# Let them in or build a wall?

Transporting inferences across borders

Presenter:

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# HTA and Clinical Regulatory bodies…

One of these things is not like the other….

## Clinical Regulatory Authorities

- **National or Supra-National Level (European)**
- **Approve medicinal products for sale, monitor their (safe) use, and take measures if safety issues arise**
- **Issue decisicions based on the objective scientific criteria of quality, safety & efficacy**
    - Explcitly excludes economic and other social considerations*
- **Typically tested under tightly controlled conditions**

## HTA Bodies

- **Regional, National and/or Supra-National Levels**
    - Encompasses both an **assessment** (scientificlly driven) and **appraisal** (w/ Ethical, Legal, Social and Economic value judgements)
    - Intended to inform decision-making, inlight of public values and those of patients served by the health system
- **Include a benefit assessment accompanying an economic evaluation (to determine "value for money" supporting an efficient allocation of resources)**
- **Major application is for recommendations about reimbursement eligibility and coverage**

*Recital 13 of Regulation (EC) 726/2004

# Agenda

1. Transportability
2. Hypothetical case study
3. Challenges when making reimbursement decisions

# Transportability

# Transportability 101

In general, to answer a research question, the data available will represent a ***sample*** from a much larger ***target population***

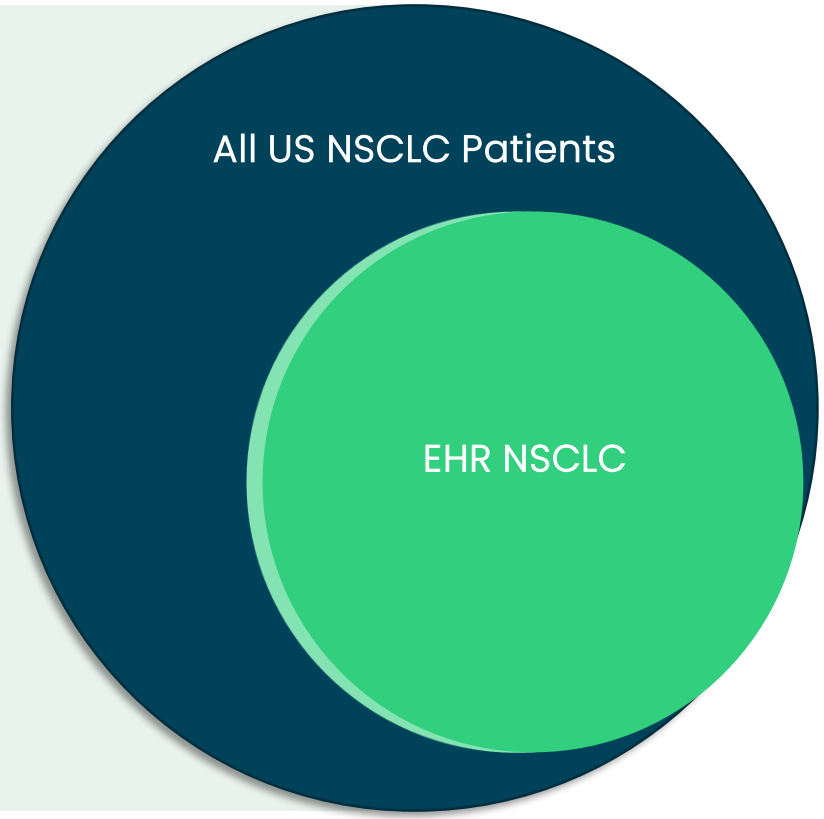


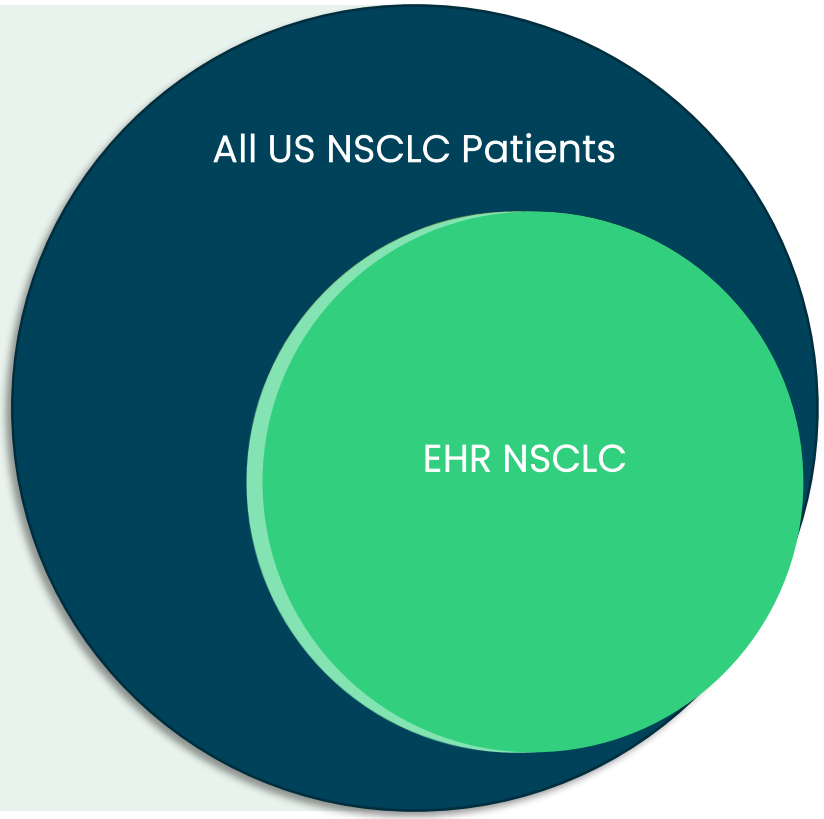

**Figure 1.** Illustration of NSCLC EDM as a sample of the broader US NSCLC population; Relevance of EHR RWE to the German NSCLC population requires assumption of transportability

References: Beal B, Altomare I, Ray J, Bargo D, Adamson B. Passport for Travel: Proposed Framework for the Transportability of Oncology Real-World Evidence. Presented at ISPOR: May 15-18, 2022, Washington, D.C.

Abbreviations: EDM, Enhanced Datamart; EHR, Electronic Health Record; NSCLC, non-small cell lung cancer; RWE, real world evidence; US, United States

# Transportability 101

Generalizability refers to how well that *sample* will *generalize* to the *target population* from which it was sampled

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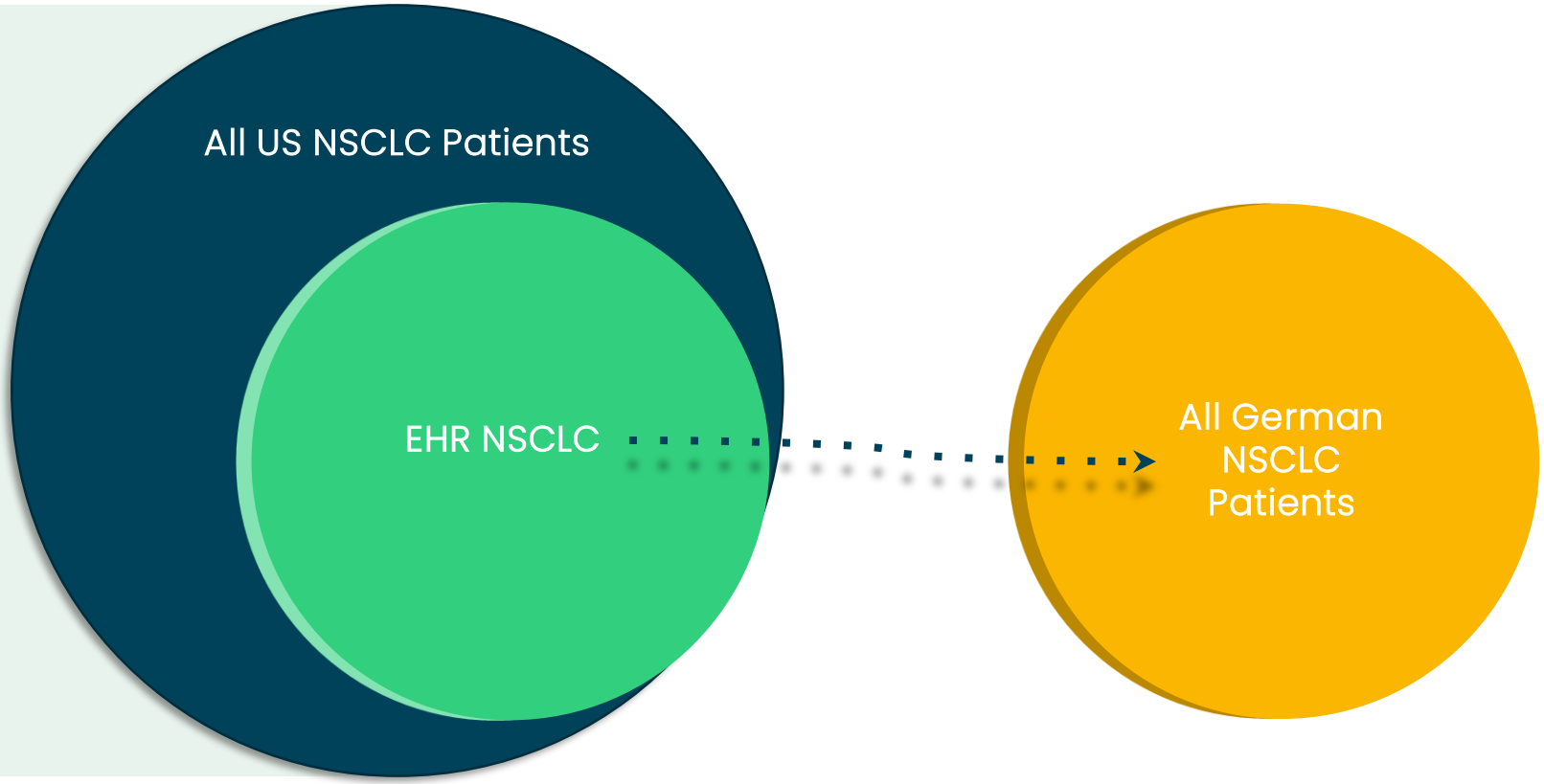
# Transportability 101

Transportability refers to how well that *sample* will *transport* to a *target population* from which the sample was not taken

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# The Elements/Taxonomy of Transportability

| | | |
|---|---|---|
| 01 | Patient Characteristics | ***Who*** the patient is<br>• Sex<br>• Biomarkers<br>• Modifiable risk factors (ie, smoking status) |
| 02 | Treatment Patterns | ***What*** therapies a patient has access to<br>• Market share of available products<br>• Country-specific guidelines<br>• Prior lines of therapy |
| 03 | Treatment Settings | ***How*** a patient receives care<br>• Visit frequency<br>• Scan frequency<br>• Access to supportive care |

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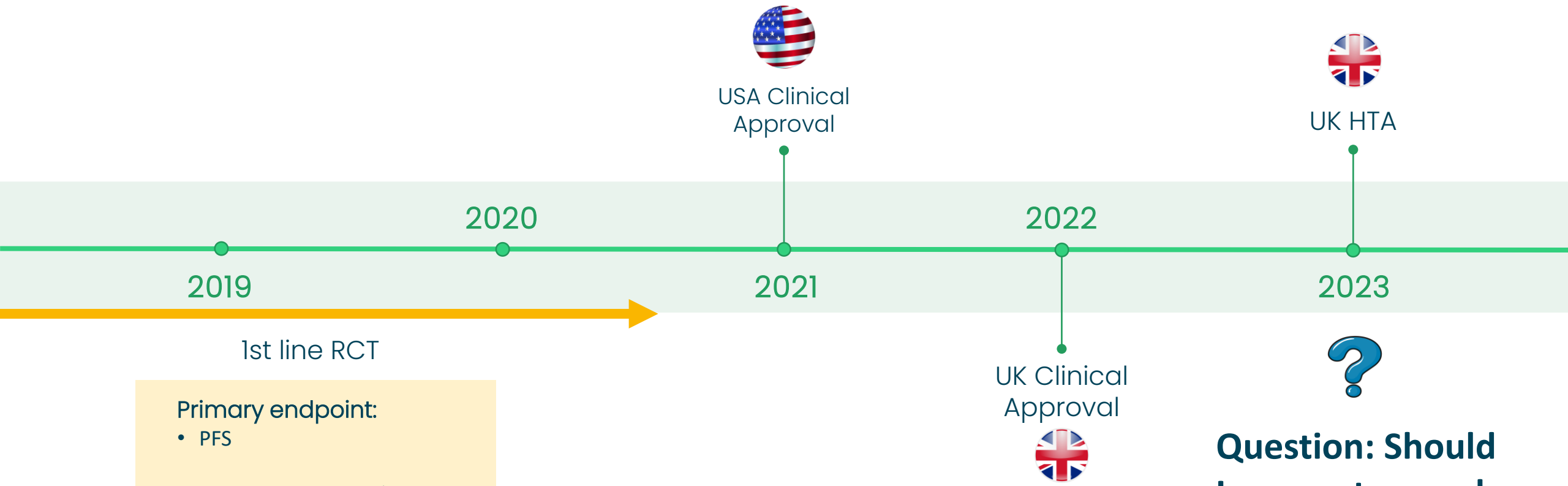
# Hypothetical case study

# Commercial development timelines for Immunotuzumab




Primary endpoint:
- PFS

Secondary endpoints:
- ORR
- Duration of response
- OS
- QoL
- Safety

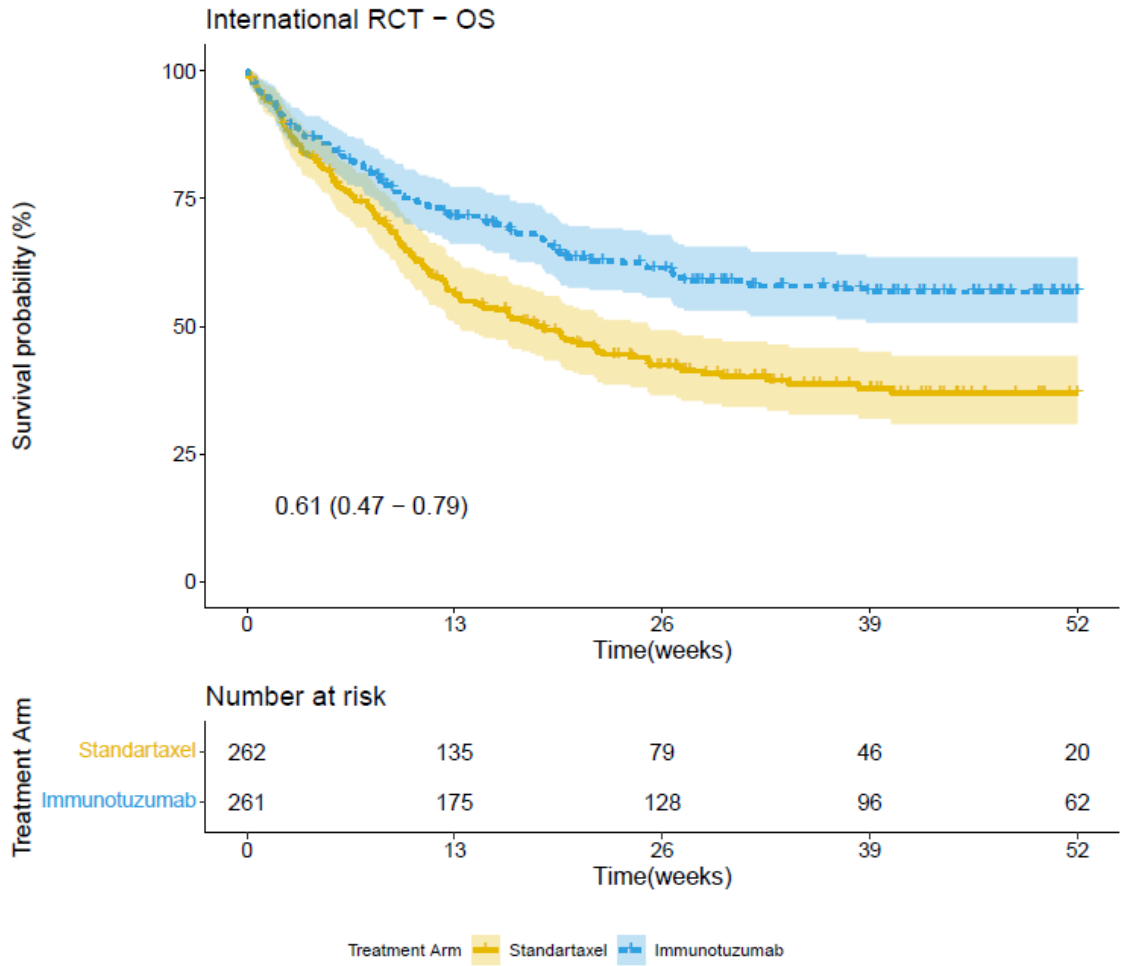
**Question: Should Immunotuzumab be reimbursed?**

Abbreviations: PFS, progression-free survival; ORR, overall response rate; OS, overall survival; QoL, quality of life; RCT, randomized controlled trial

# Committee meeting 1

# An international RCT comparing immunotuzmab to the relevant standard of care for the UK; standartaxel

**Figure 1.** Kaplan–Meier Estimates of Overall Survival in the RCT Treatment Groups



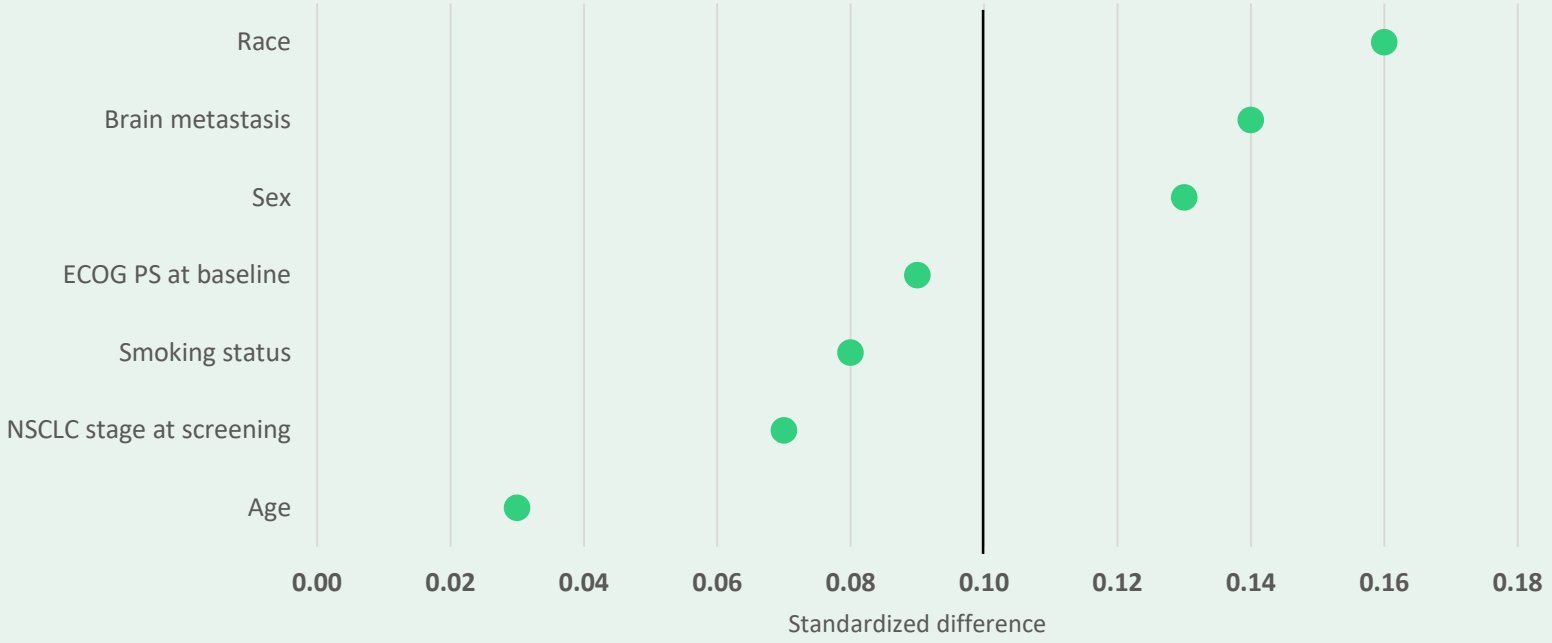

However, the RCT is **relatively small** and has relatively **immature outcome data**

The RCT also only includes a **small sample of UK patients**; not enough to support a robust subgroup analysis in the UK sub-population

Abbreviations: OS, overall survival; RCT, randomised controlled trial

# RWD are available on the characteristics of the patients receiving standard of care in the UK

Figure 2. Standardized difference of baseline characteristics of RCT & UK RWD patients



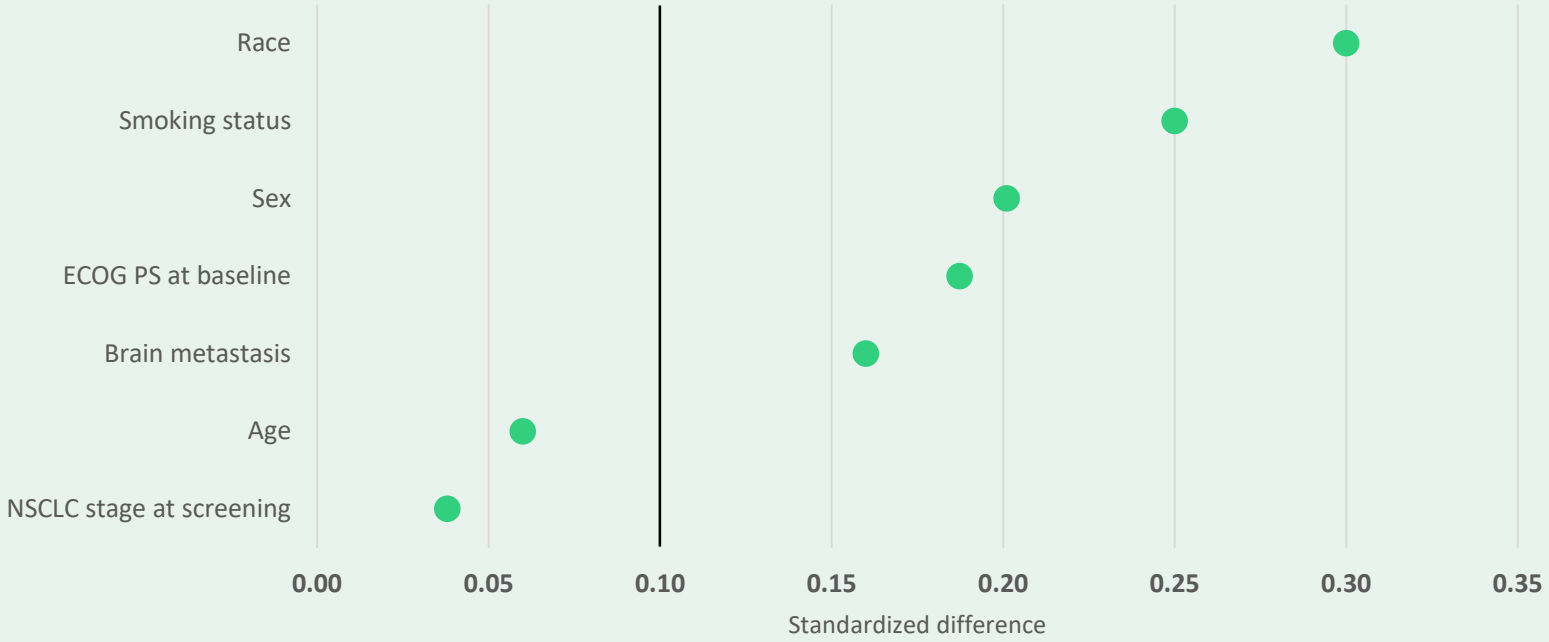

The RWD source **does not capture relevant outcome data**

The RWD has been used to make a **crude argument** in the submission that the RCT population is relatively representative of the UK population across measured characteristics

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial; RWD, real world data

# As immunotuzumab has been available in the USA for some time, relatively mature RWD on both the standard of care and immunotuzmab is available

Figure 3. Standardized difference of baseline characteristics of UK RWD & USA RWD patients



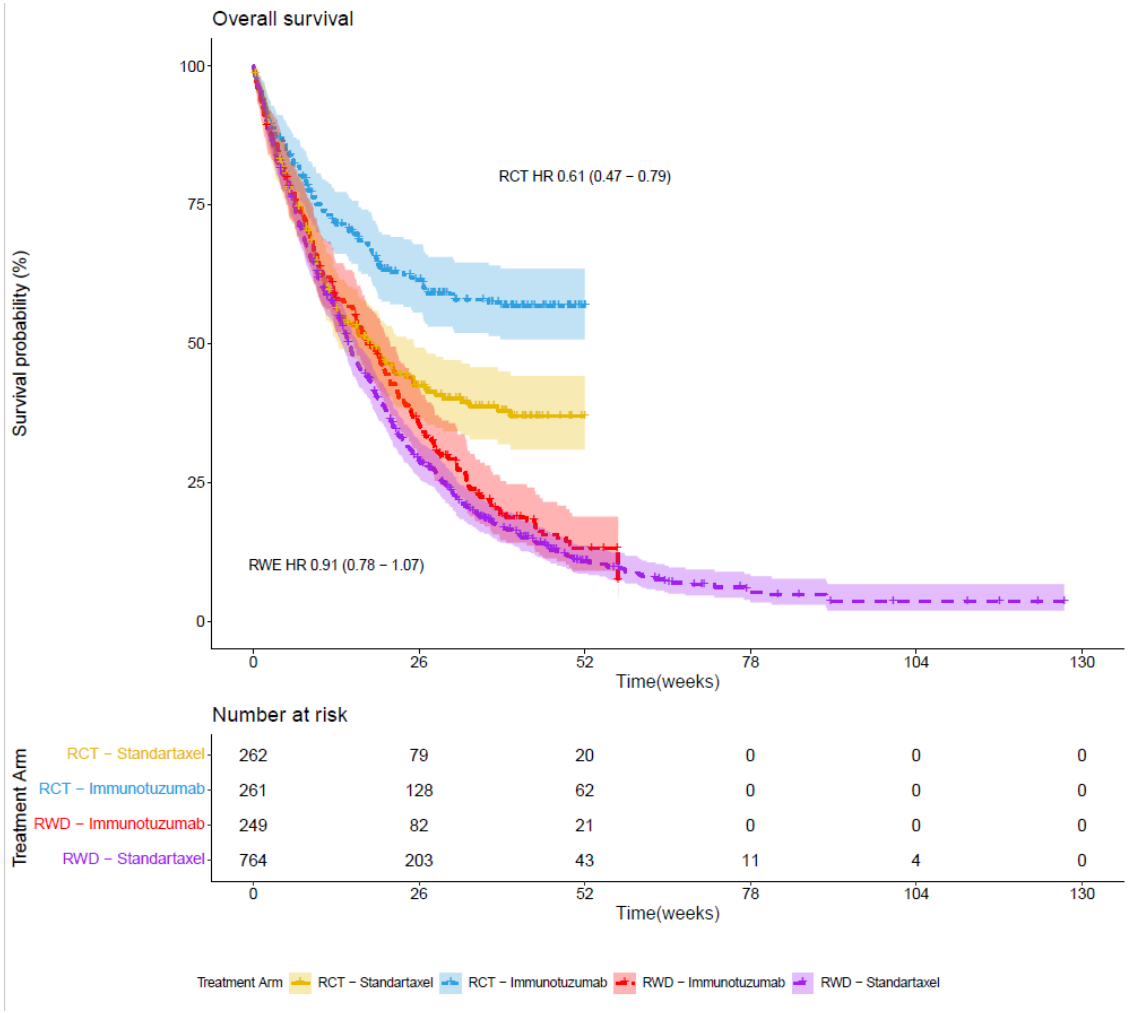

The USA has a **relatively similar population** to the UK with a different ethnic distribution

The **health systems differ considerably** with UK having a single payer system and USA having a fee-for-service / private insurance system

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer; RCT, randomised controlled trial; RWD, real world data

# As immunotuzumab has been available in the USA for some time, relatively mature RWD on both the standard of care and immunotuzmab is available

**Figure 4.** Kaplan–Meier Estimates of Overall Survival in the RCT Treatment Groups & USA RWD patients




Two options are available for the assessment to determine treatment efficacy:

Using the **RCT**

-or-

The **RWD** from the USA

Note: A high proportion of USA patients receive **Currentrexate** as a 2nd line treatment.

**Currentrexate** is not approved in the the UK.

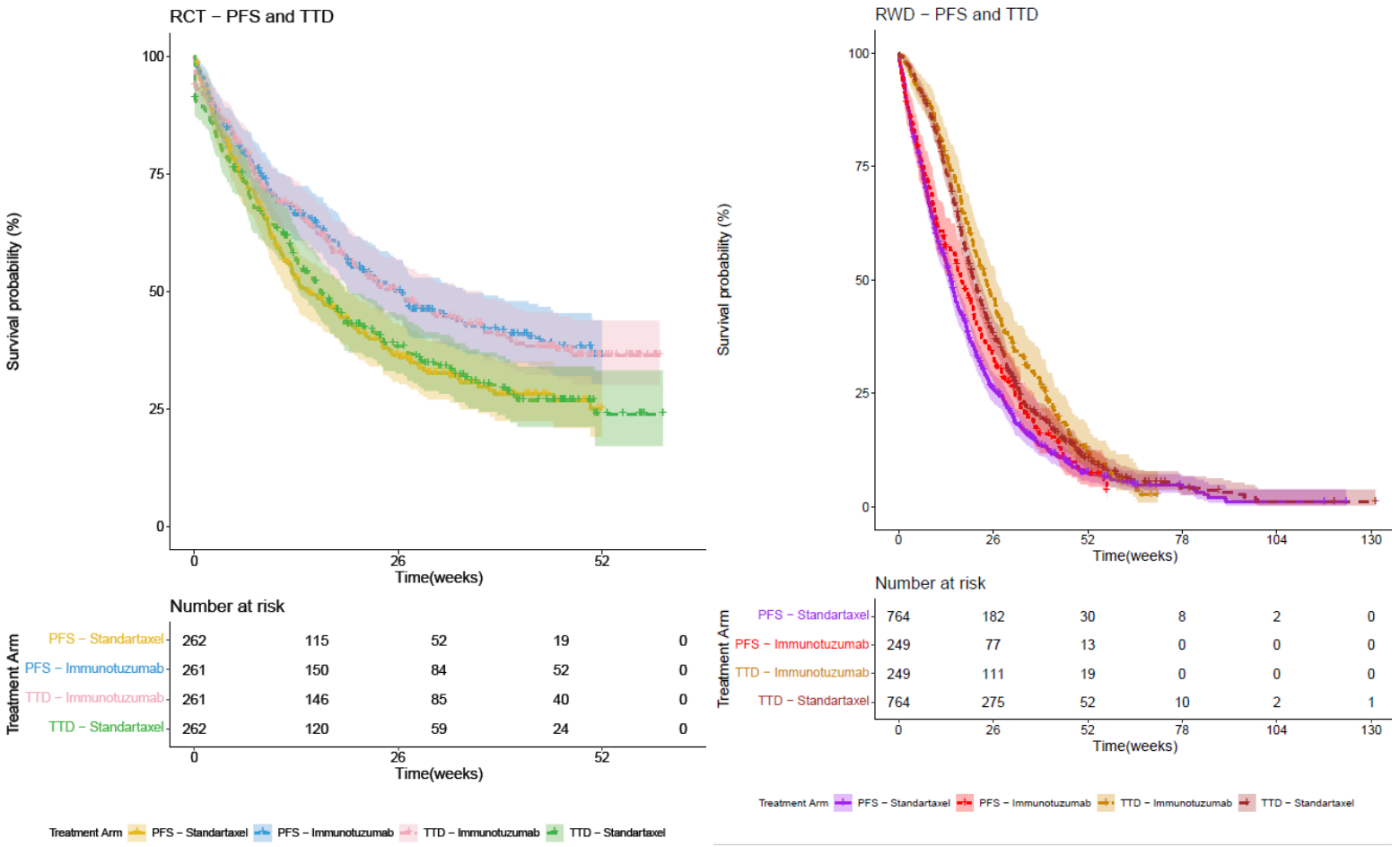
| Source | HR | 95%CI | ICER |
|---|---|---|---|
| Intl RCT | 0.61 | 0.47-0.79 | £15,000 |
| USA RWD | 0.91* | 0.78-1.07 | £60,000 |

*propensity score matched analysis based on patient characteristics listed on the previous slide in order to account for the differences in characteristics in patients who get immunotuzmab and standartaxel

Abbreviations: CI, confidence interval; ERG, evidence review group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; RCT, randomised controlled trial; RWD, real world data

# As immunotuzumab has been available in the USA for some time, relatively mature RWD on both the standard of care and immunotuzmab is available

**Figure 5.** Kaplan–Meier Estimates of Progression-Free Survival in the RCT Treatment Groups & USA RWD patients



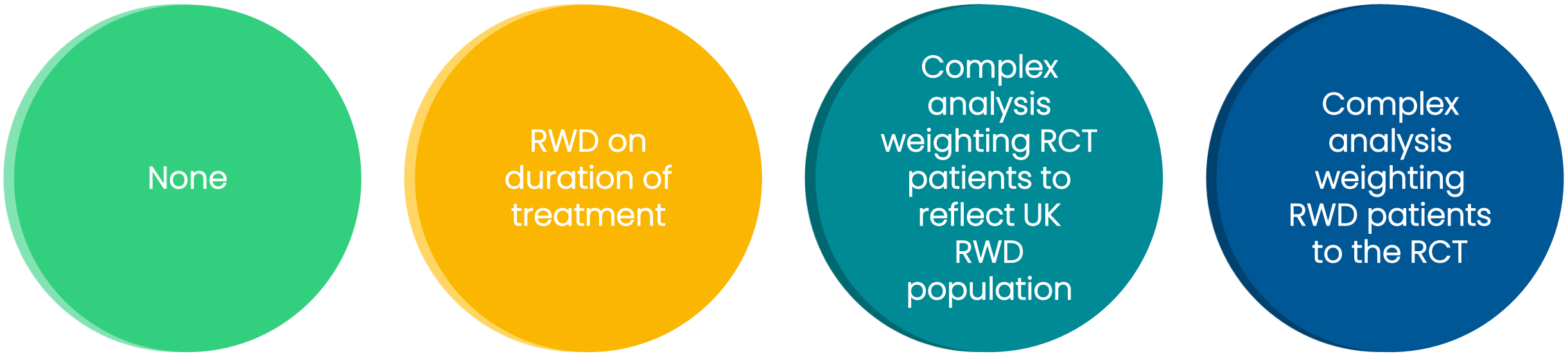

| Source | Treatment | Median PFS | Median TTD |
|---|---|---|---|
| Intl RCT | Standartaxel | 26.3 | 23.7 |
| | Immunotuzumab | 23.4 | 21.5 |
| USA RWD | Standartaxel | 17.6 | 18.1 |
| | Immunotuzumab | 17.1 | 17.6 |

Abbreviations: PFS, progression-free survival; RCT, randomised controlled trial; RWD, real world data; TTD, time-to-treatment discontinuation

# Committee meeting 1

Poll

Imagine you are the **company**, which additional analysis would you look to generate?



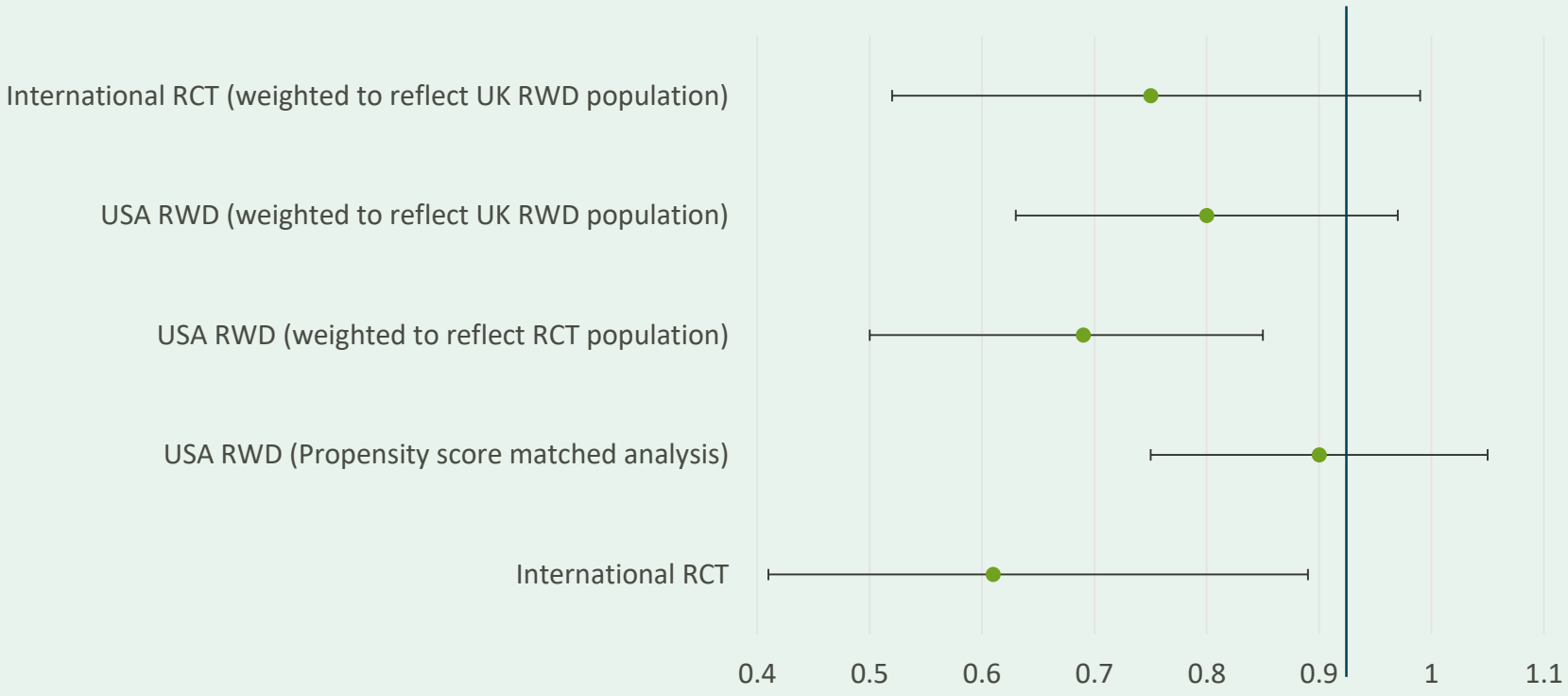

Abbreviations: RCT, randomised controlled trial; RWD, real world data

# Committee meeting 2

COMMITTEE MEETING 2

# In response to the first committee discussion several additional analyses were provided

**Figure 5.** Estimated treatment effect (hazard ratio (HR) for overall survival) for RCT and for additional analyses




| | HR | 95%CI | ICER |
|---|---|---|---|
| International RCT (weighted to reflect UK RWD population) | 0.75 | 0.52-0.99 | £25,500 |
| USA RWD (weighted to reflect UK RWD population) | 0.80 | 0.63-0.97 | £30,000 |
| USA RWD (weighted to reflect RCT population) | 0.69 | 0.50-0.85 | £19,700 |
| USA RWD (Propensity score matched analysis) | 0.91 | 0.78-1.07 | £60,000 |
| International RCT | 0.61 | 0.47-0.79 | £15,000 |

Abbreviations: CI, confidence interval; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; RCT, randomised controlled trial; RWD, real world data

# Committee meeting 2

Poll

Imagine you are a **committee member** in UK, would you support reimbursement of immunotuzumab?

# Summary

**Evidence used to inform HTA / Access / Reimbursement decisions often rely on studies designed for other purposes (Primarily assessing safety & efficacy)**

- **To what extent can we “transport” data from other sources to supplement an initial evidence package for reimbursement decisions?**
- **Important to have a clear decision problem**
    - Inferences from the RCT
    - RWD to more accurately characterize the baseline risk of ”local” patients

# Thank you

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# The Elements/Taxonomy of Transportability

Patient characteristic differences can be adjusted for, so usually are not too much of a concern

## Baseline demographics

Demographics may encompass a set of effect-modifying variables - differences in the prevalent and incident population should be considered

## Prevalence of disease

The baseline prevalence of a given disease may affect the transportability of some elements based on the mathematical association with relevant endpoints

## Preference for modifiable risk-factors

Preferences, and thus the prevalence, for modifiable risk factors (smoking, obesity, etc.) within a given population may modify the transportability of outcomes between countries if these risk-factors are known effect modifiers.

## Biomarker prevalence

For cancers with a diverse genetic etiology, there may exist significant treatment effect heterogeneity.

Therapies indicated for those cancers may lack transportability in populations with a widely different biomarker makeup.

Further, because biomarker testing rates may differ between populations, those selected into the cohort may also differ and affect the transportability of outcomes.

# The Elements/Taxonomy of Transportability

Potential for differences in how a drug is being used in the US compared to the country of interest

### Access to a given treatment

A prevalent population may not be represented in the EHR data given restriction in access based on socio-economic or variability in payer preferences for a given product.

Thus, patients selecting into a given cohort could vary and impact observed outcomes.

### Access to supportive care

Supportive care is known to improve outcomes for patients in many settings; however, access to supportive care varies within and between countries.

### Market share of the pharmaceutical(s) of interest and competitors

Environments with a large diversity of available technologies require contextualization for who selects into a cohort treated with a specific technology.

### Market share of backbone therapies used concomitantly with a therapy of interest

Even in situations where the market share for a technology of interest is the same, concomitant therapies of interest (e.g. high versus low dose dexamethasone) may differ.

If these therapies are effect-modifying, the distribution of them in the given data will affect transportability of the outcomes.

### Guideline differences between jurisdictions / localities

Because the approved label /reimbursement criteria for a given therapy may vary, the way a product is used between countries may also sometimes differ, which may present itself in what is known as the compound treatment problem. Further, labels may also influence the preceding drugs that patients have been exposed to, complicating the question of transportability.

Abbreviations: HER, electronic health record; US, United States

# The Elements/Taxonomy of Transportability

Clinical input can identify potential differences in settings

### Treatment site variation

It is thought that outcomes between academic/research institutions may be different than those observed for community practices based on available resources.

Thus, if countries differ in the distribution of these treatment sites for a given cohort of interest, outcomes would also be expected to differ.

### Differences in time-to-treatment initiation within a disease's natural history

Time-to-treatment initiation may vary dramatically between countries (driven by localitied procedures to confirm diagnosis and/or healthcare system capacity) and therefore change a particular risk set and influence outcomes

### Disease assessment frequency

Disease assessment frequency can provide erroneous conclusions about metrics such as progression free survival or other outcomes that rely on monitoring schedules, and thus the time at which observations can be made.

### Preference for end of life care

In later lines of therapy, the risk-set a country chooses to treat may be different from that of another country based on differences in preferences for hospice.

So, countries that tend to treat more aggressively may treat a sicker risk-set than that of a country that is more likely to choose for alternative end-of-life remedies