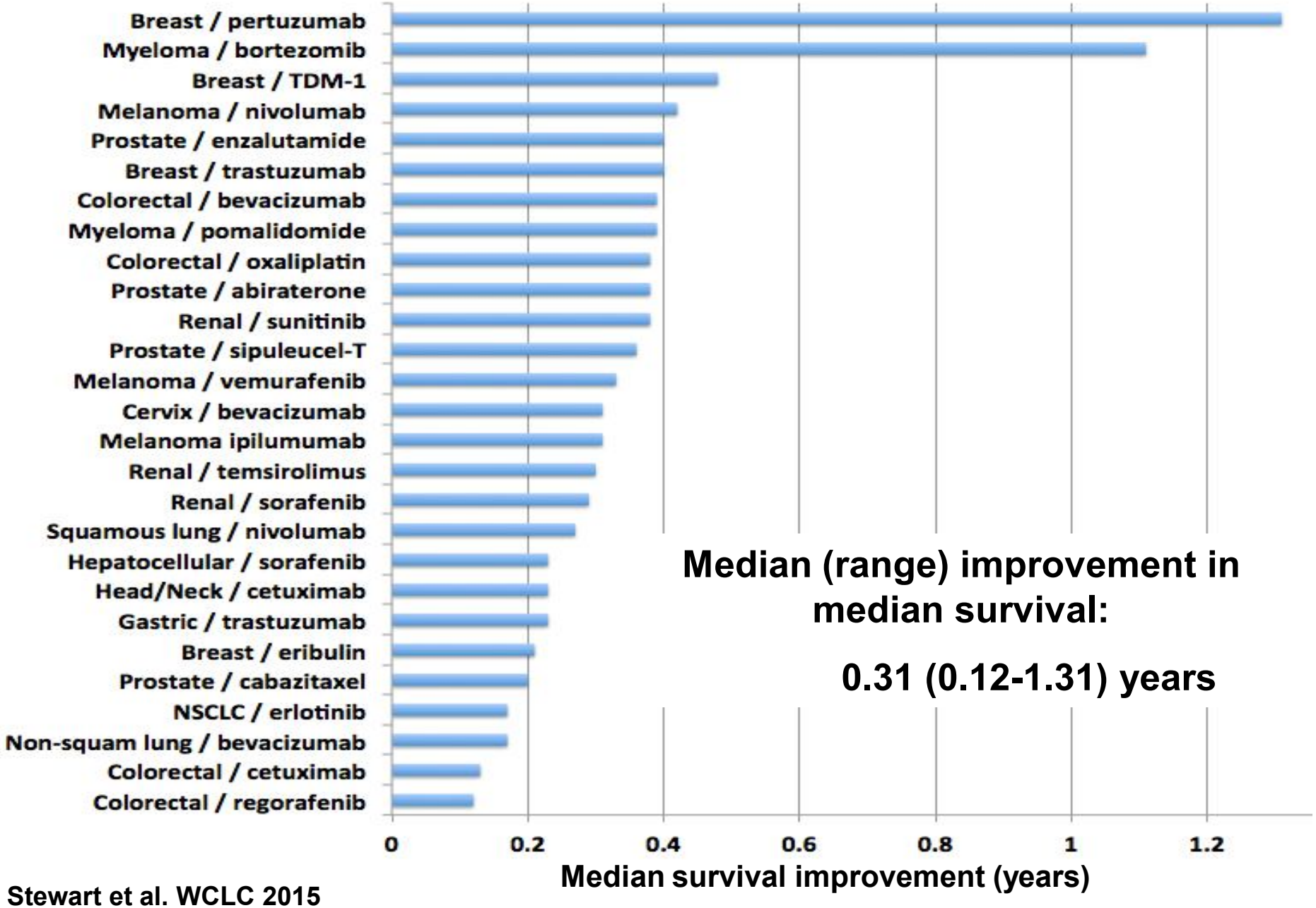


Canadian
Tulip
Festival


Message # 1

Delays in regulatory approval of effective new therapies come at a very high cost

Improvement (years) in median survival vs control arm

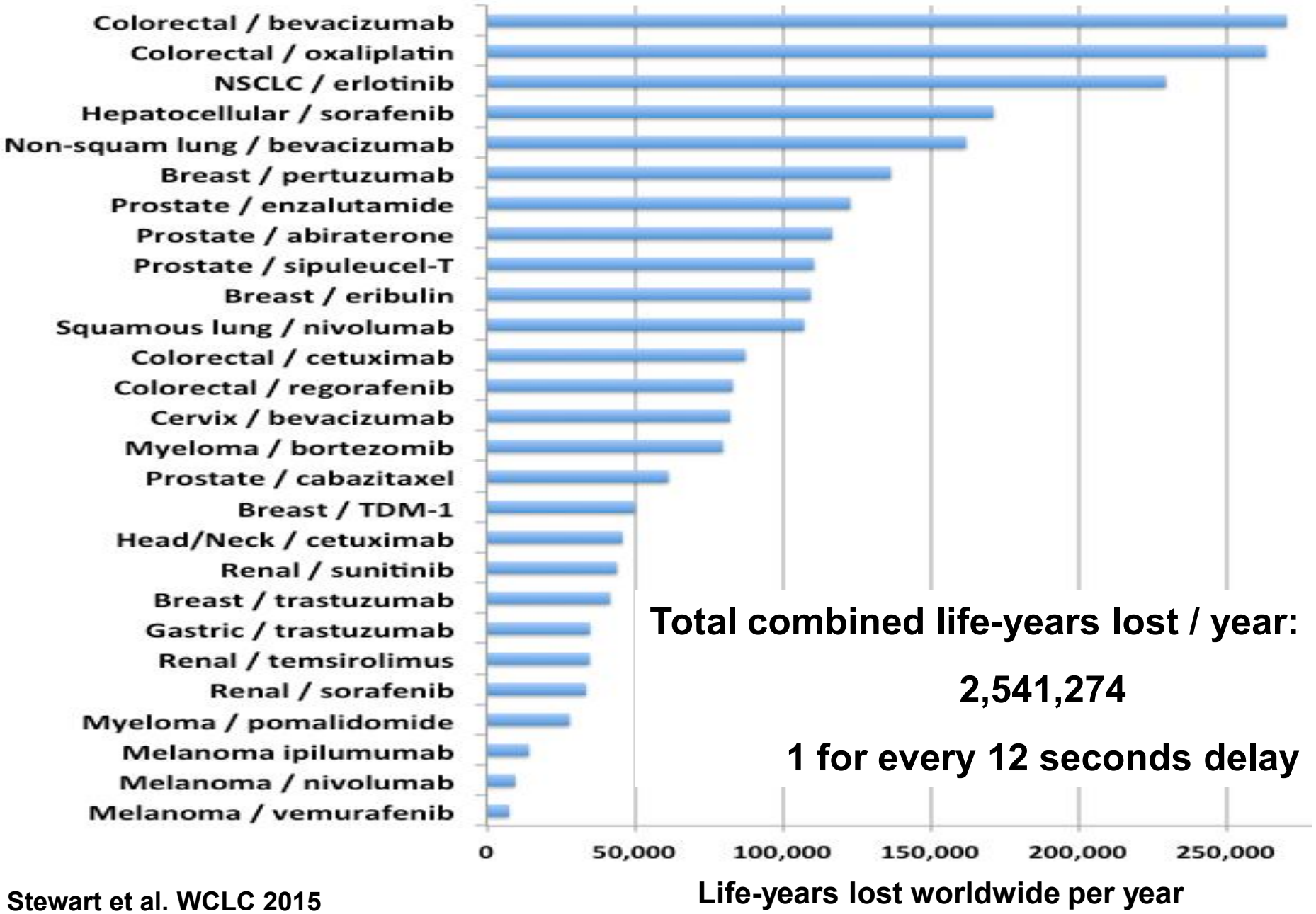


Median (range) improvement in median survival:

0.31 (0.12-1.31) years

Stewart et al. WCLC 2015

Life-years lost worldwide per year delay in drug approval



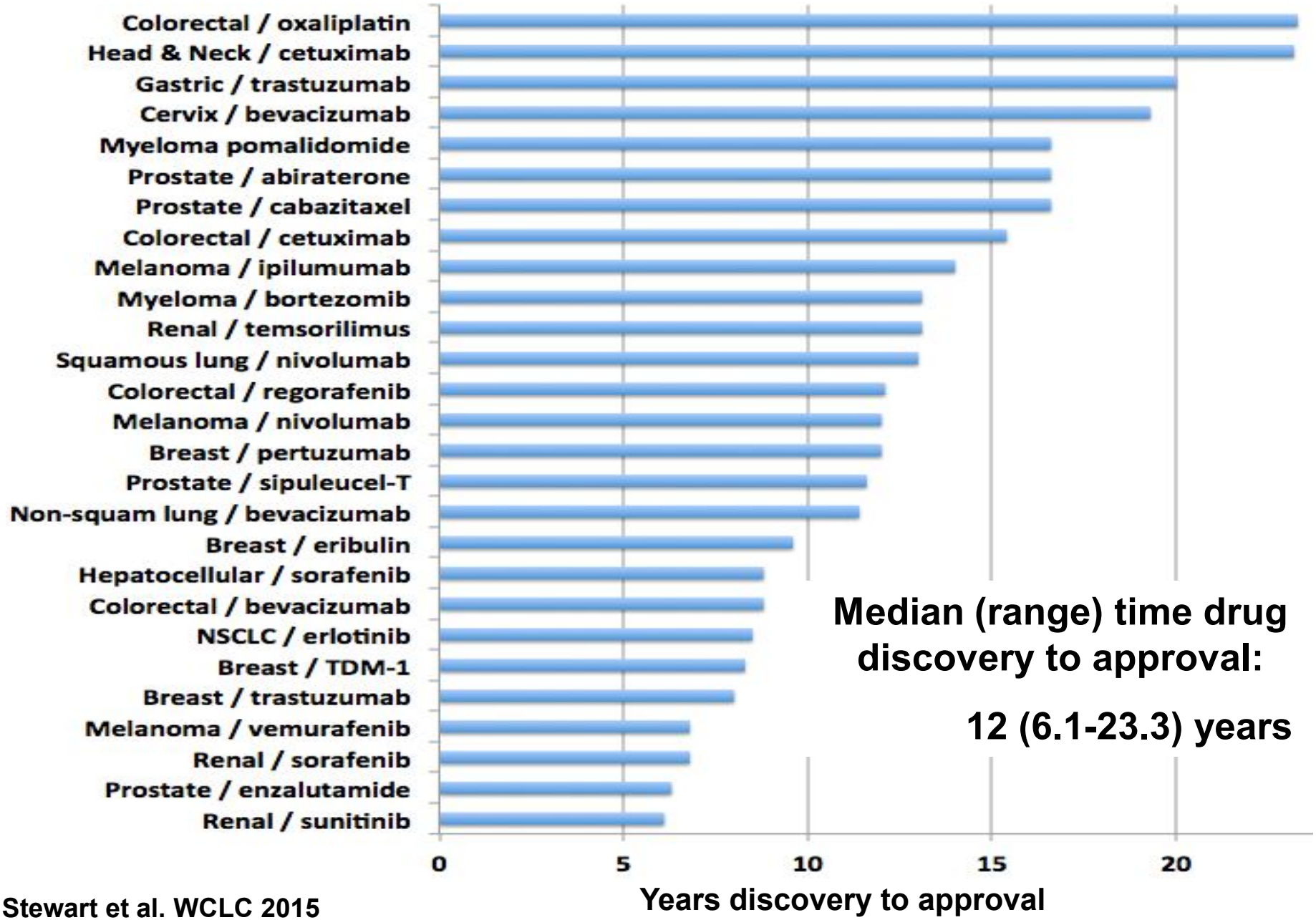
Total combined life-years lost / year:

2,541,274

1 for every 12 seconds delay

Stewart et al. WCLC 2015

Years from US patent application to US FDA approval

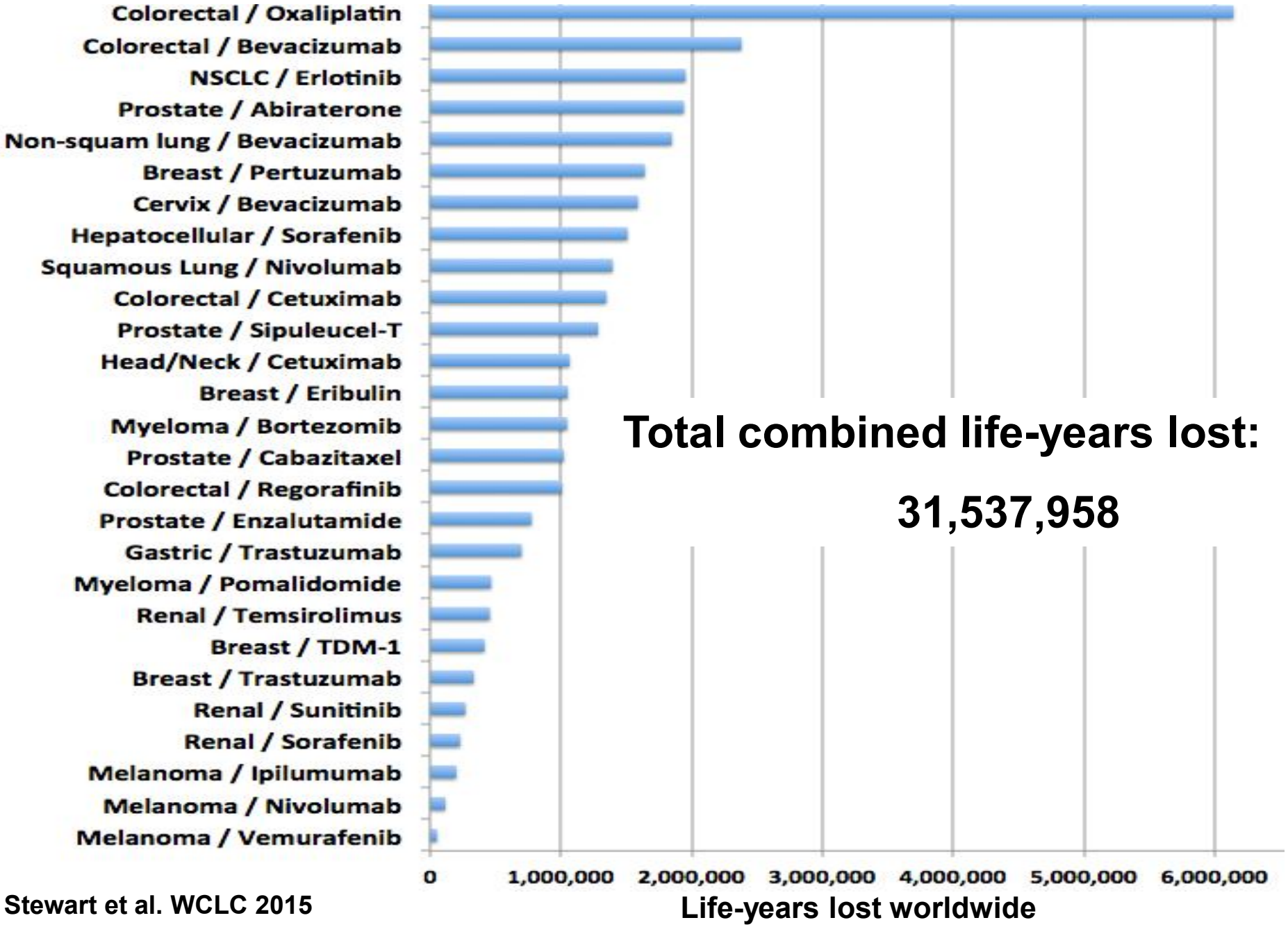


Median (range) time drug discovery to approval:

12 (6.1-23.3) years

Stewart et al. WCLC 2015

Life-years lost worldwide from patent application to approval



Total combined life-years lost:

31,537,958

Stewart et al. WCLC 2015

Time from drug discovery to approval:

-1960s: 8 years

-2000: 12.9 years (61% ↑)

Stewart et al. Clin Cancer Res 21: 4561-8, 2015

Time from drug discovery to approval:

-1960s: 8 years

-2000: 12.9 years (61% ↑)

Caused largely by increasingly stringent regulation for "patient safety"

Stewart et al. Clin Cancer Res 21: 4561-8, 2015

Message #2

Increasingly stringent clinical research regulation has had minimal impact on cancer patient safety

Toxic death rate on phase I trials: Minimal change despite ↑↑ regulation

Years	No. trials	No. patients	No. (%) toxic deaths
1979-1990*	227	6426	52 (0.8%)
1991-2002**	460	11935	58 (0.5%)

* R. Kurzrock, 2009

** E. Horstmann et al, NEJM, 2005

Stewart et al. Clin Cancer Res 21: 4561-8, 2015

Increasingly stringent regulation is intended to improve safety

- Average 5,435 patients on all phase I-III studies for approval

Stewart et al. WCLC 2015

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- For the 21 drugs included: 21 x 5,435 = 114,135 patients

Stewart et al. WCLC 2015

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} ↓ 0.3%

Stewart et al. WCLC 2015

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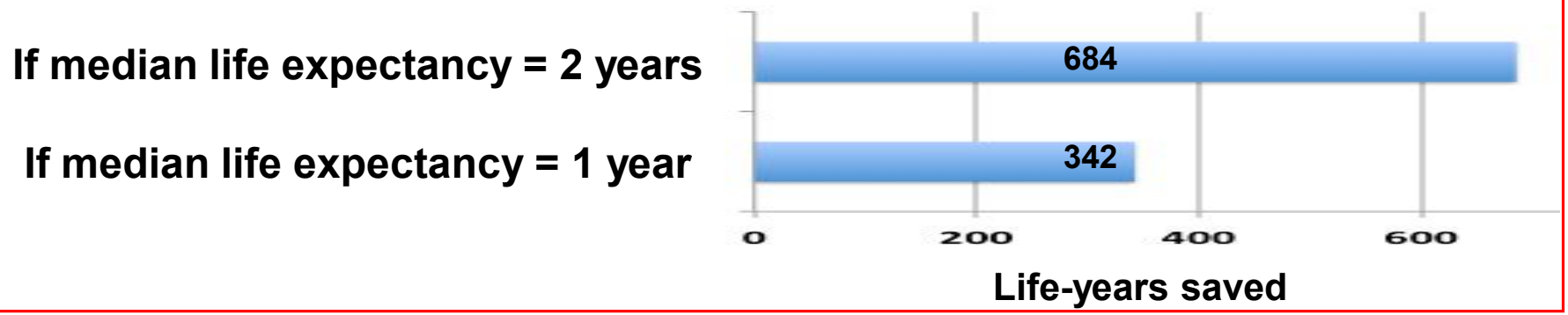
- Estimated life-years saved worldwide by enhanced study safety:



Stewart et al. WCLC 2015

342-684 life-years saved by ↓ toxic deaths by ↑ regulation (but >30M lost from delays)

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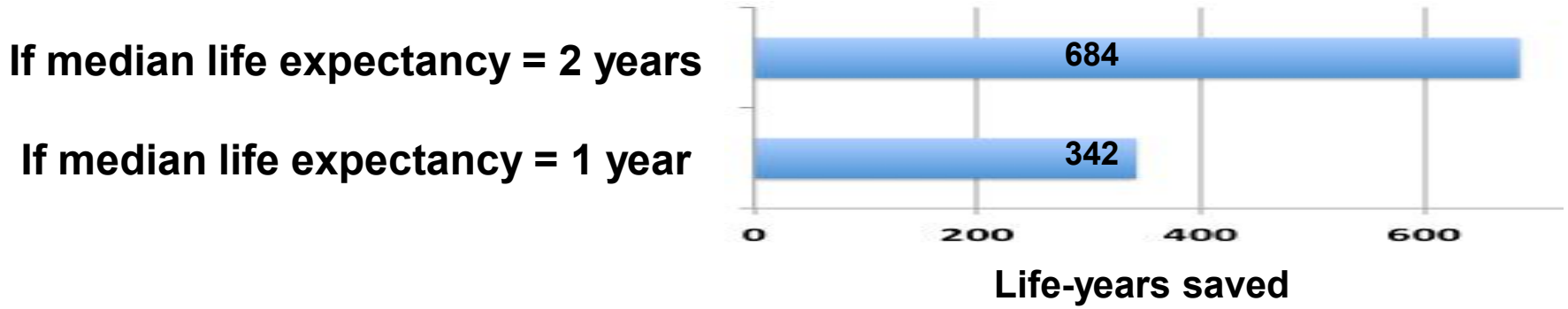

Lost vs saved = 50,000 : 1

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Stewart et al. WCLC 2015

Message #3

Excessive regulatory stringency markedly increases clinical research costs, and this directly slows progress

Exploding clinical research costs can markedly slow progress

- Inflation-adjusted annual clinical research cost ↑ much faster than inflation

Stewart et al. Clin Cancer Res 21: 4561-8, 2015

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Stewart et al. Clin Cancer Res 21: 4561-8, 2015

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Stewart et al. Clin Cancer Res 21: 4561-8, 2015

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Stewart et al. Clin Cancer Res 21: 4561-8, 2015

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- Massive costs of out-of-control excessive documentation requirements
- Costs (and delays) associated with study review, approval, activation, contract negotiations, etc

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Stewart et al. Clin Cancer Res 21: 4561-8, 2015

High research regulatory costs mean:

-Fewer ideas can be tested with available resources

Stewart et al. Clin Cancer Res 21: 4561-8, 2015

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Stewart et al. Clin Cancer Res 21: 4561-8, 2015

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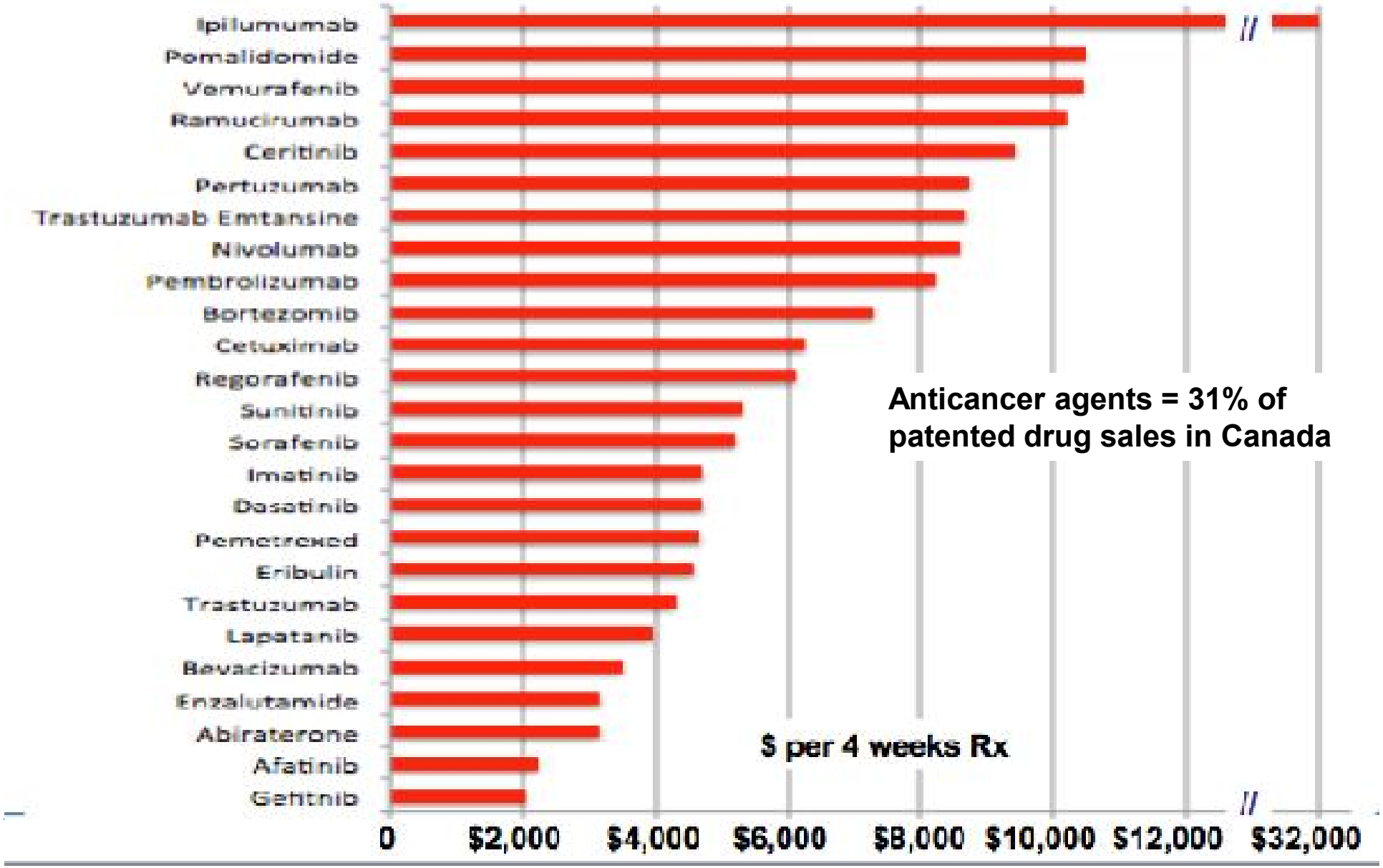
-Progress is greatly slowed

-Translates into very high therapy costs

Stewart et al. Clin Cancer Res 21: 4561-8, 2015

Average cost of 4 weeks of Rx in Canada



Message #4

As a means of protecting patients, current regulatory stringency is <u>not at all</u> cost-effective

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Costs of compliance with increasing regulatory stringency: $8,000,000 per life-year saved!

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Stewart et al. Clin Cancer Res 21: 4561-8, 2015

Clinical trials regulations much more costly than most therapies & preventive measures

Procedure	Cost/life-year saved
Clinical trial regulations (2013)*	**~$8,000,000**
Hemodialysis	$104,000
Statins for heart disease	$25,000
Colonoscopy (colon Ca)	$14,000
Adjuvant trastuzumab, breast Ca	$20,000
Paclitaxel/cisplatin ovarian Ca	$26,000

*** Extrapolated from 2007 costs**

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Stewart et al. Clin Cancer Res 21: 4561-8, 2015

Message #5: We must tackle the numerous speed bumps on the road to approval of effective new therapies!

There <u>are</u> solutions!

Publications outlining required steps, eg:

- J Clin Oncol 27:328, 2009
- J Clin Oncol 28:2925, 2010
- BMC Cancer 13:193, 2013
- J Popul Ther Clin Pharmacol 21:e56, 2014
- Clin Cancer Res 21:4561, 2015

Start by resetting the focus:

Progress-Centered Regulation for clinical research in lethal diseases!!

Stewart et al. Clin Cancer Res 21: 4561-8, 2015

Start by resetting the focus:

Progress-Centered Regulation for clinical research in lethal diseases!!

-Priority: Get effective new drugs to patients:

-as rapidly as possible

-as inexpensively as possible

Stewart et al. Clin Cancer Res 21: 4561-8, 2015

Areas that need to be addressed / opportunities

- Regulatory systems, processes, regulations and regulators for lethal diseases different and separate from those for nonlethal diseases

Stewart et al. Clin Cancer Res 21: 4561, 2015

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Stewart et al. Clin Cancer Res 21: 4561, 2015

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Stewart et al. Clin Cancer Res 21: 4561, 2015

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Stewart et al. Clin Cancer Res 21: 4561, 2015

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- “Right size” massively excessive, expensive documentation

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- Allow PI latitude for rational protocol overrides without IRB approval
  - Replace tight control of PI decisions with pragmatic accreditation

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- Simplify requirements for use of biomarkers to select trial patients
- Accelerated approval of drugs based on high phase I/II response rates without need for phase III

Stewart et al. Clin Cancer Res 21: 4561, 2015

Accelerated approval / breakthrough drug designation: the goal posts have been moved closer (phase III not required)…..

But the mud between us and the goal posts keeps getting deeper!

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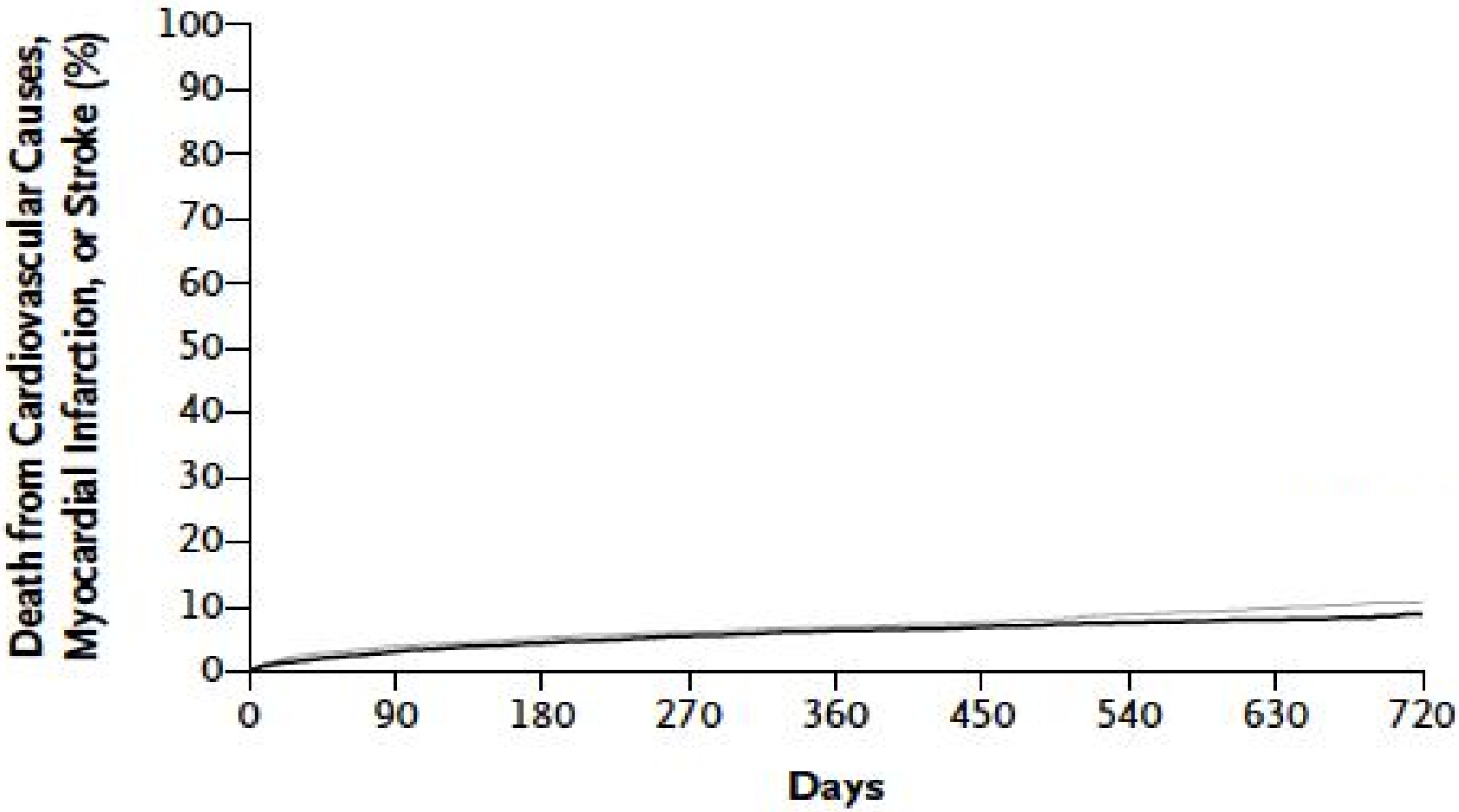
Stewart et al. Clin Cancer Res 21: 4561-8, 2015

Message #6: Aim high, not low: Riveroxaban vs placebo in patients with a recent acute coronary syndrome



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Mega, NEJM 366:9, 2012

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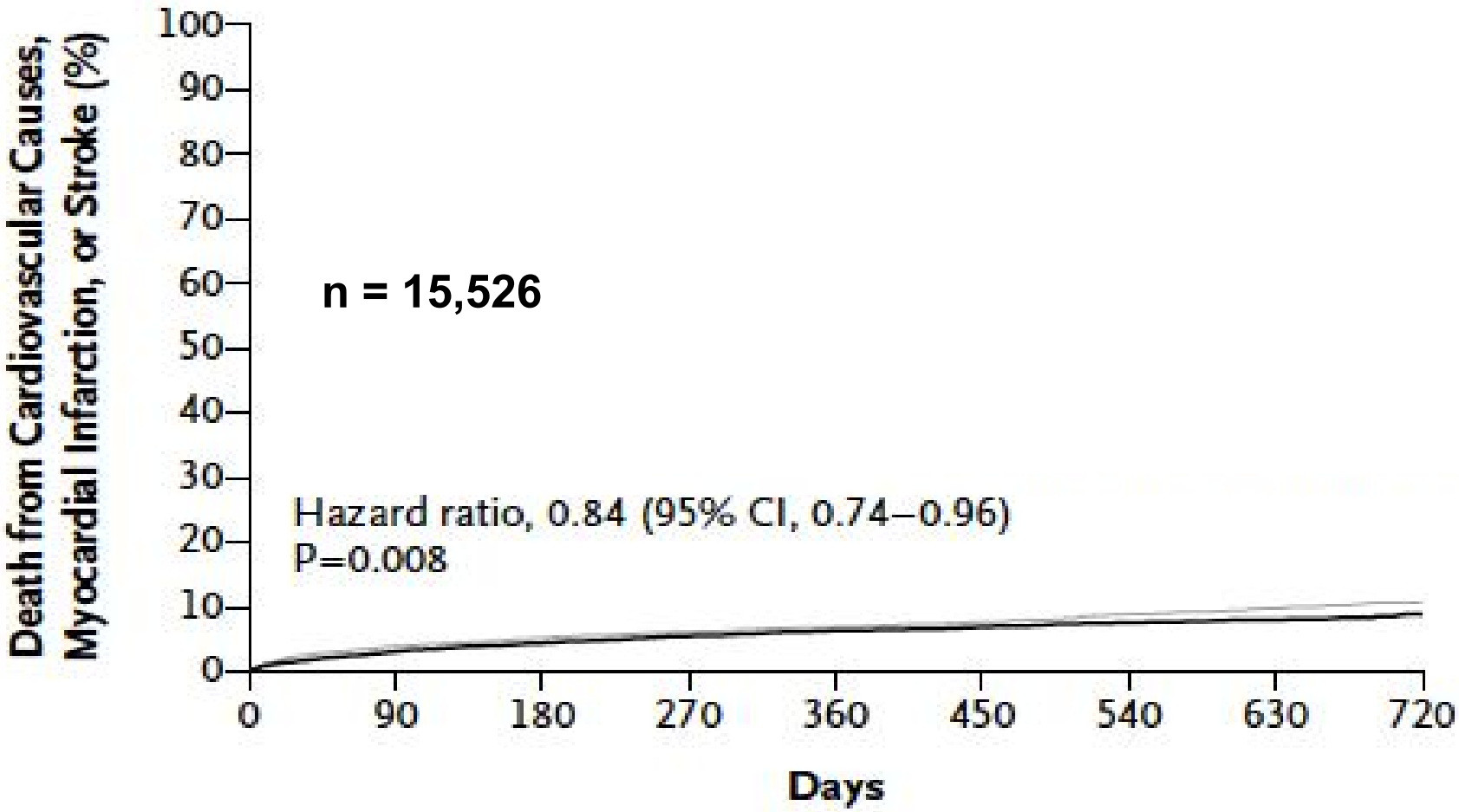

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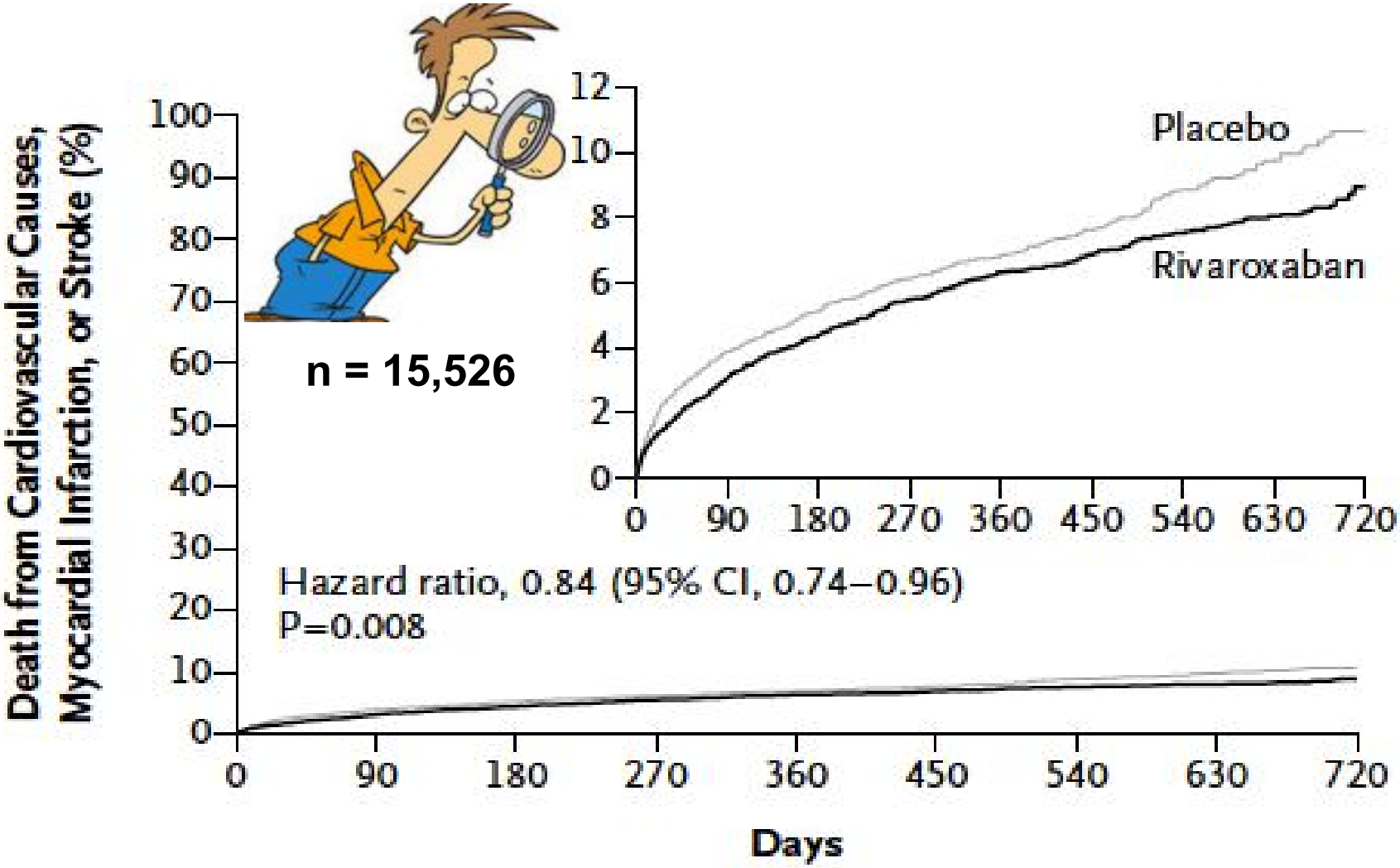

Mega, NEJM 366:9, 2012

Message #6: Aim high, not low

- Large trials:
  - → ↑ statistical power:
    - → Permits / encourages detection of small gains
      - → Lowers the efficacy bar & slows progress

Why have we gained so little?

"Every system is perfectly designed to get exactly the results it gets!"

-P Batalden, F Davidoff, 2007

We have only gained little since RCTs are often specifically designed to detect <u>small</u> gains

Message #6: Aim high, not low

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  - Impede progress:
    - ↑ no. patients needed:
      - → ↑ time required to complete a trial
      - → ↓ patients available to test other new ideas

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  - Impede progress:
    - ↑ no. patients needed:
      - → ↑ time required to complete a trial
      - → ↓ patients available to test other new ideas
    - ↑ Costs:
      - → ↓ resources to test other new ideas

Large trials are primarily about getting marginal drugs approved, <u>not</u> about helping patients!

Message #7

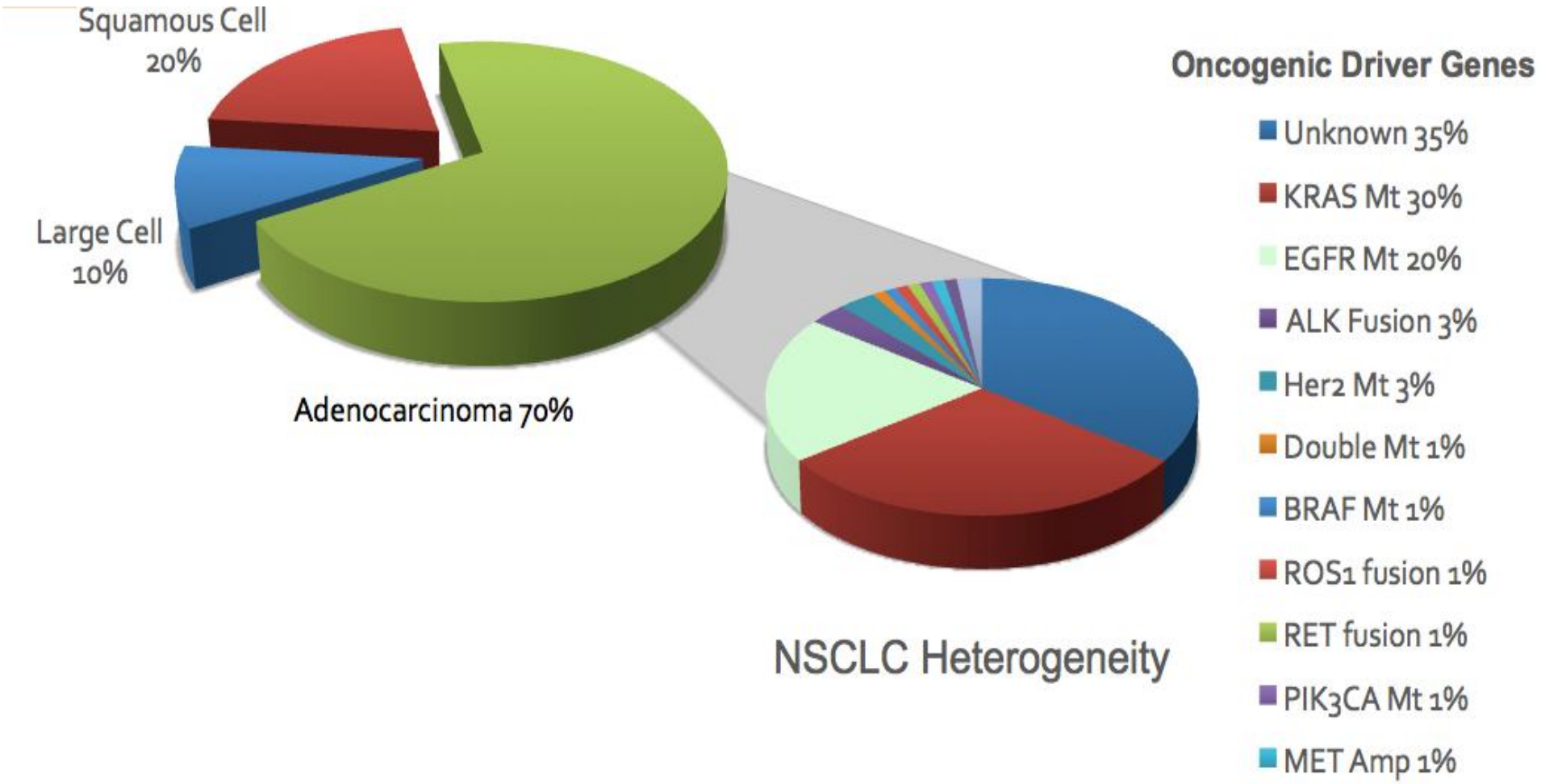
- Identify the drug target
- Select patients based on the target

-Common cancers are common since can be caused by many different mutations

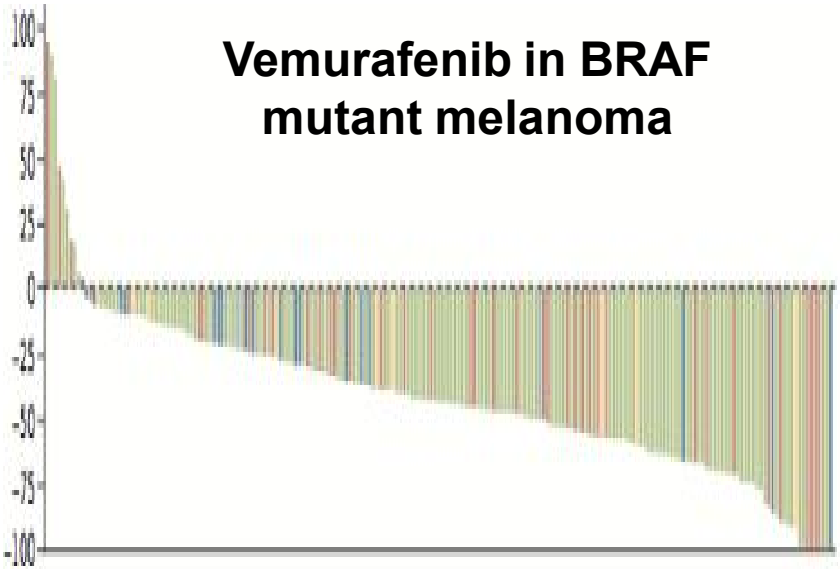
-One may need different treatments for each group of patients with cancers caused by different mutations

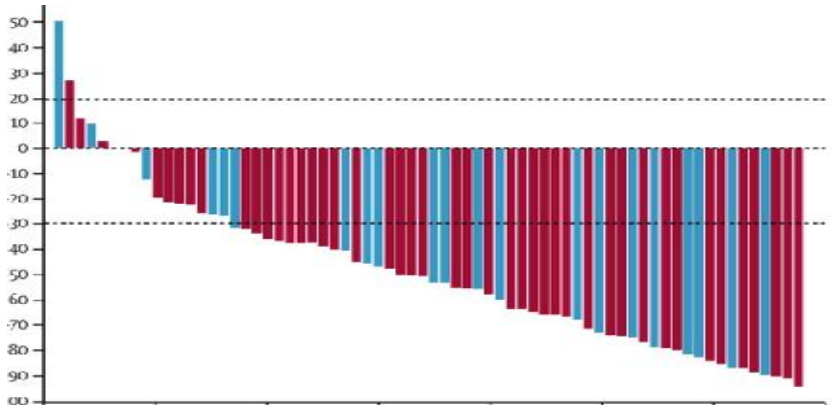
- Braiteh & Kurzrock, 2007

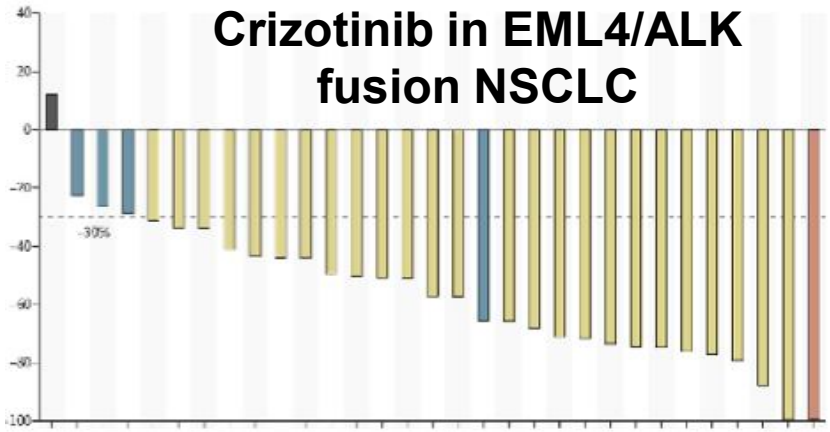
Targeted agents work in small subpopulations driven by specific mutations

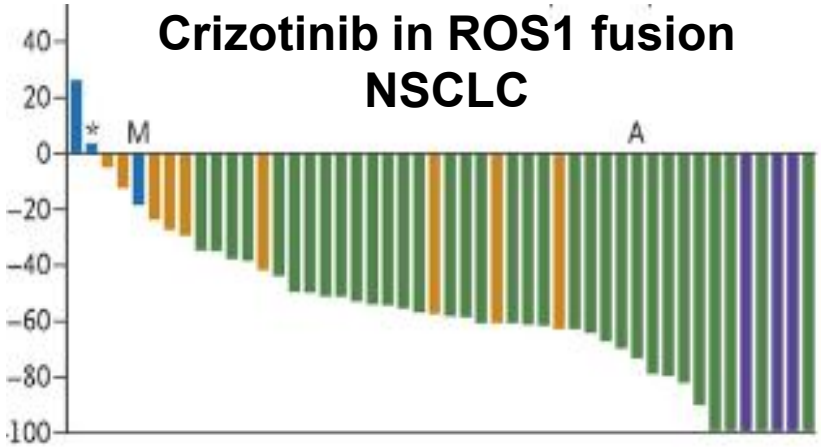


Tumor regression in > 90% of patients with target

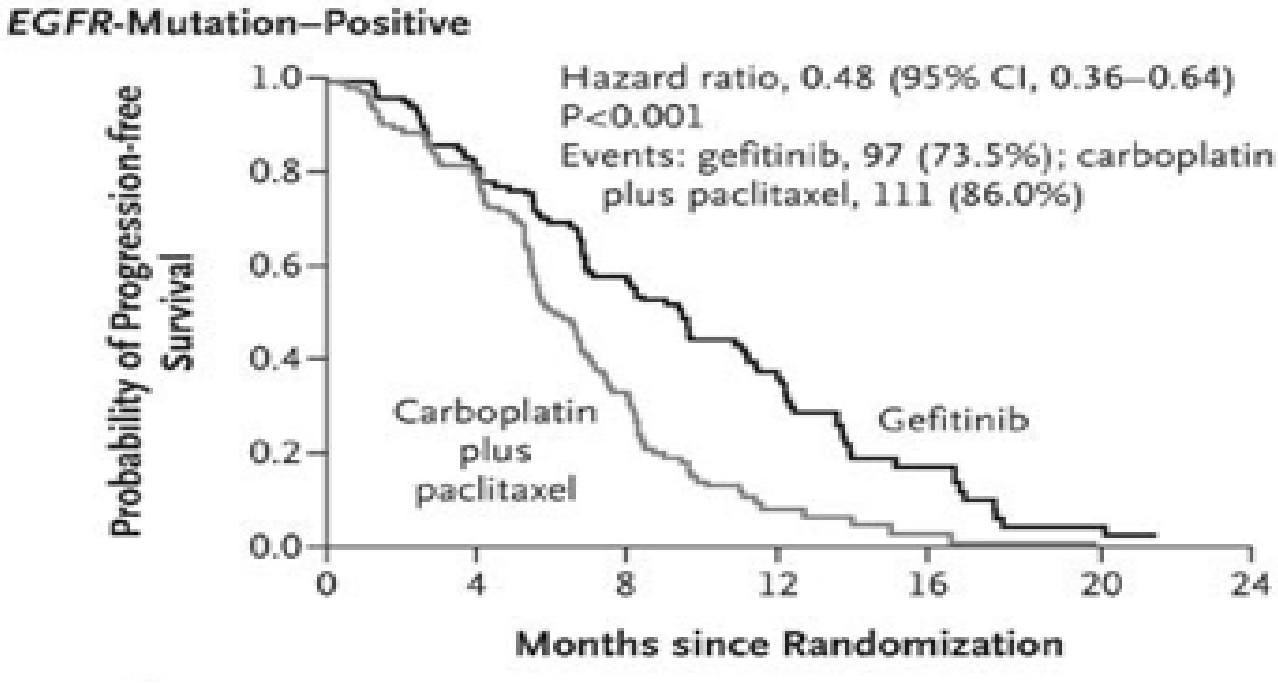








Gefitinib:
-much better than chemo in NSCLC patients with an EGFR mutation



T Mok et al, NEJM 2009

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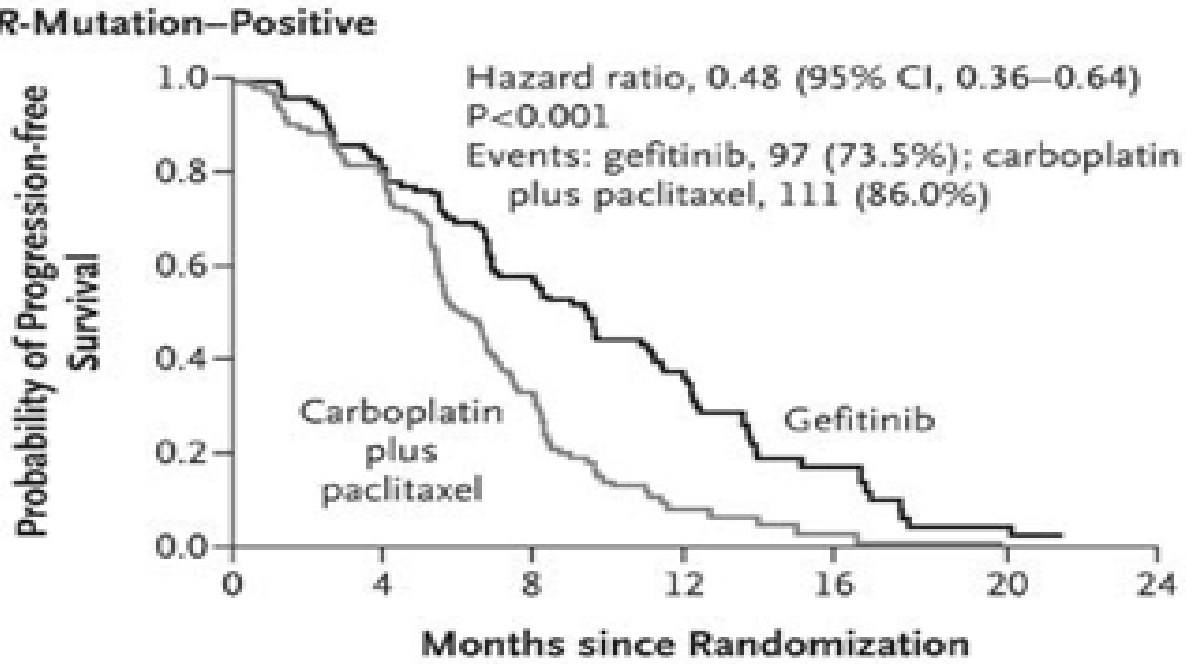
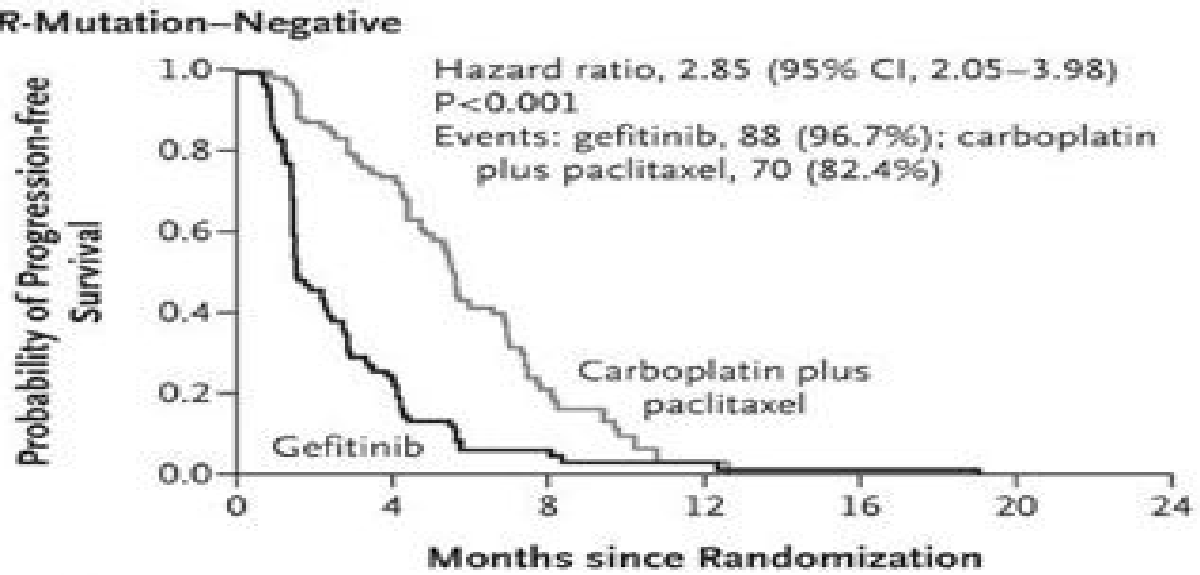


-not as good as chemo if there is no mutation

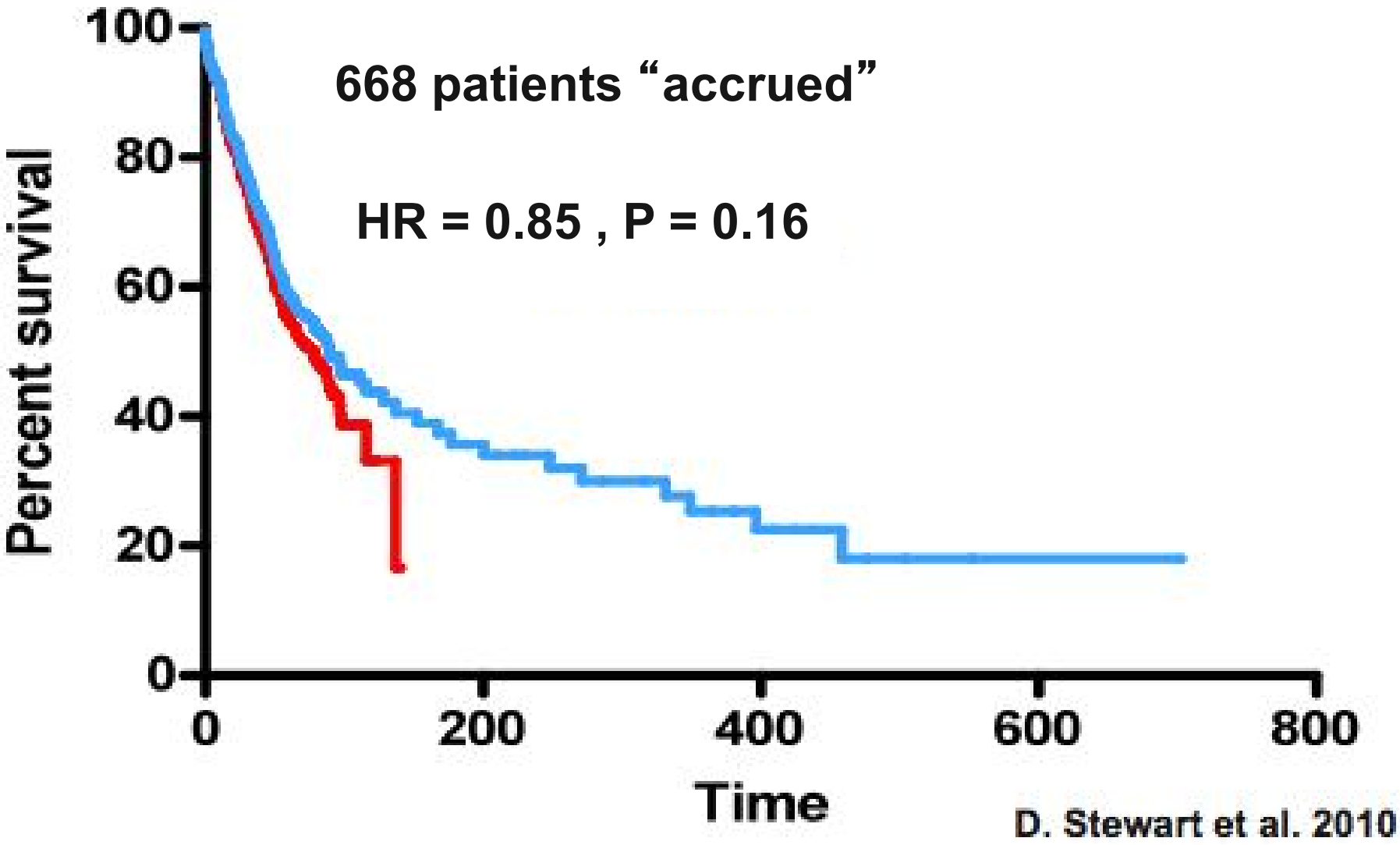


T Mok et al, NEJM 2009

Simulations

- Actual survival in 334 patients as the “control”
- Simulated experimental group:
  - Target present in 10%
  - New agent:
    - Quintuples survival in those with target
    - No effect in those without target

Therapy would be inappropriately abandoned if it hit a target present in only every 10th patient and quintupled their survival



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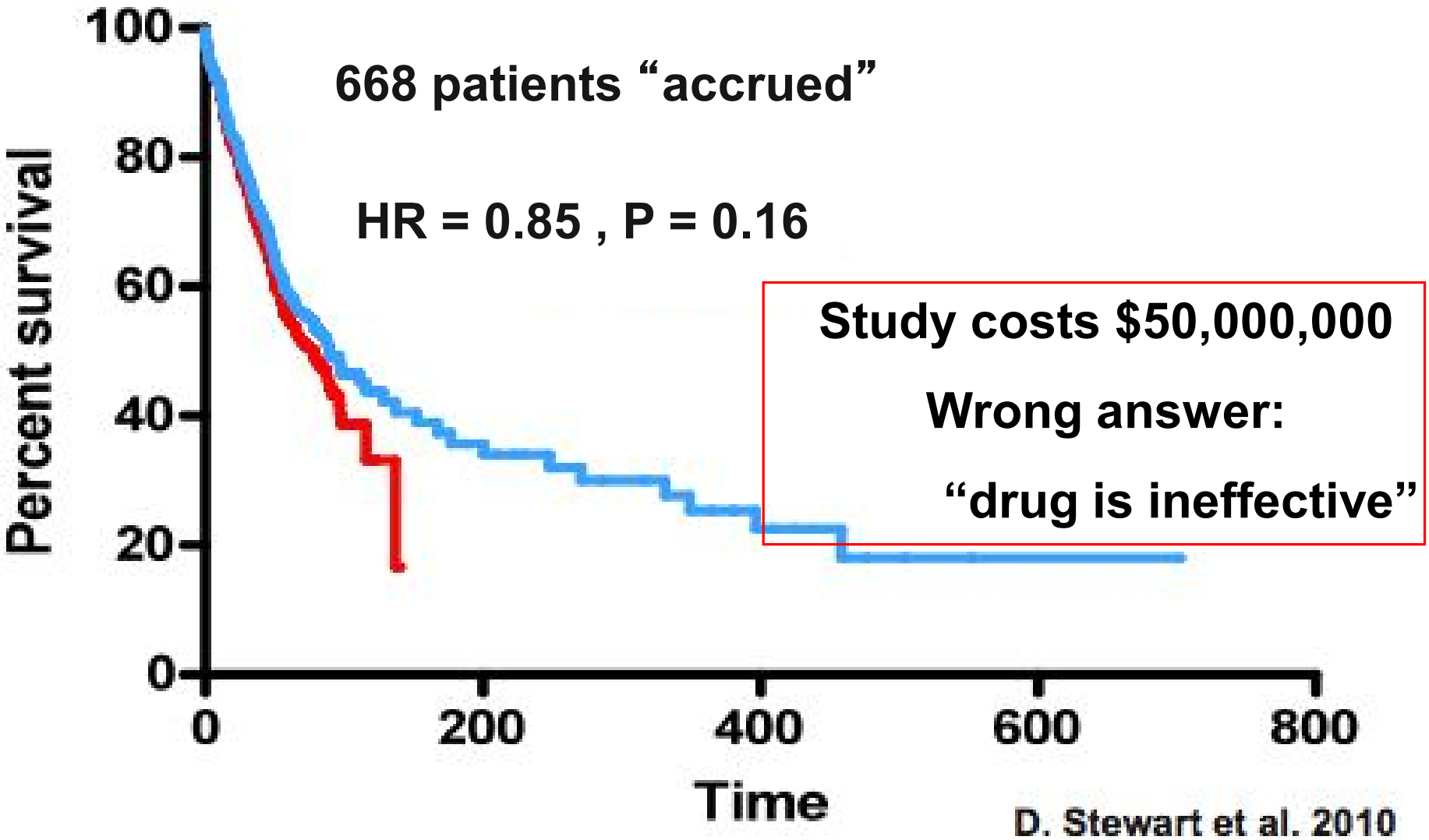
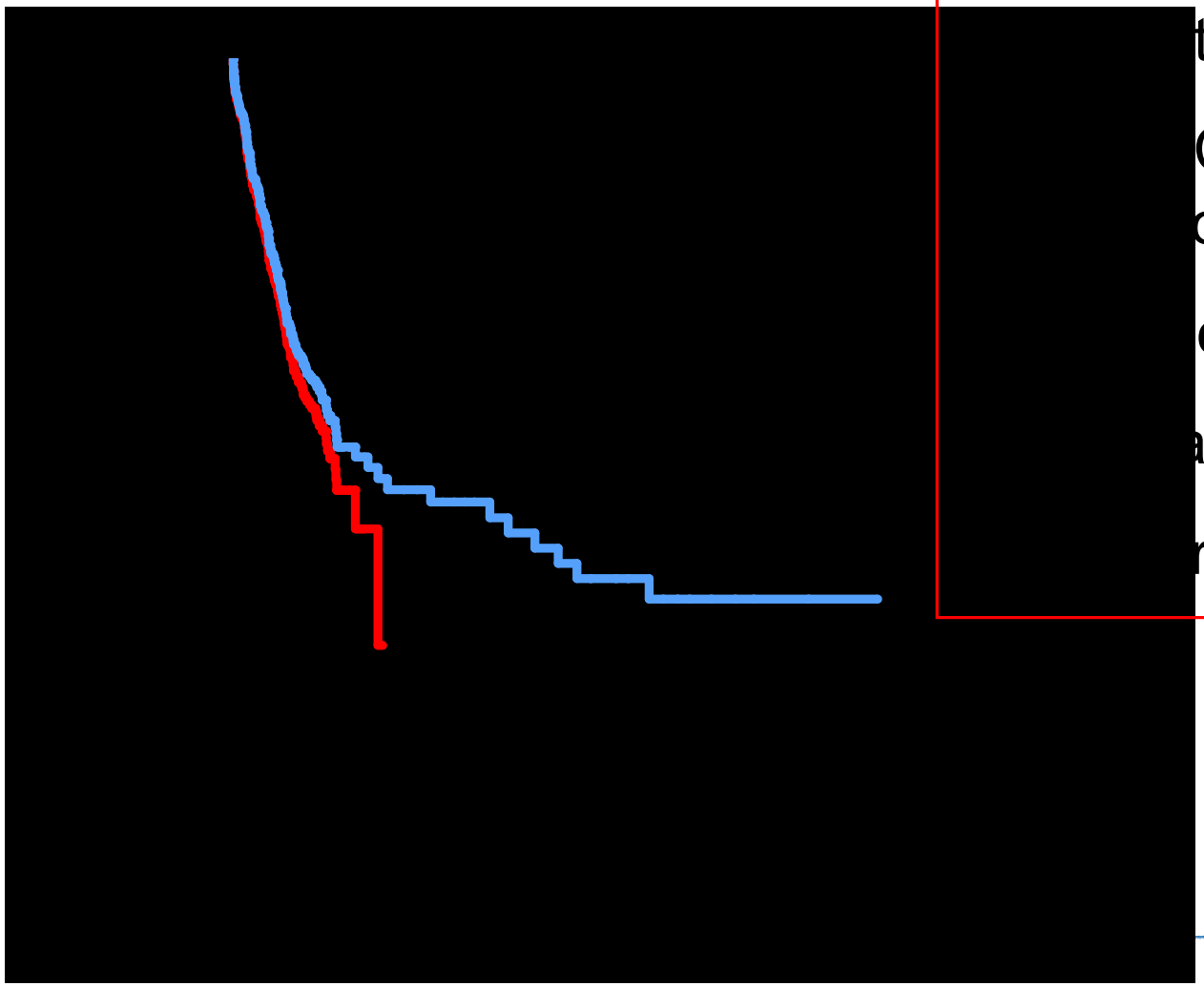


Tripling patient numbers to 2000 → magic!

↑ statistical power → p < 0.03



tandard of care

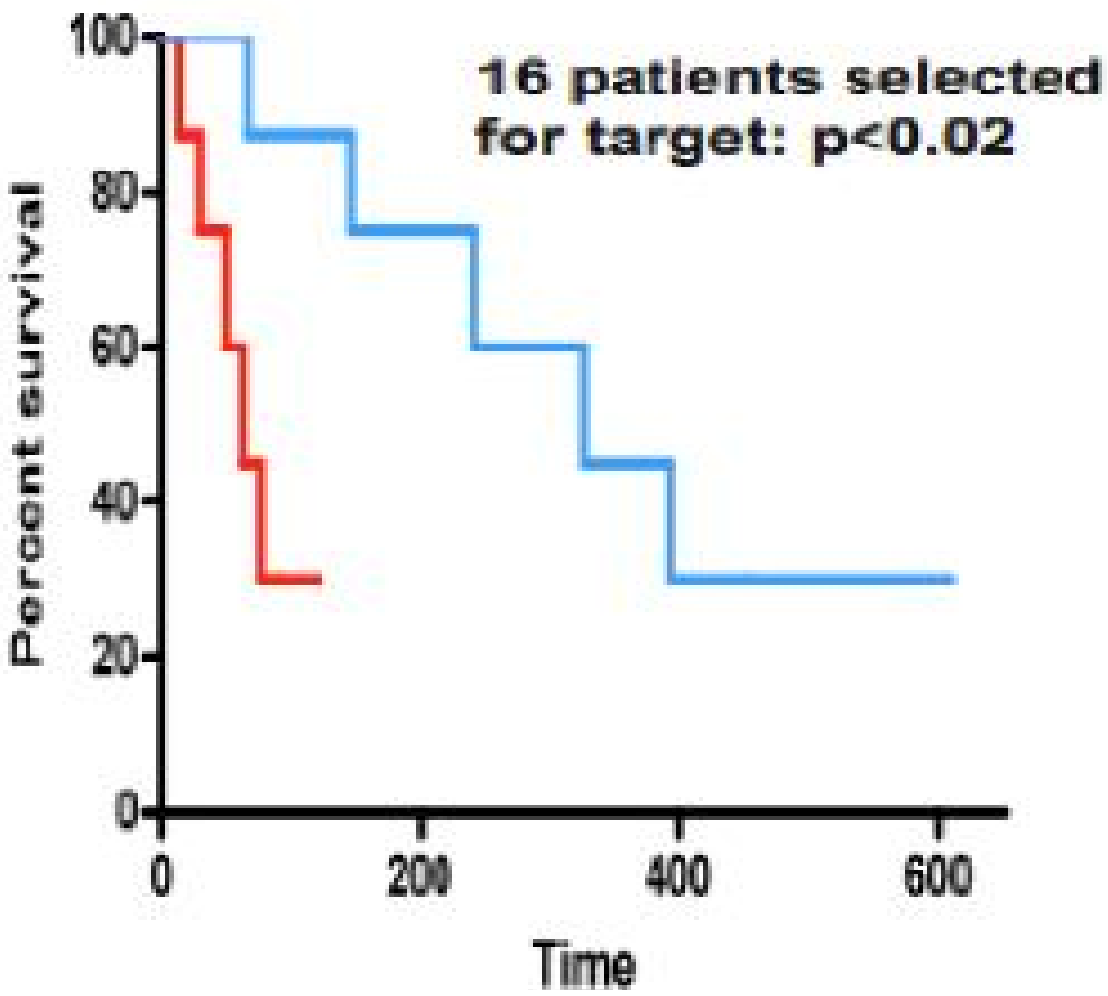
CO plenary / NEJM /
on / speakers circuit

costs $150,000,000

ave wrong answer!

rug is effective."

But if 1st identify target and select patients with target, only need 16 patients



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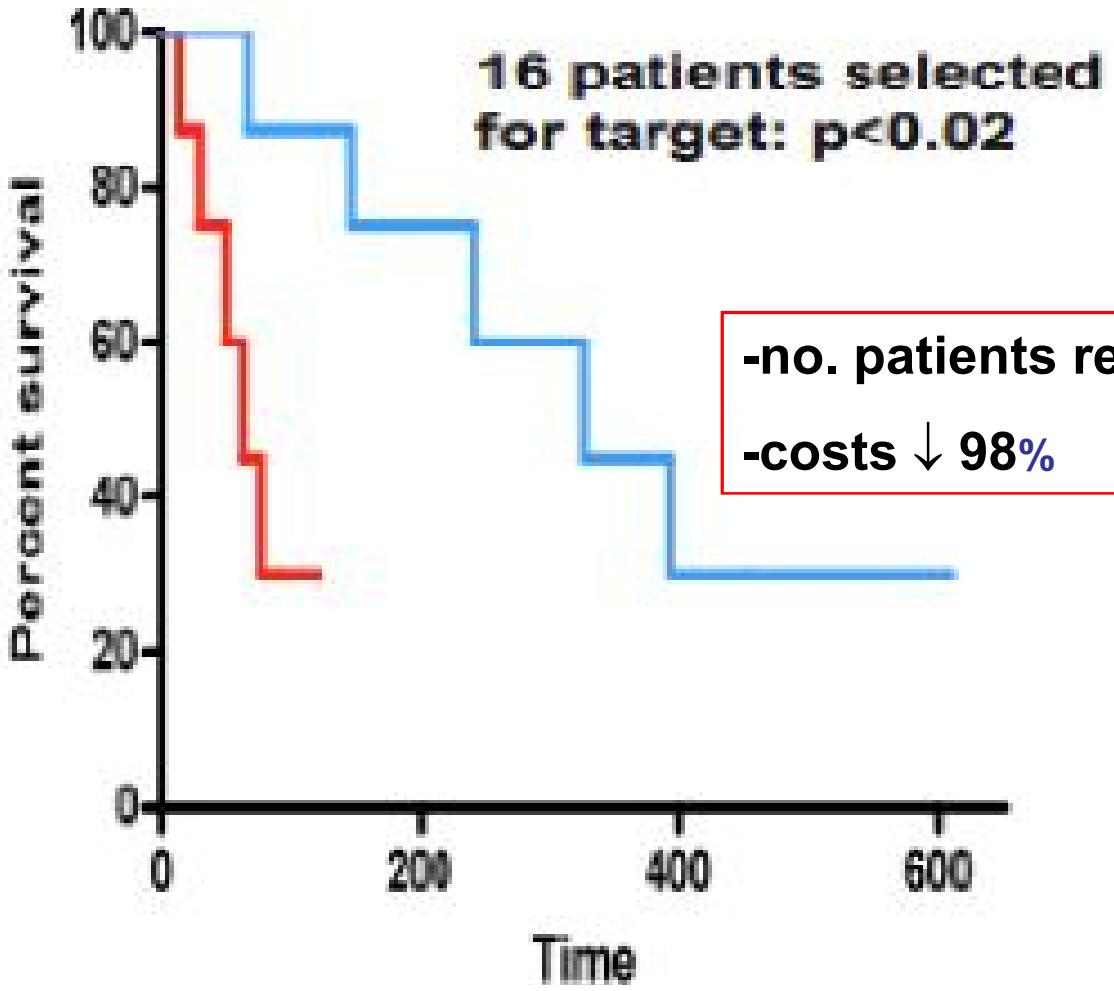

-no. patients required ↓ 99%

-costs ↓ 98%

Every 12 minutes another person in the Netherlands dies of cancer: ~5 over the past hour (and >700 worldwide)

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Stewart et al. Clin Cancer Res 21: 4561, 2015

This is unacceptable!

This is an international problem. We must all work together to fix this!

"It's not enough that we do our best; sometimes we have to do what's required."

- Winston Churchill

Life Saving Therapies Network

www.lifesavingtherapies.com

dstewart@toh.ca