The Optimal Cancer Care Alliance (OCCA) view and experience

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What we already know….

Cancer drugs are often expensive, poor value, and unaffordable

and

The dosages and treatment durations of many cancer drugs are greater than necessary

VIEWPOINT

Interventional Pharmacoeconomics—A New Discipline for a Cost-Constrained Environment

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Pharmacoeconomics is an observational science usually focused on the value and affordability of pharmaceutical interventions. We now propose the concept of interventional pharmacoeconomics (IVPE), actively seeking to disruptively decrease prescribing costs through the development of new dosing regimens while maintaining equivalent efficacy.

Scope of Opportunities

There are at least 4 strategies for IVPE. The first strategy is lower doses. Several examples exist in which dose reduction is possible while maintaining efficacy. Many oral oncology drugs with poor bioavailability have been developed and labeled to be taken under fasting conditions. Proof of concept of this strategy was recently demonstrated for abiraterone.[1] In that prospective trial,[1] 72 patients were randomized to the standard daily dose of 1000 mg of abiraterone fasting or 250 mg with food. Al

likely that a dosage of 480 mg every 8 to 12 weeks (or longer) will maintain efficacy, yielding cost reductions of at least 50%. As another example, the standard 3-weekly regimen of trastuzumab yields trough serum concentrations in excess of the target trough of 20 µg/mL, suggesting that the interval between doses could be increased, with potential cost reductions of 50% or more.

A third strategy is shorter duration of treatment. Decreasing the duration of treatment is a good opportunity for study, as exemplified by multiple trials of imatinib discontinuation for chronic myelogenous leukemia.[5] Duration of treatment has also been studied for trastuzumab in *HER2*-positive breast cancer in the Persephone trial, which demonstrated that a 50% reduction in the duration of trastuzumab treatment does not compromise efficacy in the adjuvant setting.

A fourth strategy is therapeutic substitution. Off-

Ratain, Goldstein & Lichter, JAMA Oncology, 2019

Interventional pharmacoeconomic strategies

- **Therapeutic substitution**
- **Lower dosage**
- **Less frequent dosing**
- **Shorter duration**

Ratain, Goldstein, Lichter. JAMA Oncology 2019

OPTIMAL CANCER CARE ALLIANCE

Optimal Dosage. Best Outcome.

OCCA Chairman of the Board of Directors: Ian F. Tannock

Ian Tannock, M.D., PhD, is Professor Emeritus of Medical Oncology at the Princess Margaret Cancer Centre and the University of Toronto in Toronto, Canada. His clinical research has focused on methodology for clinical trials, and he has led global practice-changing trials for prostate cancer. Dr. Tannock was a member of the Board of Directors of the American Society of Clinical Oncology (ASCO) from 2001 to 2004. He received honorary degrees (DSc) from London University, UK (2009) and from the Universidad de la República, Uruguay (2020). He is the only non-European to be given the European Society of Medical Oncology (ESMO) award (2012) and he received the Allen Lichter Award for leadership and innovation from ASCO in 2019. Dr. Tannock is a Member of the Order of Canada.

OCCA Treasurer: Mark J. Ratain

Mark Ratain, M.D., has been a faculty member in the Department of Medicine at The University of Chicago since 1986, and is currently the Leon O. Jacobson Professor of Medicine, the Director of the Center for Personalized Therapeutics and Chief Hospital Pharmacologist. In addition, he serves as the Associate Director for Clinical Sciences in the University's Comprehensive Cancer Center. Dr. Ratain's research has historically focused on the development of new oncology drugs and diagnostics, but is increasingly focused on the new discipline of interventional pharmacoeconomics. He is the recipient of awards from multiple organizations, including the American Association of Pharmaceutical Scientists, the American Society for Clinical Pharmacology and Therapeutics, the American Society of Clinical Oncology, the American College of Clinical Pharmacology, and the Pharmaceutical Research and Manufacturers Association Foundation.

OCCA Chairman of the Board Emeritus: Allen S. Lichter

Allen S. Lichter, M.D., earned his bachelor's and medical degrees from the University of Michigan. He trained in radiation oncology at University of California, San Francisco, before joining the faculty at Johns Hopkins University, and later the National Cancer Institute. He served as Chair of the Department of Radiation Oncology at the University of Michigan (1894-1996) and as Dean of the Medical School at Michigan (1998-2006). A former President of the American Society of Clinical Oncology (ASCO), he served as CEO of ASCO from 2006-2016. He also served as chairman of the board of the Optimal Cancer Care Alliance from 2017-2021. He is a member of the National Academy of Medicine.

OCCA Directors:

Pre-marketing vs Post-marketing?
- roles of governments and legislation

Endless Opportunities

Drug	Current Dosage	Recommended Dosage
Ibrutinib	420 mg	140 mg
Erlotinib	150 mg	25–100 mg
Dasatinib	100 mg	50 mg
Pembrolizumab	200 mg	2 mg/kg
Abiraterone	1,000 mg fasting	250 mg with food
Lapatinib	1,250 mg fasting	500 mg with food
Pazopanib	800 mg fasting	400–600 mg with food
Nivolumab	Every 2–4 weeks	Every 8–12 weeks
Atezolizumab	Every 2–4 weeks	Every 8–12 weeks
Pembrolizumab	Every 3–6 weeks	Every 8–12 weeks

Adapted from Serritella et al. (2020)

How do we turn opportunity into impact?

Two Approaches

- Running de-escalation clinical trials…..Main results come later
- Implementing Health Policies …….. NOW
  - Weight-based dosing of checkpoint inhibitors

Running Clinical Trials – Learning from Failures

Where, Who, How, When, Which

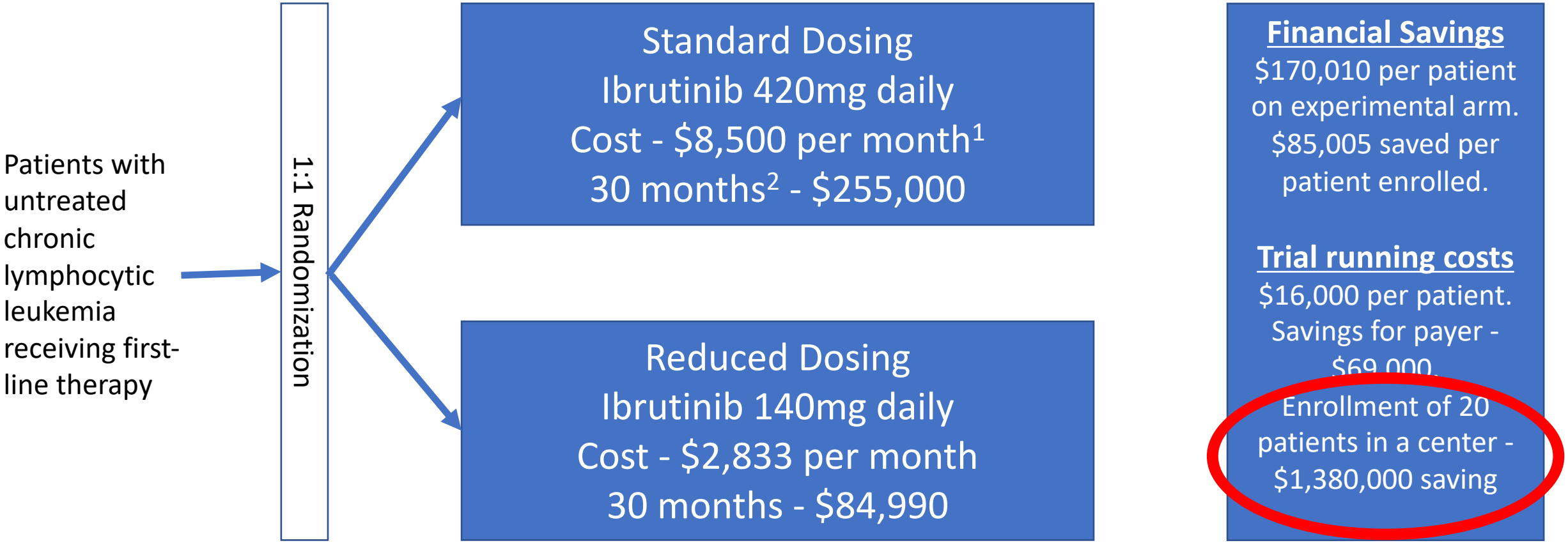
Where and Who?

- High / Low / Middle Income Countries
- Capital Cities?
- USA?
  - Where in USA?
- Europe?
  - Trastuzumab
  - Denosumab
  - Netherlands
- Cultural Interest?
- Incentive Structure?

How - Funding of trials

- Successful payer funded mechanisms
  - The Netherlands
  - Switzerland
  - UK?

Financing de-escalation trials - Ibrutinib in CLL

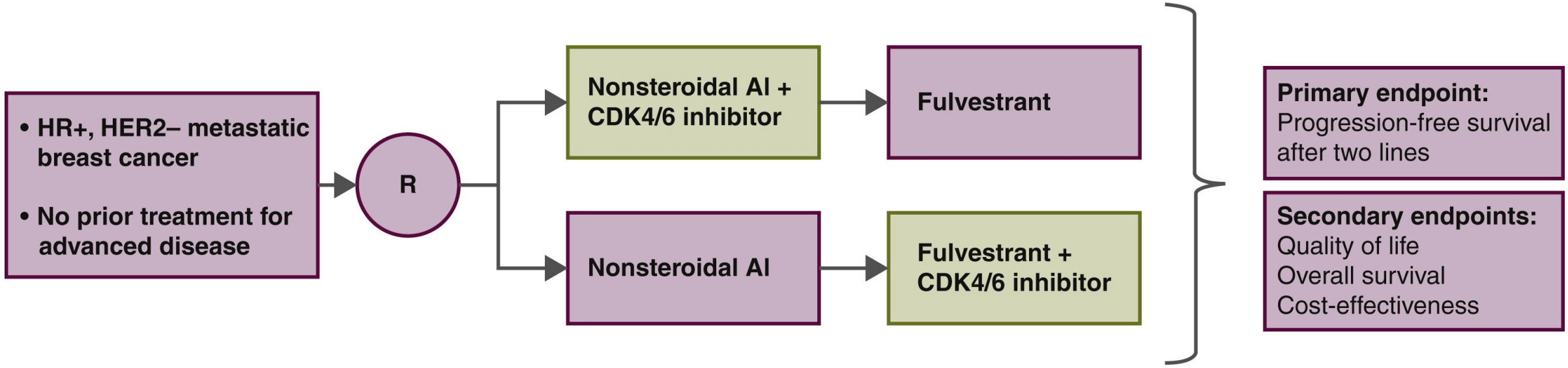


[1] Barnes JI et al. Cost-effectiveness of ibrutinib as first-line therapy for chronic lymphocytic leukemia in older adults without deletion 17p. Blood Adv. 2018 Aug 14;2(15):1946-1956.

[2] This estimate of 30 months is likely a vast underestimation. (Based on Barr PM et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. Haematologica. 2018 Sep;103(9):1502-1510.) Median treatment duration with ibrutinib was 29 months. With a median follow up for this extended analysis of 29 months 79% of patients remain on first-line ibrutinib.

Goldstein, Lichter and Ratain. Health Affairs Blog 2019.

A revolving research fund to study efficient use of expensive drugs: big wheels keep on turning



Van Ommen Nijjjhof et al, Annals of Oncology 2021

Trial Designs and Levels of Evidence

- Surrogate endpoints?
- Width of non-inferiority margin?

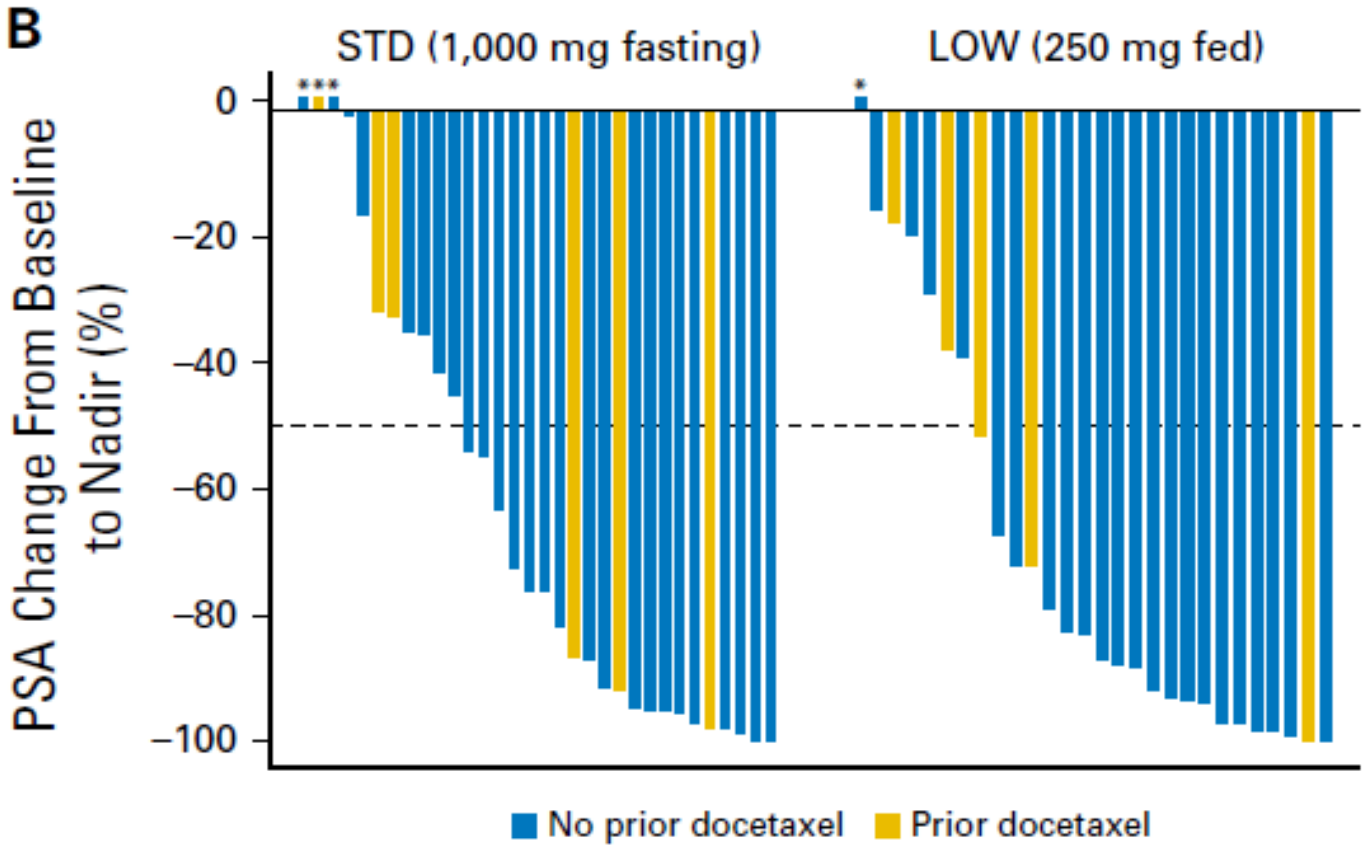
comments

Near-Equivalence: Generating Evidence to Support Alternative Cost-Effective Treatments

Ian F. Tannock, MD, PhD[1]; Mark J. Ratain, MD[2]; Daniel A. Goldstein, MD[3]; Allen S. Lichter, MD[4]; Gary L. Rosner, ScD[5]; and Leonard B. Saltz, MD[6]

Tannock et al., JCO, 2021

Abiraterone in Prostate Cancer

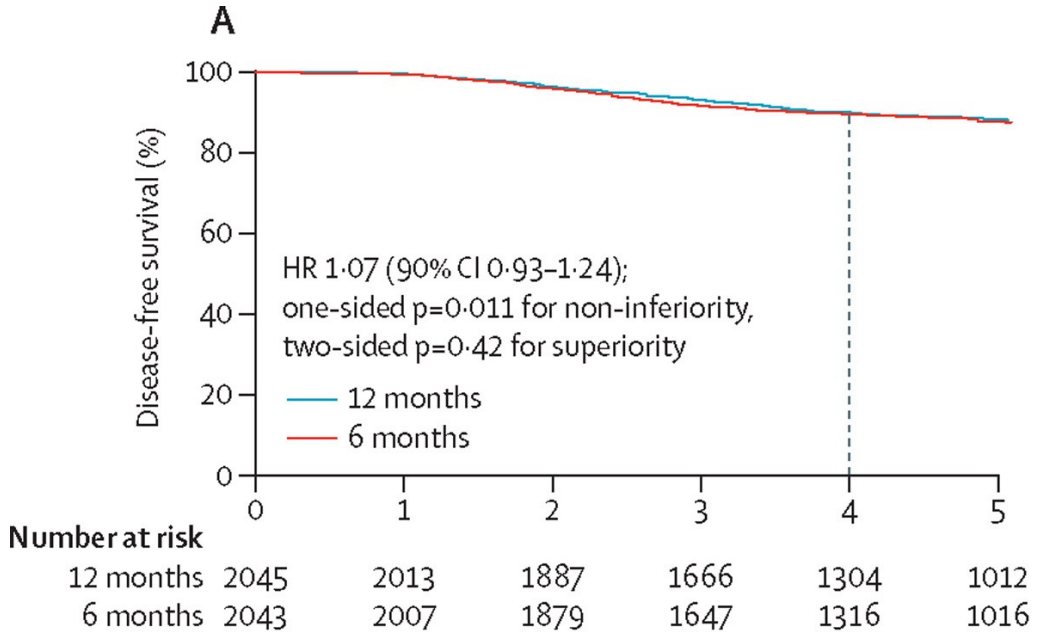


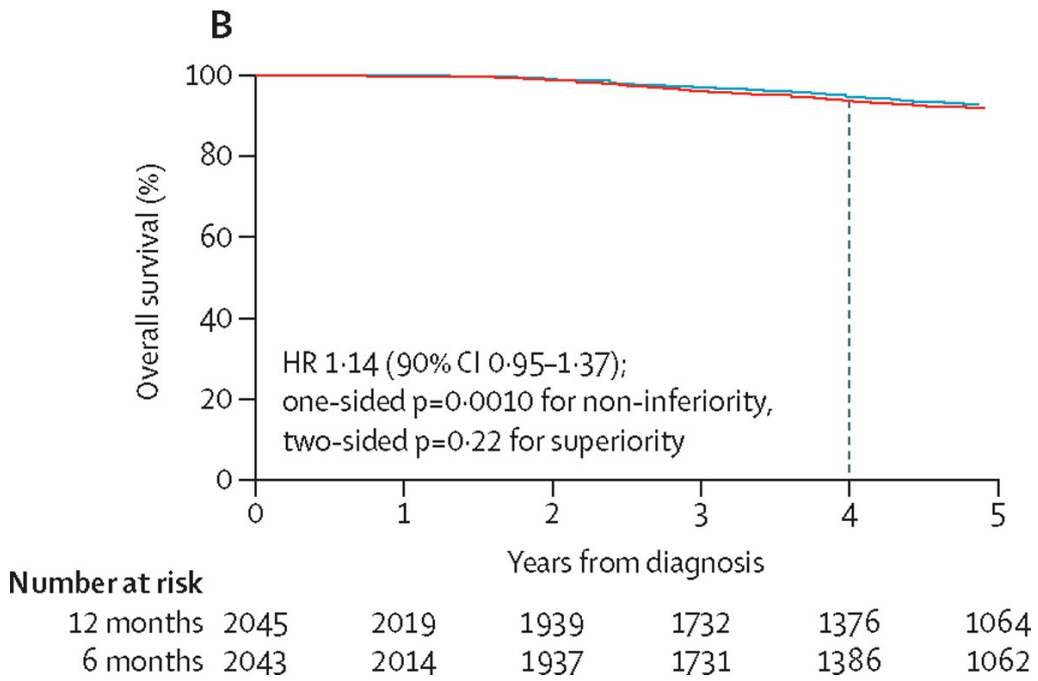
1000mg without food
Vs
250 mg with food

Szmulewitz et al, JCO 2018

Duration of adjuvant trastuzumab

- Persephone trial
- 12 months vs 6 months of trastuzumab





Earl et al., Lancet, 2019

When and Which - Choosing the Right Drug at the Right Time

- Patent runway and the treatment landscape
- Aim to run a trial before the market is set

- Lessons from abiraterone, ibrutinib

Finding the right people in the right places

The importance of improving safety

The role of Policy-Makers and Payers

- Involvement in trial design
- Evaluation of trial results to implement policy

Summary for clinical trials

- Right Place
- Right People
- Right Drug
- Right Dose
- Right Funding
- Right Design
- Right Level of Evidence
- Improve Safety

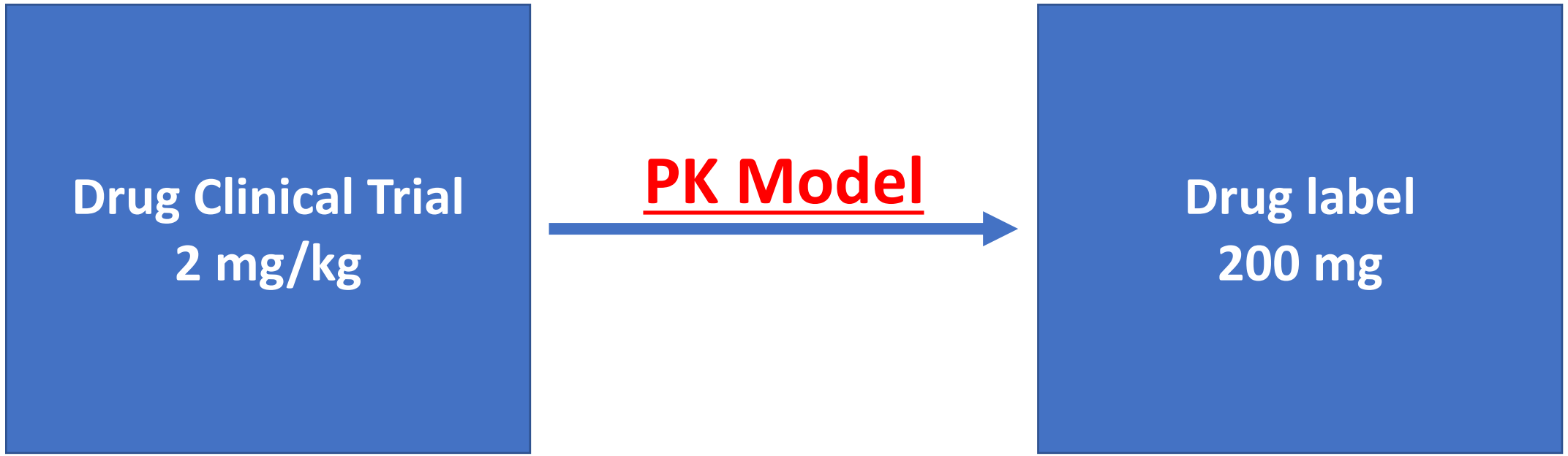
Policy Implementation without need for trial

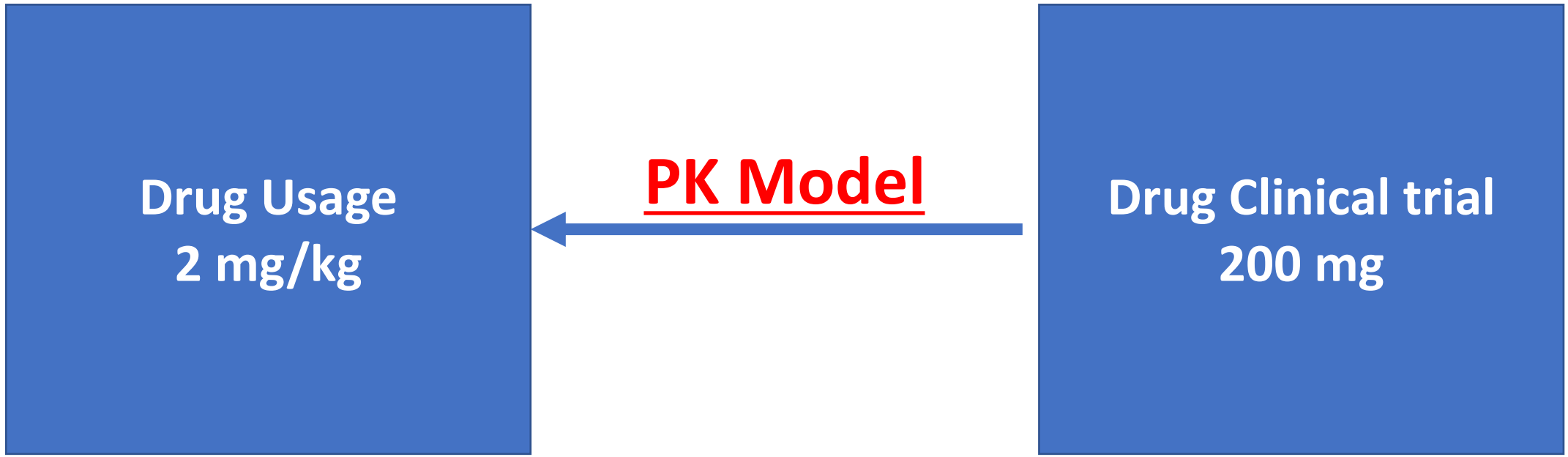
The Dosing of Pembrolizumab

- Labelled dosing initially 2 mg/kg every 3 weeks
- Changed to 200 mg every 3 weeks
- Average patient of 75 kg requires only 150 mg
- If using 2 mg/kg, US could save $0.8 billion annually – but dependent on vial sharing

Goldstein et al. JNCI, 2017

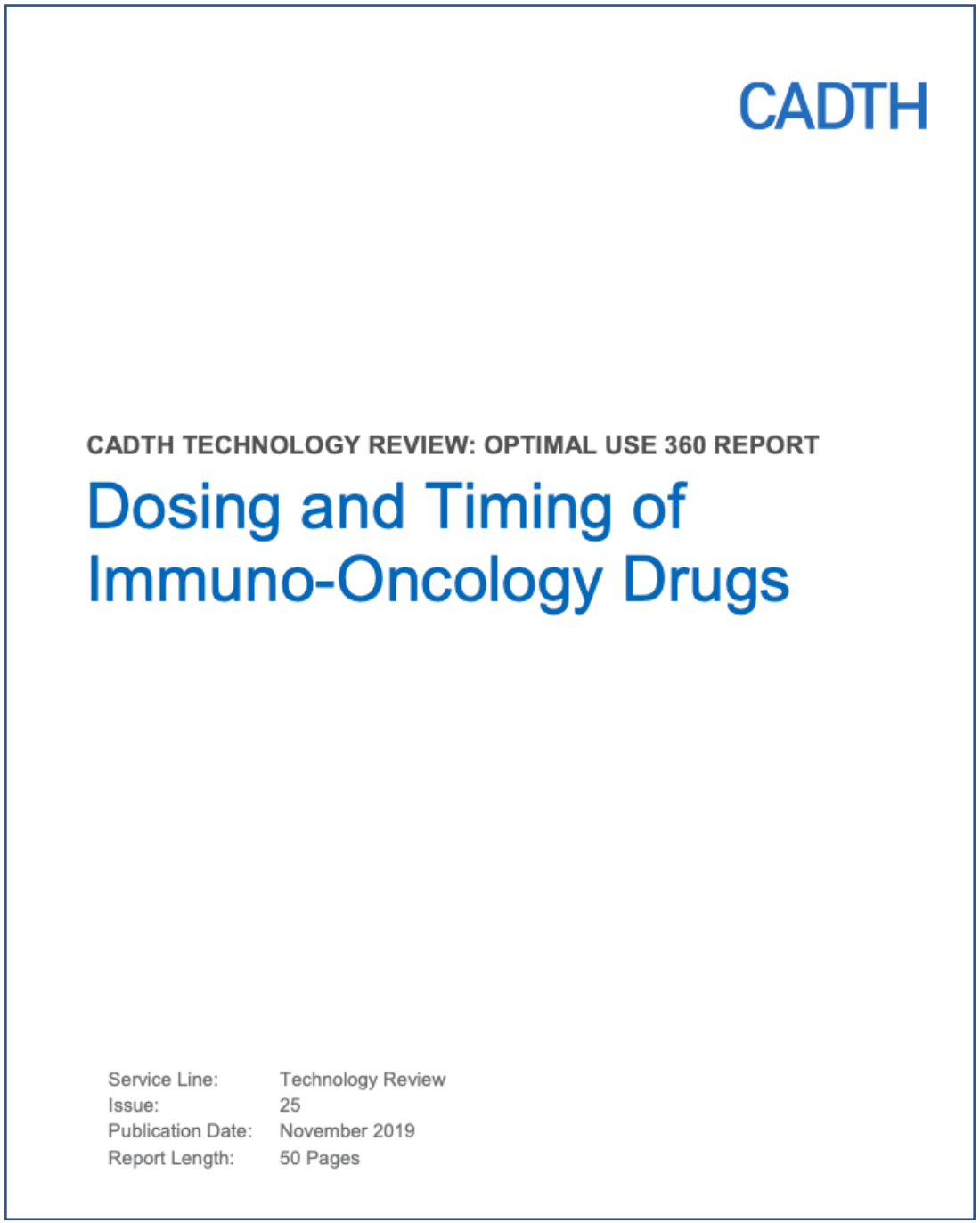
Drug Label in 2nd Line Lung cancer and melanoma




Drug Usage
2 mg/kg
PK Model
Drug Clinical trial
200 mg

Canada leading the way…..

Canada


CADTH
CADTH TECHNOLOGY REVIEW: OPTIMAL USE 360 REPORT
Dosing and Timing of Immuno-Oncology Drugs
Service Line: Technology Review
Issue: 25
Publication Date: November 2019
Report Length: 50 Pages

Conclusion

Evaluation of exposure-response relationships and multiple dosing regimens of pembrolizumab indicates that 2 mg/kg every three weeks, with a 200 mg upper dose cap, is the most efficient dosage to deliver target engagement of 95% based on the trough or end of dosage interval concentration. This dose is the most efficient at body weights below or at the

Most Canadian provinces now use weight-based pembrolizumab

Countries currently using forms of weight-based dosing

- Canada (most provinces)
- Denmark
- Israel (partially)
- Iceland
- Netherlands (Erasmus)
- USA (Kaiser Permanente – most indications)

The potential benefit of weight-based dosing of Pembrolizumab

- $20 billion in annual sales
  - 25% less drug infused
  - **$5 billion annual savings globally**
- Use of savings to help patients for:
  - Other underfunded healthcare services
  - Reduced insurance premiums
  - Reduced personal financial toxicity
- Possible potential for reduced duration of immune related adverse events

Many thanks to Collaborators

- University of Chicago
  - Mark Ratain
- National Cancer Institute, USA
  - Doug Figg
  - Cody Peer
- OCCA
  - Allen Lichter
  - Ian Tannock
  - Len Saltz
- Clalit Health Services
  - Doron Netzer
  - Dorit Hoffnung Gabbay
- Rabin Medical Center
  - Eli Rosenbaum