Evidence Synthesis and Value Generation in Wake of the New EU HTA Legislation:

A Case Study on Estimands and PICOs

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08-MAY-2023

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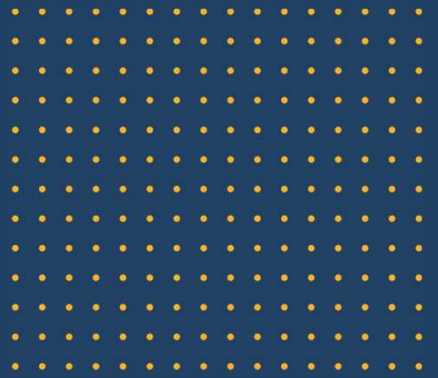
End-to-End Biometrics

Introduction

Or: Why does this matter?



ONCOLOGY TRIALS 2021



Plus 56% from 2016 [1]

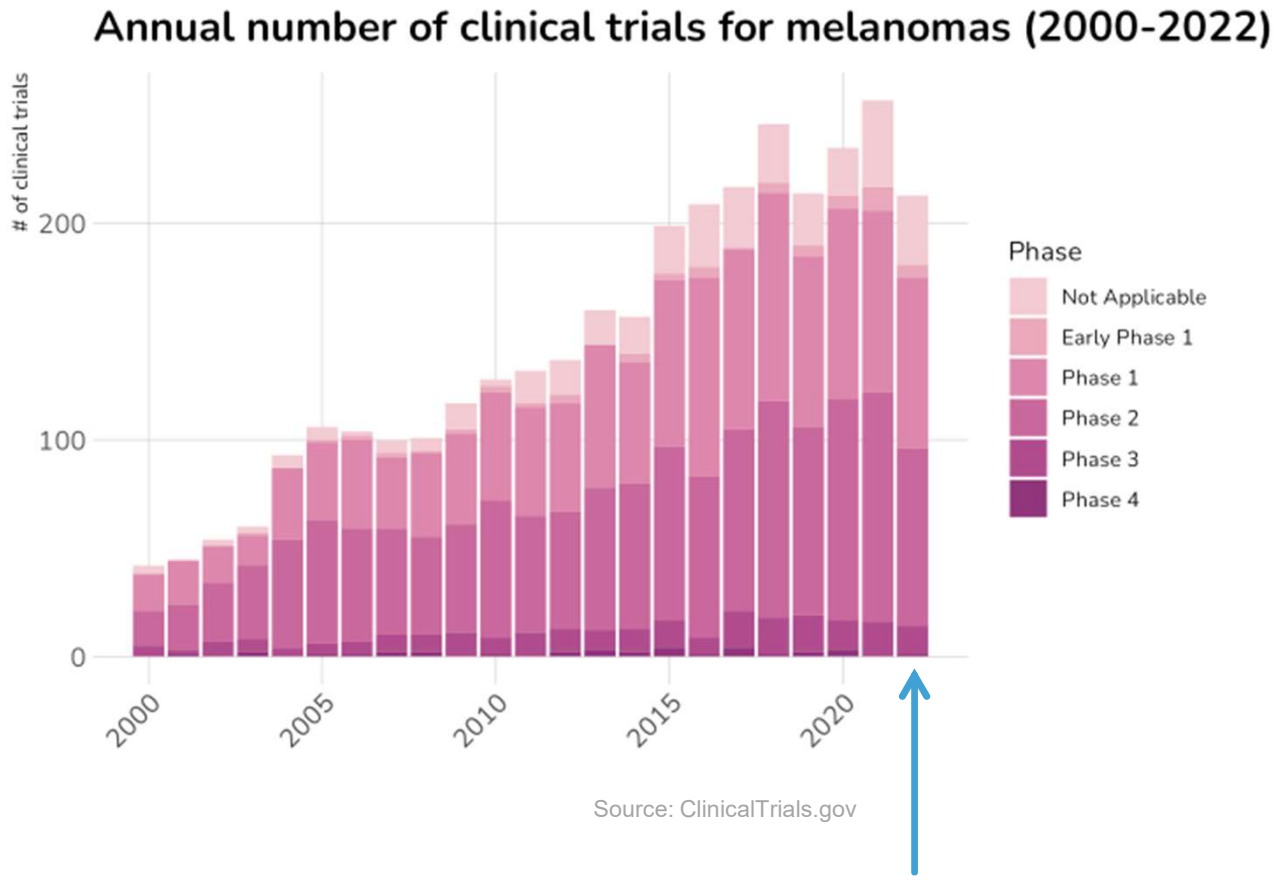
FROM 15,267 ASSETS IN DEVELOPMENT 2021



34% were oncology [2]

1 https://www.iqvia.com/insights/the-iqvia-institute/reports/global-oncology-trends-2022
2 https://www.pwc.com/gx/en/industries/pharmaceuticals-life-sciences/publications/pharma-oncology.html

215 new trials registered in 2022



Starting with Oncology in 2025: EU HTA Obligatory

Only for 6 countries!



6 EU countries

+ EU HTA

+ Safety (Germany)

+ 1 Outcome
+ 1 Sub-group

Based on Joint PSI & EFSPI HTA SIG Webinar: "Statistics in EU HTA - PICOs, Estimands & More!"; 14NOV2022



Collaboration between Market Access and earlier phases



Earlier planning of value dossiers

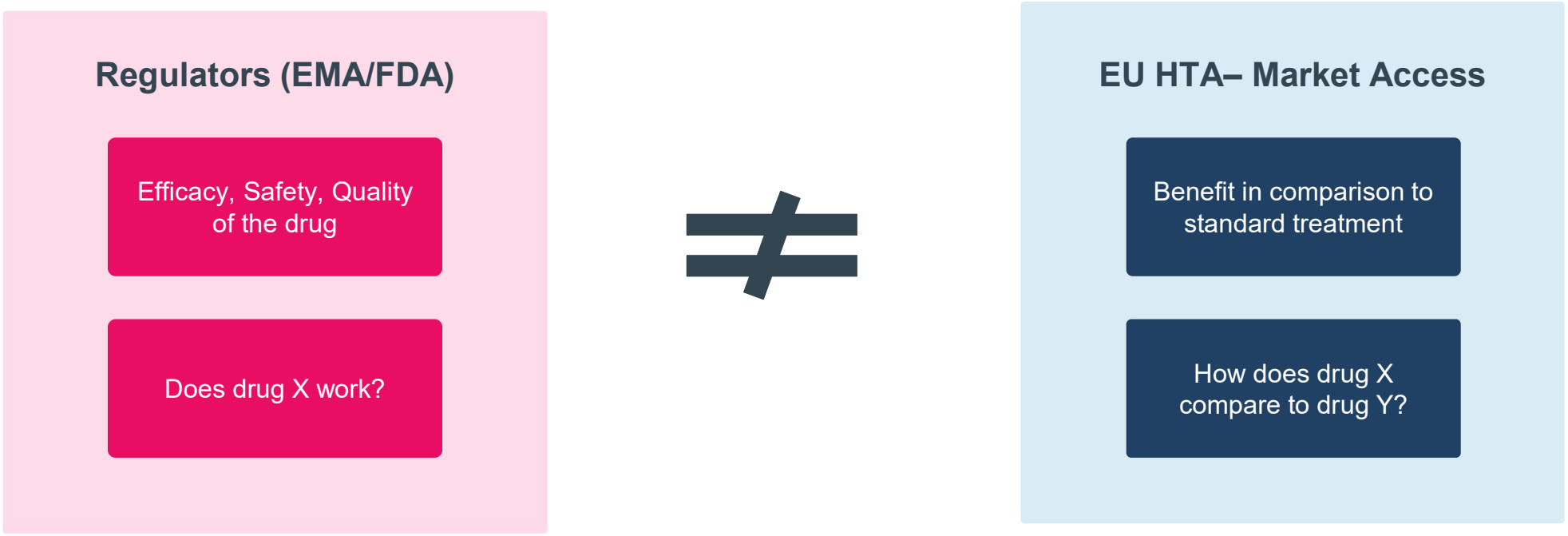


Flexibility in reacting to changes on the market

EU HTA

EU HTA

- Market Access usually supported by Phase III studies, originally targeting Regulators (EMA/FDA)



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EU HTA

- Market Access usually supported by Phase III studies, originally targeting Regulators (EMA/FDA)

Regulators (EMA/FDA)

Estimand

≠

EU HTA– Market Access

PICO

Based on Joint PSI & EFSPI HTA SIG Webinar: "Statistics in EU HTA - PICOs, Estimands & More!"; 14NOV2022

Estimands and PICOs

The different languages we speak

Estimand



Treatment



Population



Variable



Population level summary



Intercurrent Events

Estimand – KEYNOTE 716 Study

The trial will compare treatment with Pembrolizumab 200 mg IV with Placebo in Participants with surgically resected high-risk Stage II melanoma.

The primary comparison of interest is the Hazard Ratio (HR) of the Recurrence-free Survival (RFS) between treatment arms.

The primary comparison will be made without regard to changes to any therapies (Treatment Policy Strategy).


Treatment


Population


Population level summary


Variable


Intercurrent Events

PICO



Population

Participants with surgically resected high-risk Stage II melanoma



Intervention

treatment with Pembrolizumab 200 mg IV



Comparator

Placebo



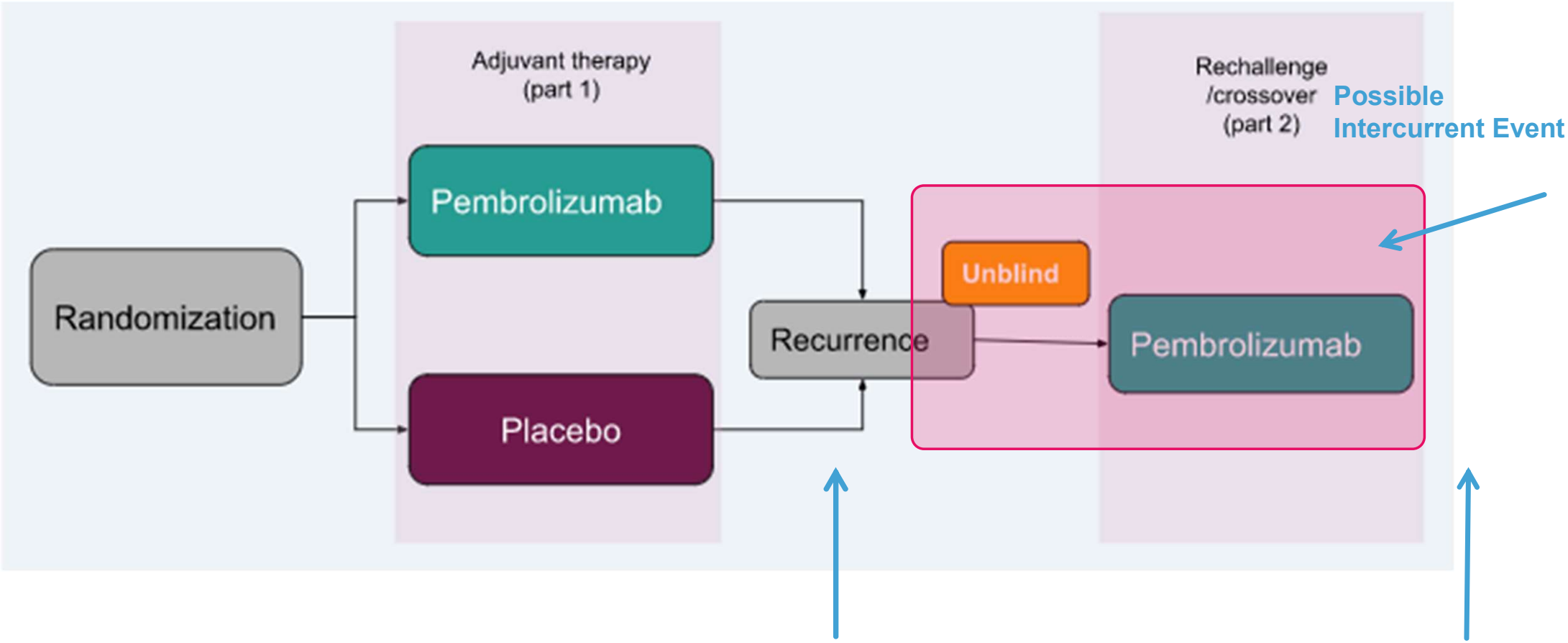
Outcome

the Hazard Ratio (HR) of the Recurrence-free Survival (RFS) between treatment arms.

What about Intercurrent Events?

Example I:
Intercurrent Events

Why Intercurrent Events matter



PICO



Population

Intervention

Comparator

Outcome





Treatment



Population



Population level summary



Variable



Intercurrent Events

Take-away I

- Always define your Estimand!
  - Implicit assumptions and decisions are made visible
  - Translate between your Estimand and PICO
- Intercurrent Events matter
  - ...even when they are not defined

Example II:
PICO / Estimand

PICO

Clinical Study:



Participants with surgically resected high-risk Stage II melanoma



treatment with Pembrolizumab 200 mg IV



~~Placebo~~

Requested by Germany:

Placebo
Interferon alfa



the Hazard Ratio (HR) of the Recurrence-free Survival (RFS) between treatment arms.

No additional Benefit!

PICO

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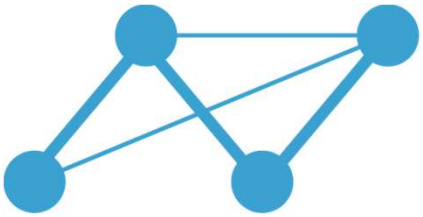

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PICO

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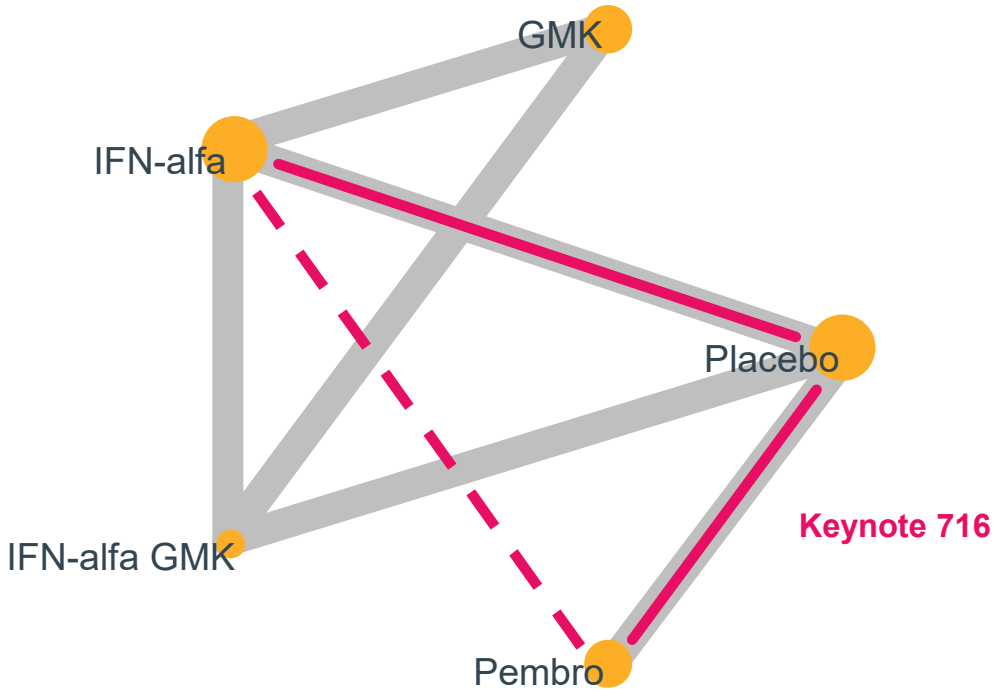
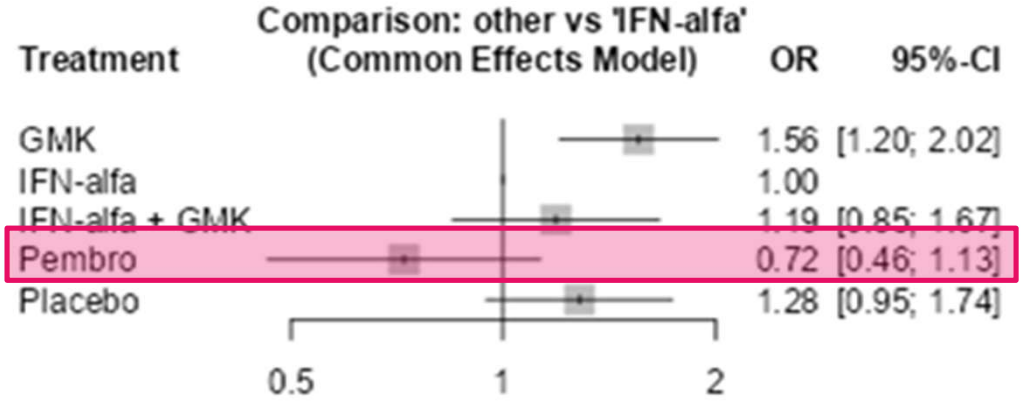
End-to-End Biometrics



Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial; https://doi.org/10.1016/S1470-2045(22)00559-9

A Pooled Analysis of Eastern Cooperative Oncology Group and Intergroup Trials of Adjuvant High-Dose Interferon for Melanoma; 10.1158/1078-0432.CCR-1103-3

PICO



Pembrolizumab shows promising treatment effect compared to Interferon-alfa in the treatment of Participants with surgically resected high-risk Stage II melanoma

Take-away II

- Communication about study populations need to be early as possible
  - HEOR professionals should be able to provide input in design of studies for Regulatory approval, since these will most likely be needed for Market Access and Pricing Negotiations.
- Continuous monitoring of therapeutic landscape and competitors necessary
  - National Authorities do not request their PICOs based on studies used for Regulatory Approval. The PICO is based on the national heath policy. By monitoring the market, we can be prepared for changes in national health policies and generate (indirect) evidence

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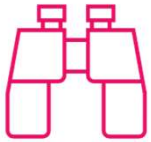

Flexibility in reacting to changes on the market

Thank you!

Find us at **BOOTH 1225** for demos on:

- Network Meta-Analysis
- Data Visualization

CONTACT US



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