Extrapolation & Generalizability of treatment effects over time

Keith R Abrams PhD
Department of Health Sciences, University of Leicester, UK

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu

Extrapolation

• HTA is concerned with evaluating health technologies in the "real world", i.e. clinical practice, in order to make health policy decisions

• For HTA it is often important to assess impact of decisions (& therefore effectiveness) over a lifetime time horizon (of patients) …

• BUT because RCTs are usually short-term in nature we often have to extrapolate (especially for Overall Survival [OS]) using parametric survival models, e.g. exponential, Weibull etc. …

• BUT different parametric survival models typically can have very different behaviours especially in the right-hand tail of the distribution.

• BUT because of different behaviour in the tails, different models can lead to very different estimates of Restricted Mean Survival Time (RMST), and potentially different decisions.
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115303, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu

### Extrapolation - Example

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115303, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu

### Potential Methods

- Sensitivity analysis – fit a number of different parametric models & explore differences
- Possibly use a measure of "statistical fit" to chose between them e.g. AIC, BIC, DIC*
- Obtain RWE Individual Patient Data (IPD) [usually with longer follow-up] to blend with RCT data
- Use summary RWE to help chose between different models or derive weights to average over the different models using Bayesian Model Averaging (BMA) methods

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115303, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu
JMDB Methods

- **JMDB (OS to 30 months)** – fit Exponential, Weibull & Log-Normal parametric models to Gemcitabine & Pemetrexed arms separately for both unweighted and weighted (using FRAME) data
- Use **UK Cancer Registry** on NSCLC OS at 5 years to derive weights & average over the three models
- Compare **RMST (AUC) at 5 years** (72 months)
- Also use a simple average over models (uniform/equal weights)

---

**JMDB: Extrapolation**

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

www.imi.europa.eu

JMDB: Results (Unweighted)

<table>
<thead>
<tr>
<th>OS (72 months)</th>
<th>Gemcitabine</th>
<th>Pemetrexed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (SE)</td>
<td>DIC</td>
</tr>
<tr>
<td>Exponential</td>
<td>12.95 (0.62)</td>
<td>3337.93</td>
</tr>
<tr>
<td>Weibull</td>
<td>12.85 (0.48)</td>
<td>3301.66</td>
</tr>
<tr>
<td>Log-Normal</td>
<td>14.98 (0.79)</td>
<td>3369.55</td>
</tr>
</tbody>
</table>

Lower DIC is better statistically & a difference >3 is usually considered important

JMDB: Extrapolation

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

www.imi.europa.eu
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115303, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu

### JMDB: Extrapolation

#### OS: Unweighted - Gemcitabine

- **UK Cancer Registry**
- **JMDB: Exponential**
- **JMDB: Weibull**
- **JMDB: Log-Normal**

**Log-odds of survival @ 5 years**

**Density**

- **OS: Unweighted - Gemcitabine**
- **Log-odds of survival @ 5 years**
- **Density**
- **UK Cancer Registry**
- **JMDB: Exponential**
- **JMDB: Weibull**
- **JMDB: Log-Normal**

99.9%

0.01%

0.0%

---

### JMDB: Results (Unweighted)

<table>
<thead>
<tr>
<th>OS (72 months)</th>
<th>Gemcitabine</th>
<th>Pemetrexed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (SE)</td>
<td>DIC</td>
</tr>
<tr>
<td>Exponential</td>
<td>12.95 (0.62)</td>
<td>3337.93</td>
</tr>
<tr>
<td>Weibull</td>
<td>12.85 (0.48)</td>
<td>3301.66</td>
</tr>
<tr>
<td>Log-Normal</td>
<td>14.98 (0.79)</td>
<td>3369.55</td>
</tr>
<tr>
<td>Uniform weights</td>
<td>12.85 (0.48)</td>
<td>-</td>
</tr>
<tr>
<td>UK CR Weights</td>
<td>12.95 (0.62)</td>
<td>-</td>
</tr>
</tbody>
</table>

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115303, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.

www.imi.europa.eu
### JMDB: Results (Weighted)

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>Pemetrexed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC (SE)</td>
<td>DIC</td>
</tr>
<tr>
<td>Exponential</td>
<td>15.32 (1.32)</td>
<td>935.29</td>
</tr>
<tr>
<td>Weibull</td>
<td>14.61 (1.14)</td>
<td>933.01</td>
</tr>
<tr>
<td>Log-Normal</td>
<td>17.13 (1.59)</td>
<td>935.92</td>
</tr>
<tr>
<td>Uniform weights</td>
<td>15.13 (1.54)</td>
<td>-</td>
</tr>
<tr>
<td>UK CR Weights</td>
<td>17.08 (1.62)</td>
<td>-</td>
</tr>
</tbody>
</table>

**Discussion**

- Using model averaging and reweighting of RCT both using RWE allows extrapolation (over time) and generalisability to a target population.
- Other parametric distributions could be used – logistic & gamma will be similar to log-normal & Weibull respectively.
- UK CR data is age/sex matched to JMDB but not stage.
- Could incorporate beliefs about the relevance of RWE, i.e. should we accept UK CR at ‘face-value’ even after adjustment?
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu

Backup Slides
**JMDB Technical Methods**

- **Re-create** JMDB IPD (OS to 30 months) from KM's
- Fit Exponential, Weibull & Log-Normal models to Gemcitabine & Pemetrexed arms separately for both unweighted and weighted data using **MCMC in WinBUGS** & calculate AUC (SE)
- Use UK Cancer Registry on NSCLC OS at 5 years to derive **inverse Gaussian weights** & average over the three models using Bayesian Model Averaging (BMA)
- Compare with BMA using uniform/equal weights
BMA – 1

- Bayes’ Factor (BF) for \( M_0 \) cf. \( M_1 \) \((B_{01})\) is given by \( P(D|M_0)/P(D|M_1) \)
- Assume \( k+1 \) models \( M_0, \ldots, M_k \)

\[
P(M_k \mid D) = \frac{\alpha_k B_{k0}}{\sum_{j=0}^k \alpha_j B_{j0}}
\]

\[
\alpha_j = \frac{P(M_j)}{P(M_0)} \quad \text{&} \quad B_{jj} = 1
\]

BMA – 2

- Assume obtain an estimate of \( \mu \) (e.g. AUC) from each model
- Model averaged estimate of mean and variance of \( \mu \)

\[
E[\mu \mid D] = \sum_{j=0}^k E[\mu \mid D, M_j]P(M_j \mid D)
\]

\[
V[\mu \mid D] = \sum_{j=0}^k P(M_j \mid D)V[\mu \mid D, M_j] + \sum_{j=0}^k P(M_j \mid D)(E[\mu \mid D, M_j] - E[\mu \mid D])^2
\]
• Gelfand (1996) – Harmonic Mean approach:

\[
P(D \mid M_j) \approx \frac{1}{\sum_{i=1}^{m} \frac{1}{L(\theta_i \mid M_j)}}
\]

• Requires proper prior distributions
• Use plausible ‘vague’ priors
• Monitor deviance node in WinBUGS & process output in R

The research leading to these results has received support from the Innovative Medicines Initiative joint Undertaking under grant agreement no 115303, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in-kind contribution.

www.imi.europa.eu
Prediction of Drug Effectiveness based on RCT Efficacy Data & Real-World Evidence

- A CASE STUDY ON RHEUMATOID ARTHRITIS -

ISPOR 19th Annual European Congress
November 1st, 2016
Vienna, Austria

Eva-Maria Didden, on behalf of GetReal
Institute of Social and Preventive Medicine (ISPM), University of Berne, Switzerland

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

www.imi.europa.eu

Motivation

Gap in treatment outcomes between RCT and real-world populations

DAS28 – Disease Activity Score (28 examined joints)
DMARD – Disease Modifying Anti-Rheumatic Drug

Change in DAS28 after 6 months

Conventional DMARD (cDMARD)
Biologic DMARD (bDMARD)
**Research Task**

Predicting the effectiveness of a new bDMARD in patients with *Rheumatoid Arthritis* (RA) who are likely to receive this treatment in the real world of a healthcare system.

**Availability of individual participant data:**
- RCT data on the new bDMARD
- no real-world data (RWD) on the new bDMARD
- RWD on an existing similar bDMARD

**Definitions**

- **Treatment predictor:** predictor of real-world treatment decision.
- **Prognostic factor:** associated with the clinical outcome independent of treatment decision → measure of the natural course of the disease.
- **Effect modifier:** associated with the clinical outcome in interaction with treatment decision → acts differently in different treatment arms.
### Suggested Framework

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Evidence used</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Identify a market-approved drug (S) which is similar to the new drug (N) you want to make predictions about.</td>
<td>Expert advice</td>
</tr>
<tr>
<td>b) Estimate the relative efficacy of drug N and account for any relevant effect modifiers.</td>
<td>RCT data (on N), expert advice</td>
</tr>
<tr>
<td>Identify the relevant prognostic factors and assess their impact on disease progression.</td>
<td>RWD (on S), RCT data (on N), expert advice</td>
</tr>
<tr>
<td>c) Identify the relevant treatment predictors to determine the profile of patients who are likely to receive N.</td>
<td>RWD (on S), expert advice</td>
</tr>
<tr>
<td>d) Predict treatment outcome in patients who are likely to receive N.</td>
<td></td>
</tr>
</tbody>
</table>

**Two drugs are assumed to be «similar» if they...**

... are prescribed for the same purpose.

... are administered to the same types of patients, i.e. to patients

- with similar physical attributes,
- with comparable disease and treatment histories,
- with similar living conditions, etc.

We could identify a bDMARD (\( \rightarrow S \)) which is similar to the new bDMARD of interest (\( \rightarrow N \))
b) Modelling of treatment effect

1. Selection of the relevant prognostic factors and effect modifiers
   i. Follow the clinical experts’ advice
   ii. Perform statistical variable selection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prognostic factors</th>
<th>Effect modifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-months change in DAS28</td>
<td>RF-positivity, disease duration</td>
<td>RF-positivity</td>
</tr>
<tr>
<td></td>
<td>baseline DAS28, obesity/body-mass index</td>
<td># [previous anti-TNF agents]</td>
</tr>
</tbody>
</table>

2. Estimation of...
   ...the efficacy of \( N \), accounting for the selected effect modifiers \( \leftarrow \) RCT data
   ...the impact of the prognostic factors \( \leftarrow \) RCT data on \( N \) and RWD on \( S \)

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115303, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

www.imi.europa.eu

---

c) Modelling of treatment assignment

1. Selection of the relevant treatment predictors
   i. Follow the clinical experts’ advice
   ii. Perform statistical variable selection

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selected treatment:</td>
<td></td>
</tr>
<tr>
<td>bDMARD vs. cDMARDs</td>
<td></td>
</tr>
</tbody>
</table>

```
<table>
<thead>
<tr>
<th>Treatment predictors</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF-positivity, disease duration</td>
<td>selected treatment:</td>
</tr>
<tr>
<td>baseline ESR</td>
<td></td>
</tr>
<tr>
<td># [previous cDMARDs], # [previous anti-TNF agents]</td>
<td></td>
</tr>
<tr>
<td># [concomitant cDMARDs]</td>
<td></td>
</tr>
<tr>
<td>steroids (y/n)</td>
<td></td>
</tr>
</tbody>
</table>
```

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115303, resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.

www.imi.europa.eu

---
d) Prediction of drug effectiveness in a simulated real-world patient population

i. Predict treatment decision «bDMARD N vs. cDMARDs»

ii. Predict treatment outcome in those patients who were assigned to receive N.

iii. Compare the predicted treatment outcome with the outcome observed in patients taking cDMARDs.
Discussion

**Deliverable**

Comprehensive *inference framework* to connect information from various sources

- Prediction of real-world treatment effect
- Assessment of the efficacy-effectiveness gap

**Possible extensions:**
- Use of aggregate data as prior information
- Comparison of more than two treatment arms

**Internal model validity:** satisfied

**External model validity:** model transferability between countries not ensured
- different healthcare systems
- different patient profiles

---

Didden et al. (2016/17), *Prediction of Real-World Treatment Effectiveness based on Trial and Registry Data*, in progress.

---

ACKNOWLEDGEMENTS

- **Institute of Social and Preventive Medicine, University of Bern, Switzerland:**
  Noemi Hummel, Yann Ruffieux, Orestis Efthimiou, Georgia Salanti, Matthias Egger

- **Health Technology Assessment Group, F. Hoffmann-La Roche Ltd, Basel, Switzerland:**
  Sandro Gsteiger

- **Hôpitaux Universitaires de Genève, HUG, Switzerland:**
  Axel Finckh

- **Inselspital, Department of Rheumatology, Immunology and Allergology, Berne, Switzerland:**
  Stephan Reichenbach

---

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking (EU contribution: €625 000), resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.

www.imi.europa.eu
PREDICTING TREATMENT EFFECTIVENESS OVER TIME IN REAL WORLD FROM TRIAL EFFICACY DATA

Re-weighting of RCT data to more appropriately reflect the baseline characteristics of a real-world population

Mark Belger

November 1st 2016

Objectives

• Exploring how “real-life” clinical data can be brought in earlier in drug development

• To review the NSCLC case study on RCT reweighting methodology & obtain feedback from participants to refine the approach

• Assessment of potential application in regulatory and HTA decision making process
Study team

• Keith Abrams (Uni Leicester)
• Pall Jonsen (NICE)
• Stefan Schwoch
• Mark Belger
• Alan Brnabic
• Michael Happich
• Katherine Winfree
• Allicia Girvan

IMI, GetReal & RWE challenges
<table>
<thead>
<tr>
<th>RCT vs RWE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Patient benefit and harm in experimental and closely monitored research studies, normally RCTs.</strong></td>
</tr>
<tr>
<td><strong>• Design minimises bias - high internal validity</strong></td>
</tr>
<tr>
<td><strong>• Generalisability questionable</strong></td>
</tr>
<tr>
<td>- restricted entry criteria</td>
</tr>
<tr>
<td>- unrepresentative settings</td>
</tr>
<tr>
<td><strong>• Patient benefit and harm when the technology is actually applied in everyday practice.</strong></td>
</tr>
<tr>
<td>- pragmatic clinical trials</td>
</tr>
<tr>
<td>- observational studies</td>
</tr>
<tr>
<td>- synthesis</td>
</tr>
<tr>
<td><strong>• ISPOR: “evidence used for decision-making that is not collected in conventional randomized controlled trials (RCTs)”</strong></td>
</tr>
<tr>
<td><strong>• “Dirty” - a lot of variability and biases</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RWE Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Phase III trials too short to capture relevant effects, need to use models:</strong></td>
</tr>
<tr>
<td>Considerable uncertainty in RWE predictions</td>
</tr>
<tr>
<td><strong>• RWE likely to be influenced by factors (adherence etc.) not captured in Phase III, model-based estimates unreliable:</strong></td>
</tr>
<tr>
<td>RWE biased?</td>
</tr>
<tr>
<td><strong>• Phase III patient population too broad/poor fit to care pathway (?targeting of therapy):</strong></td>
</tr>
<tr>
<td>Uncertainty in RWE for target sub-populations</td>
</tr>
<tr>
<td><strong>• Phase III comparator not appropriate for local HTA: indirect meta-analysis (for RWE) not robust:</strong></td>
</tr>
<tr>
<td>No credible RWE estimate</td>
</tr>
<tr>
<td><strong>• Phase III trial event rates for comparator not in line with available RW evidence for comparator:</strong></td>
</tr>
<tr>
<td>RWE biased?</td>
</tr>
</tbody>
</table>
Studies included

JMDB RCT

Outcome: and resource use of non-small cell lung cancer (NSCLC) patients treated with first-line platinum-based chemotherapy across Europe: FRAME prospective observational study

Reweighting GetReal case study
The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution. www.imi.europa.eu

GetReal WP1 Case Studies
MC 03 June 2015 Slide 9

Weighting Approaches

- Two key approaches employed
  1. Inverse propensity score method (IPS)¹
  2. Entropy balancing method²
- Both approaches calculate weights for the RCT population (JMDB) subject to matching selected baseline characteristics to the general population of interest (FRAME observational study)
- Weights are assessed for outliers and are applied to the RCT outcome of interest to estimate the weighted treatment effect
- Error of weighted treatment effect comes from the Bootstrap sampling distribution of weighted treatment effect

² Hainmueller Political Analysis 2012 20(1):25-46
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FRAME (N=948)</th>
<th>JMDB (N=1209)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years – mean (SD)</td>
<td>62.3 (9.86)</td>
<td>59.7 (9.34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time since diagnosis – month (SD)</td>
<td>2.8 (12.61)</td>
<td>1.9 (7.75)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>293 (31%)</td>
<td>405 (33.5%)</td>
<td>0.211</td>
</tr>
<tr>
<td>Non-Asian n (%)</td>
<td>930 (98%)</td>
<td>997 (83%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>297 (31%)</td>
<td>277 (23%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>484 (51%)</td>
<td>585 (48%)</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>121 (13%)</td>
<td>195 (16%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>46 (5%)</td>
<td>152 (13%)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytological</td>
<td>242 (26%)</td>
<td>453 (38%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Histopathological</td>
<td>706 (74%)</td>
<td>756 (62%)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis subtype n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>725 (77%)</td>
<td>861 (73%)</td>
<td>0.095</td>
</tr>
<tr>
<td>Large Cell Carcinoma</td>
<td>77 (8%)</td>
<td>145 (12%)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>146 (15%)</td>
<td>203 (17%)</td>
<td></td>
</tr>
<tr>
<td>Stage n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>206 (22%)</td>
<td>273 (23%)</td>
<td>0.470</td>
</tr>
<tr>
<td>IV</td>
<td>742 (79%)</td>
<td>937 (77%)</td>
<td></td>
</tr>
<tr>
<td>ECOG n (%)</td>
<td>0</td>
<td>446 (37%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1</td>
<td>275 (29%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>673 (73%)</td>
<td>753 (63%)</td>
<td></td>
</tr>
<tr>
<td>Number of Metastatic Sites n (%)</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>0-1</td>
<td>771 (81%)</td>
<td>288 (24%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>157 (17%)</td>
<td>296 (24%)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>20 (2%)</td>
<td>625 (52%)</td>
<td></td>
</tr>
<tr>
<td>Prior Radiotherapy n (%)</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prior Surgery n (%)</td>
<td>Yes</td>
<td>Yes</td>
<td>0.122</td>
</tr>
<tr>
<td>CV History n (%)</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lung History n (%)</td>
<td>Yes</td>
<td>Yes</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

The research leading to these results has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement no [115303], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies in kind contribution.

www.imi.europa.eu

GetReal WP1 Case Studies
MC 03 June 2015 Slide 12
Primary analysis

As reference JMDB (RCT) results:

Sensitivity analysis

fairly consistent results for HR
better balance comes at the expense of higher variability
Limitations

• Definitions of variables can be different between RCT and RWE studies
  – Baseline characteristics
  – Outcome measures
• Unmeasured confounders
• Non-overlapping propensity scores
• Specific categories of a variable are not available in RCT

Challenges addressed?

• Phase III trials too short to capture relevant effects, need to use models: Considerable uncertainty in RWE predictions ✓
• RWE likely to be influenced by factors (adherence etc.) not captured in Phase III, model-based estimates unreliable: RWE biased? ?
• Phase III patient population poor fit for local population/general care received may not reflect care in HTA country: RWE biased? ✓
• Phase III patient population too broad/poor fit to care pathway (?targeting of therapy): Uncertainty in RWE for target sub-populations ✓
• Phase III comparator not appropriate for local HTA: indirect meta-analysis (for RWE) not robust: No credible RWE estimate ❌
• Phase III trial event rates for comparator not in line with available RW evidence for comparator: RWE biased? ✓