Use Case: Amivantanab vs RW Clinical practice

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ORIGINAL RESEARCH

An Adjusted Treatment Comparison Comparing Amivantamab Versus Real-World Clinical Practice in Europe and the United States for Patients with Advanced Non-Small Cell Lung Cancer with Activating Epidermal Growth Factor Receptor Exon 20 Insertion Mutations

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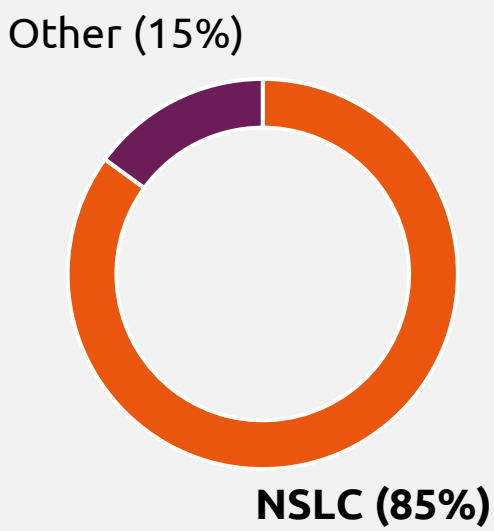
Use Case: Amivantanab vs RW Clinical practice

Lung Cancer

Lung cancer

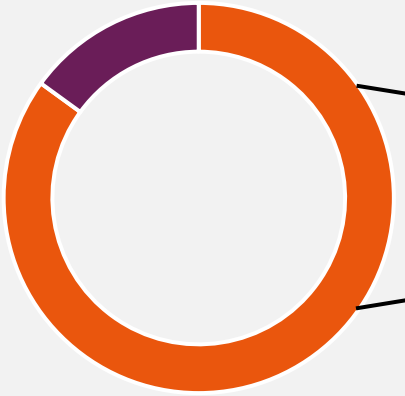


Use Case: Amivantanab vs RW Clinical practice

Lung Cancer

Lung cancer

Other (15%)

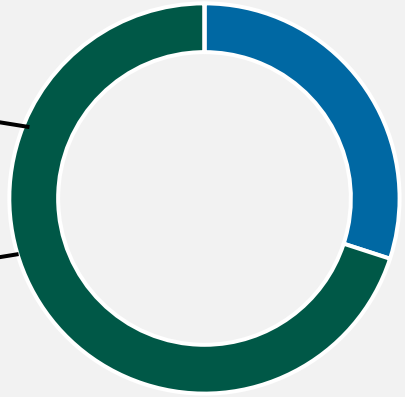


NSLC (85%)

NSCLC mutations

These percentages may differ based on ethnicity

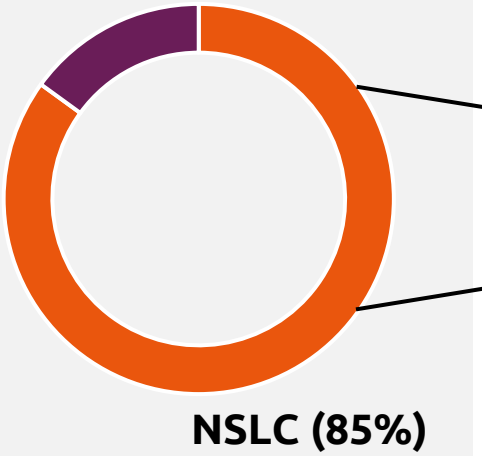
EGFR (30%)



Use Case: Amivantanab vs RW Clinical practice

Lung Cancer

Lung cancer



NSCLC mutations

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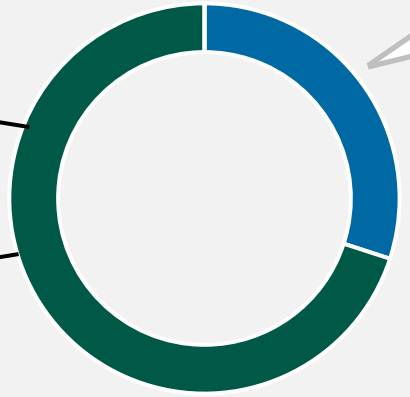
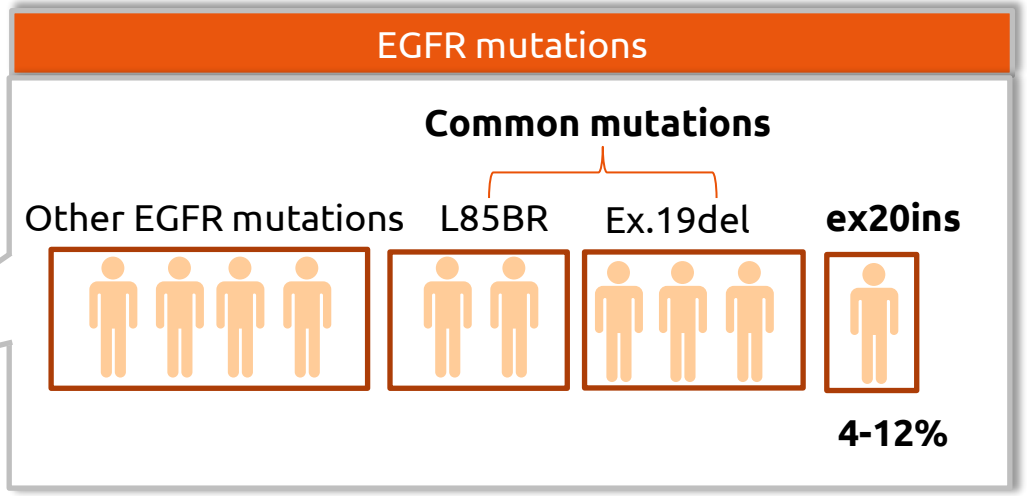
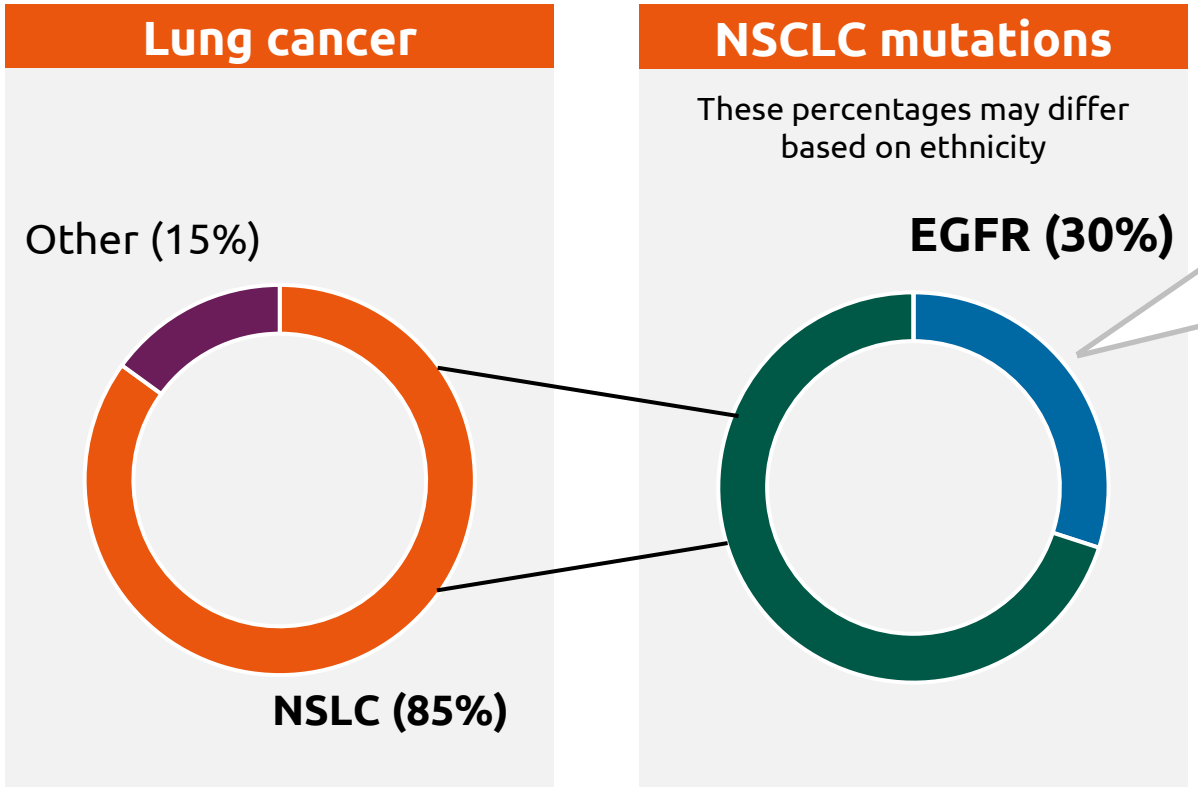




Use Case: Amivantanab vs RW Clinical practice

Lung Cancer

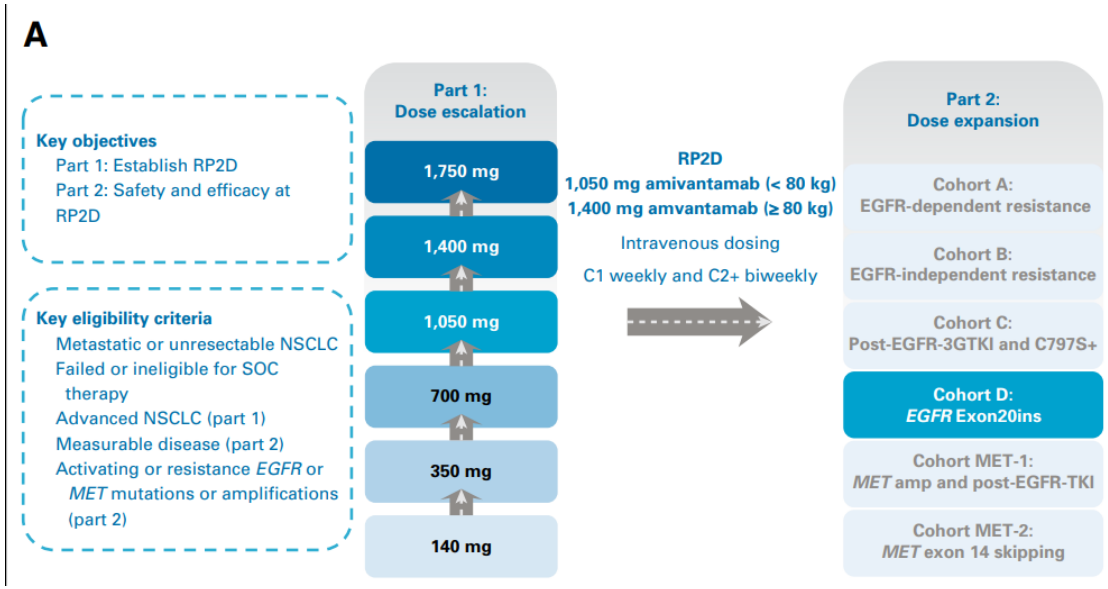


- EGFR Exon20ins
  - Frequency (EU+US): 0.3% to 2.6% of all NSCLC cases
  - Poor prognosis compared with patients with common EGFR mutations
  - Lack of effective targeted treatment and specific guidelines

Use Case: Amivantanab vs RW Clinical practice

CHRYSALIS trial (NCT02609776)

FIH: phase I dose-escalation, and dose-expansion study



(Park, J Clin Oncol. 2021)

Use Case: Amivantanab vs RW Clinical practice

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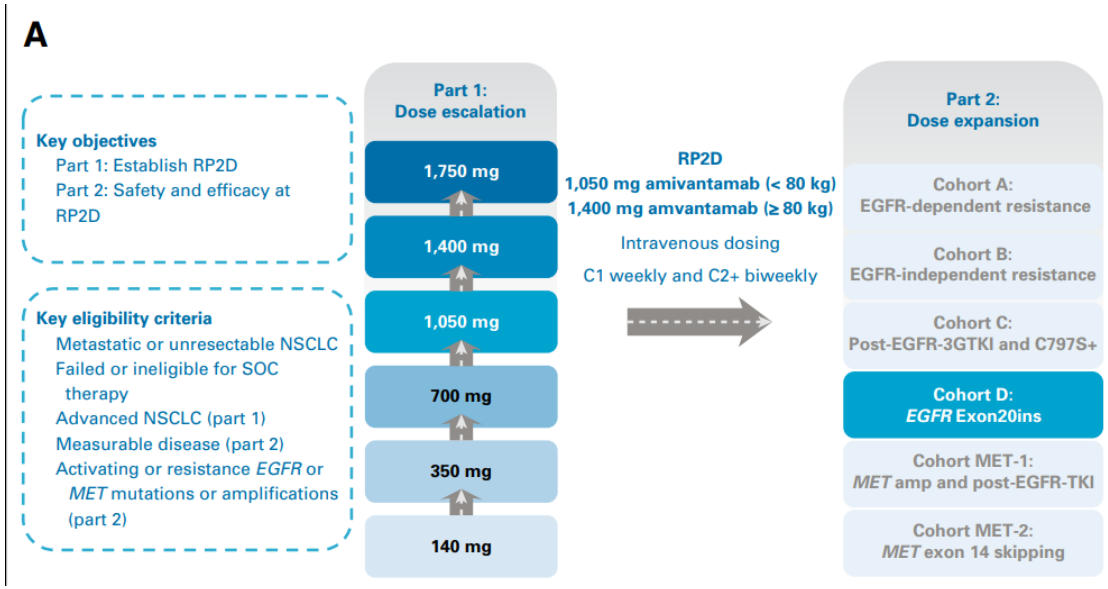
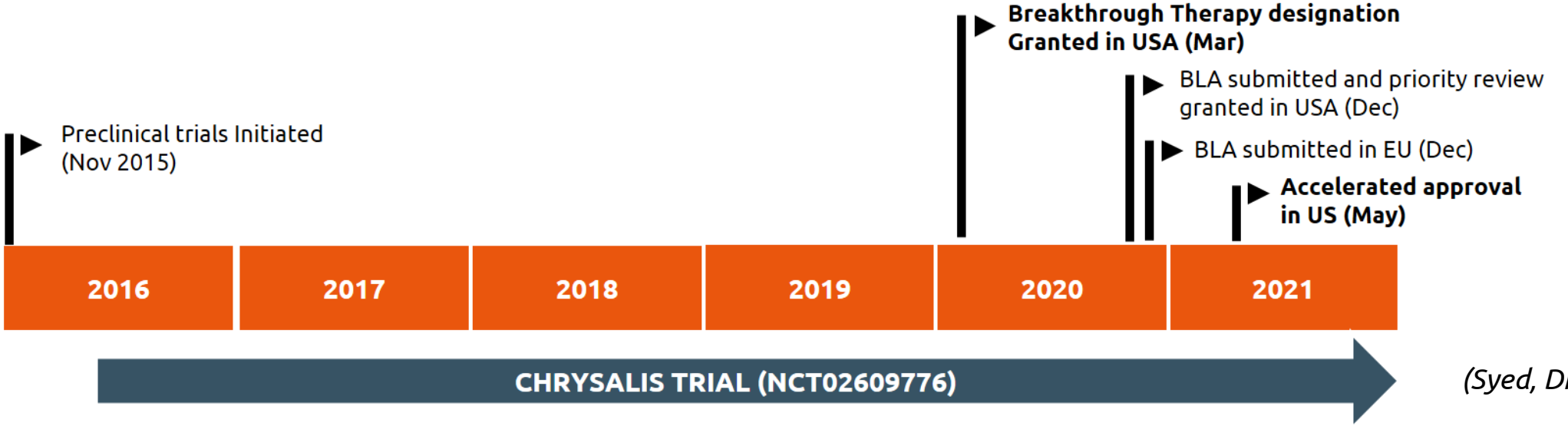


(Park, J Clin Oncol. 2021)

- Dose Expansion Phase
  - Primary endpoint (Dose Expansion): Overall Response Rate
  - Key Secondary endpoints: Duration of Response, Clinical benefit rate, PFS and OS
- Cohort D+: Post-platinum EGFR Exon20ins population treated at RP2D
  - Safety Population: n=114 (Data Cut-off: 08 June 2021)
  - Pivotal Efficacy population: n= 81
  - Objective Response Rate: 40 % (95%CI=[29 to 51])
  - Clinical Benefit Rate: 74% (95%CI=[63 to 83])

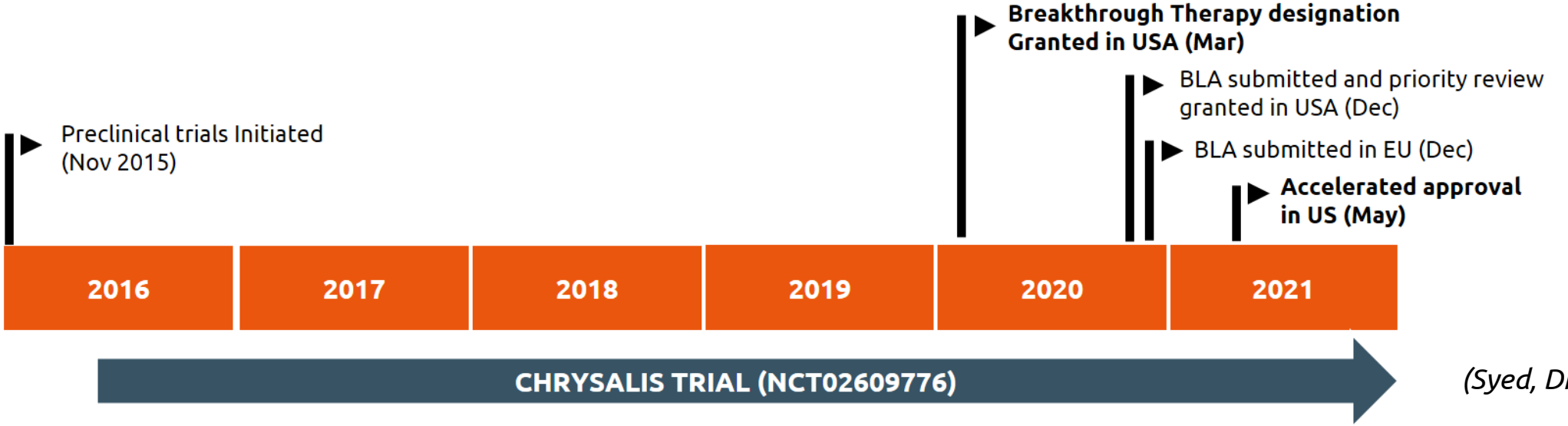
Use Case: Amivantanab vs RW Clinical practice



(Syed, Drug 2021)

- Regulatory approval based on single arm trial evidence

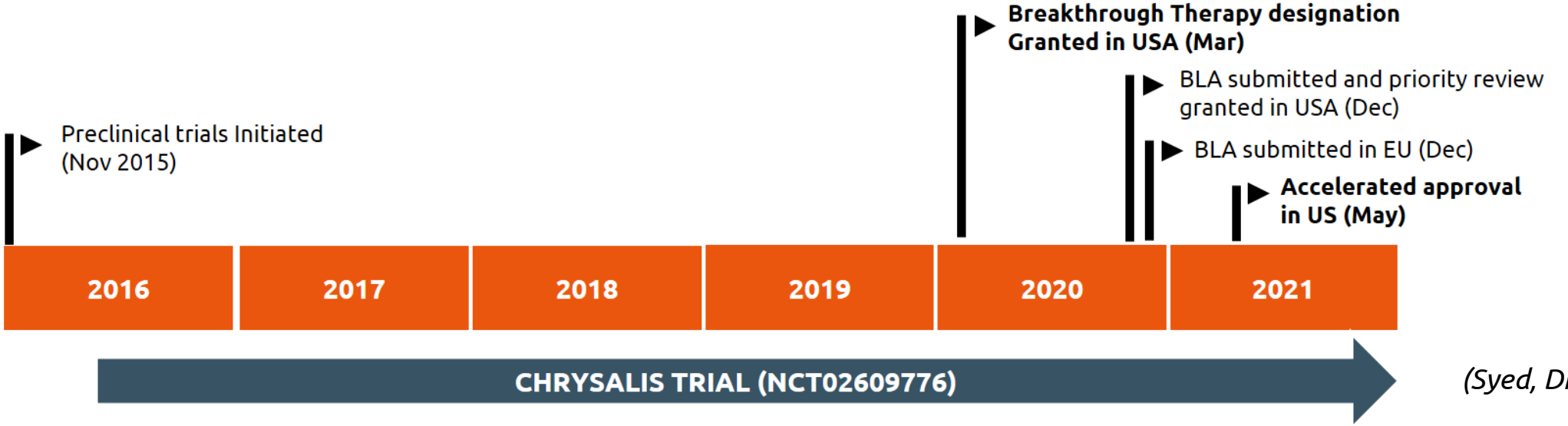
Use Case: Amivantanab vs RW Clinical practice



(Syed, Drug 2021)

- Regulatory approval based on single arm trial evidence
- RCT was not a "feasible" option
  - Severity of the disease, Lack of clinical equipoise
  - EGFR Exon20ins mutations are rare
  - Identifying EGFR Exon20ins via conventional PCR methods is challenging

Use Case: Amivantanab vs RW Clinical practice



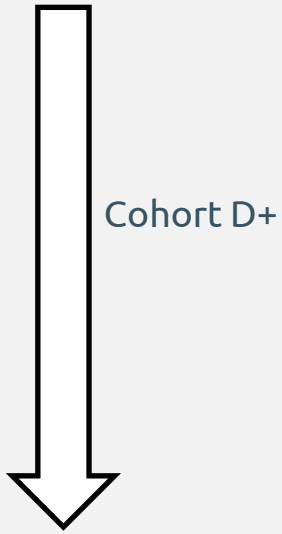
(Syed, Drug 2021)

- Regulatory approval based on single arm trial evidence
- RCT was not a “feasible” option
- Individual patient data (IPD)-based adjusted treatment comparison of amivantamab
- Primary objective: To compare the efficacy of amivantamab, as assessed in the CHRYSALIS trial, to RWCP from Europe and the US in patients with advanced EGFR-mutated NSCLC with Exon20ins following platinum-based therapy at 2L+.

Use Case: Amivantanab vs RW Clinical practice

CHRYSALYS and Real-World Data Sources

CHRYSALYS



EGFR Exon20ins who had progressed on or after prior platinum-based chemotherapy
(Data Cut-off: 08 June 2021)

Use Case: Amivantanab vs RW Clinical practice

CHRYSALYS and Real-World Data Sources

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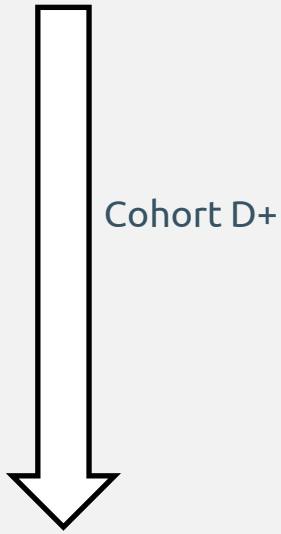

EGFR Exon20ins who had progressed on or after prior platinum-based chemotherapy
(Data Cut-off: 08 June 2021)

RW Clinical Practice

Flatiron, ConcertAI and COTA

CRISP NGM

Public Health England

ESME*

Use Case: Amivantanab vs RW Clinical practice

CHRYSALYS and Real-World Data Sources

CHRYSALYS

Cohort D+

N=114

EGFR Exon20ins who had progressed on or after prior platinum-based chemotherapy
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RW Clinical Practice

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Eligibility Criteria

Main analysis: EU + US cohort (401 lines)
Sensivity Analysis: - EU cohort (195 lines)
- US cohort (206 lines)

Use Case: Amivantanab vs RW Clinical practice

CHRYSALYS and Real-World Data Sources

CHRYSALYS

Cohort D+

N=114

EGFR Exon20ins who had progressed on or after prior platinum-based chemotherapy
(Data Cut-off: 08 June 2021)

Endpoint

Common to all RWCP: OS, TTNT
Other: PFS (Not available in PHE), ORR (not available from ESME)

RW Clinical Practice

Flatiron, ConcertAI and COTA

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ESME*

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Sensivity Analysis: - EU cohort (195 lines)
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Use Case: Amivantanab vs RW Clinical practice

Adjustment Methodology

- Objective: To reduce the treatment assignment bias, and mimic randomization

Use Case: Amivantanab vs RW Clinical practice

Adjustment Methodology

Potential counfounders

- Strategy
  - Systematic literature review
  - Clinical expert opinion
- Seven key variables

Use Case: Amivantanab vs RW Clinical practice

Adjustment Methodology

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NGM, CRISP, PHE, and US

IPD available

CHRYSALIS

N=114

ESME

IPD not available

Use Case: Amivantanab vs RW Clinical practice

Adjustment Methodology

Potential counfounders

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NGM, CRISP, PHE, and US

IPD available

CHRYSALIS

N=114

ESME

IPD not available

Common variables between all sources
4 keys variables

Propensity Score Weigthing

Use Case: Amivantanab vs RW Clinical practice

Adjustment Methodology

Potential counfounders

- Strategy
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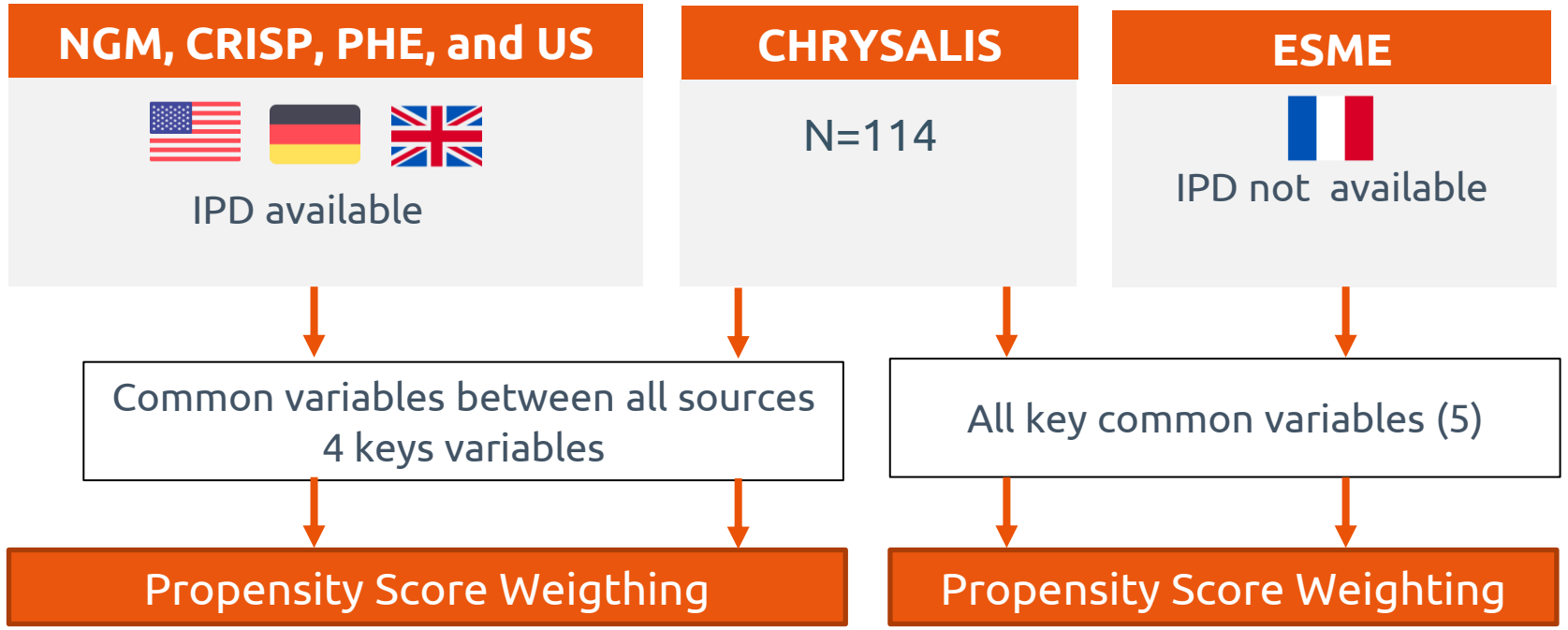

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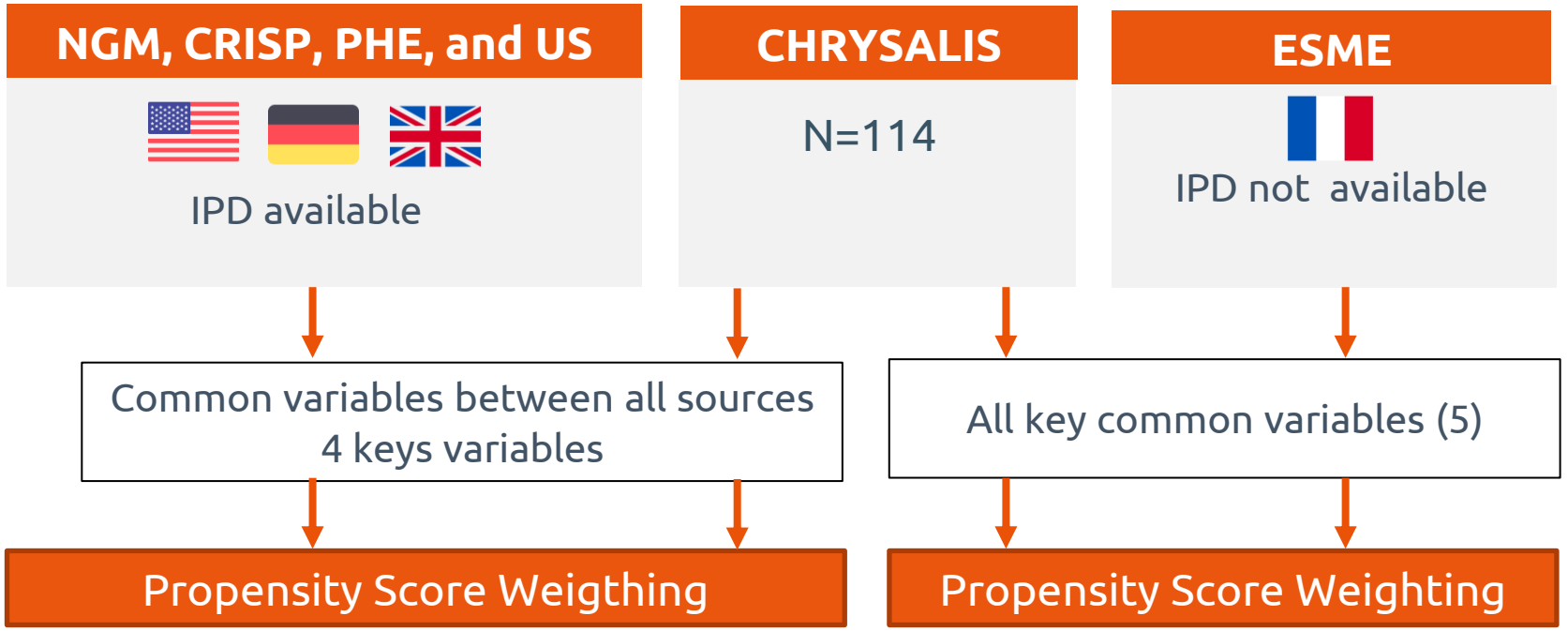


- Methods for controlling counfounder: Inverse Probability weigthing
- Target population: Treated population
- Estimand: Average Treatment effect in the Treated (ATT)

Use Case: Amivantanab vs RW Clinical practice

Baseline Patient and Disease Characteristics

	CHRYSALIS	NGM, CRISP, PHE US
		Unadjusted
Prior Line of Treatment		
1	48 (42.1%)	155 (44.4%)
2	34 (29.8%)	108 (30.9%)
3	15 (13.2%)	52 (14.9%)
4	17 (14.9%)	34 (9.7%)
Presence of Brain Met.	29 (25.4%)	132 (37.8%)
Age		
<=55	30 (26.3%)	97 (27.8%)
>55 to <=60	20 (17.5%)	54 (15.5%)
>60	64 (56.1%)	198 (56.7%)
Gender – Male	44 (38.6%)	137 (39.3%)

Before adjustment

- EU+US (excluding ESME)
  - Comparable prior to adjustment
- ESME:
  - ESME differ substentially from the CHRYSALYS data

Use Case: Amivantanab vs RW Clinical practice

Propensity Score Weigthing – Balance diagnostic

	CHRYSALIS	NGM, CRISP, PHE US	
		Unadjusted	adjusted
Prior Line of Treatment			
1	48 (42.1%)	155 (44.4%)	147 (42.1%)
2	34 (29.8%)	108 (30.9%)	105 (30.1%)
3	15 (13.2%)	52 (14.9%)	45 (12.9%)
4	17 (14.9%)	34 (9.7%)	52 (14.9%)
Presence of Brain Met.	29 (25.4%)	132 (37.8%)	89 (25.5%)
Age			
<=55	30 (26.3%)	97 (27.8%)	88 (25.3%)
>55 to <=60	20 (17.5%)	54 (15.5%)	63 (18.1%)
>60	64 (56.1%)	198 (56.7%)	198 (56.6%)
Gender – Male	44 (38.6%)	137 (39.3%)	135 (38.6%)

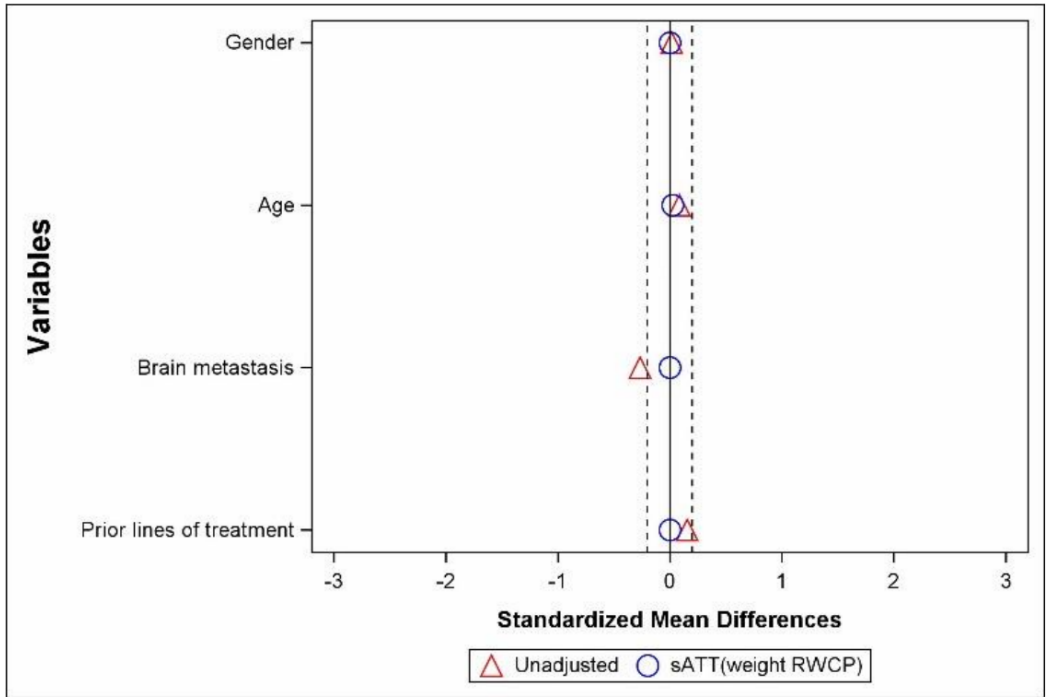
After adjustment

- Objective: To determine if the propensity score weigthing has removed observed systematic differences between CHRYSALYS and RWCP.
- EU+US (excluding ESME)
  - Comparability improve
- ESME:
  - Similarity between the data sets improve. Some differences remain

Use Case: Amivantanab vs RW Clinical practice

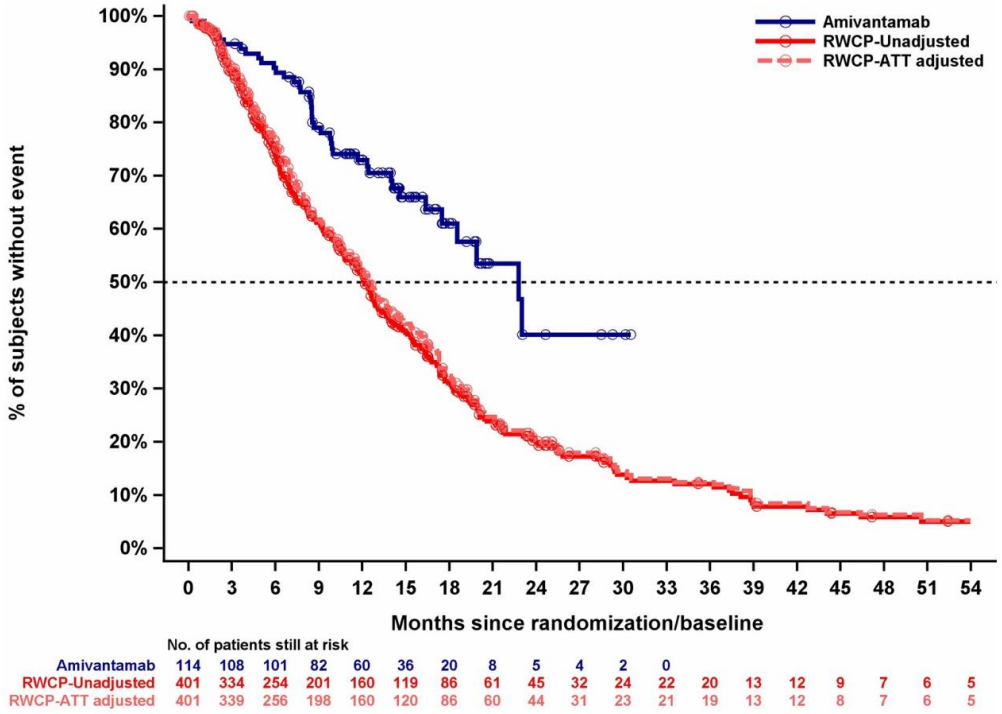
Propensity Score Weigthing – Balance diagnostic

- Objective: To determine if the propensity score weigthing has removed observed systematic differences between CHRYSALYS and RWCP.
- Good overlap between PS distributions between the CHRYSALIS cohort and the EU + US cohort
- The SMDs after ATT weighting improved and became closer to 0



Use Case: Amivantanab vs RW Clinical practice

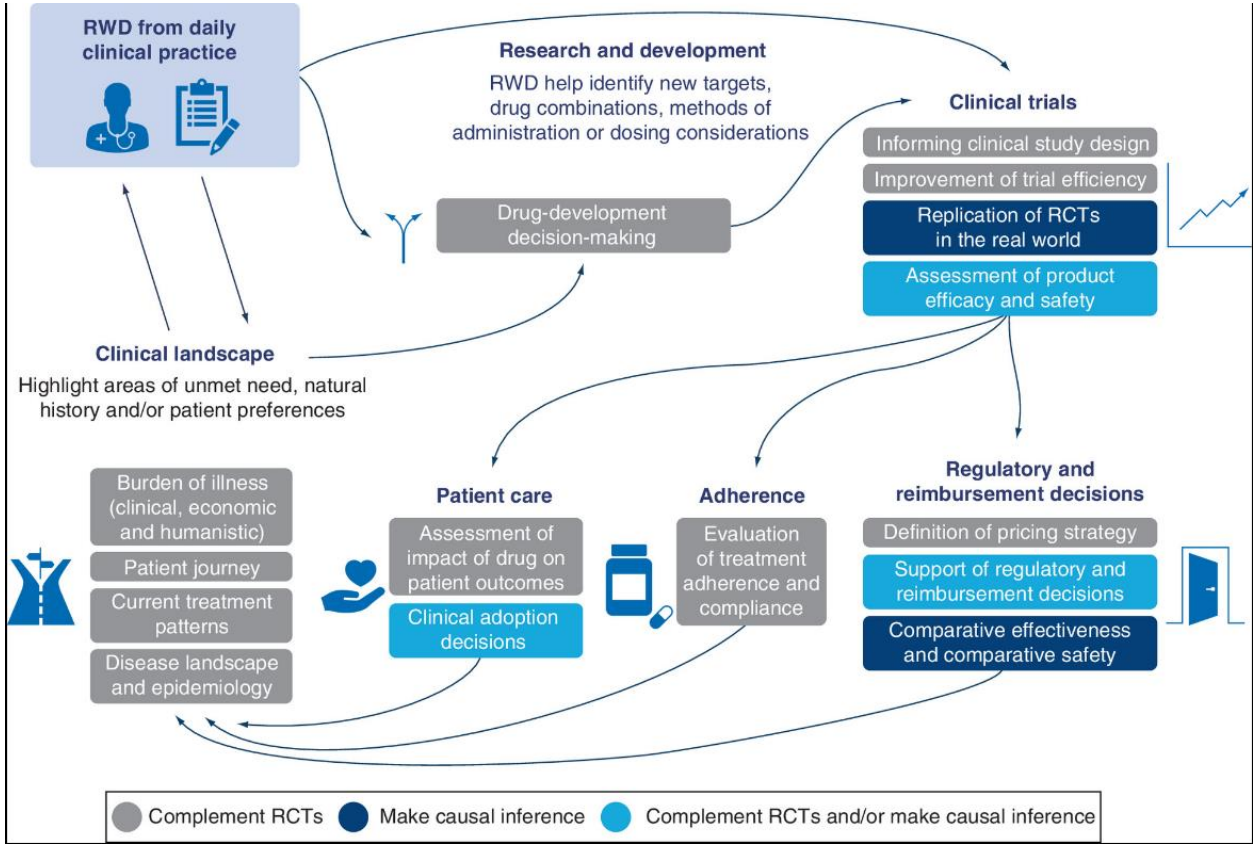
Efficacy Analysis – Overall Survival



- Median OS RWCP:
  - Unadjusted : 12.1m 95%CI=[10.7; 14.1]
  - ATT Adjusted : 12.5 95%CI=[10.7; 14.1]
- Comparison:
  - Amivantanab vs RWCP: HR=0.45 (95%CI=[0.32; 0.62])
  - Adjust. Amivantanab vs RWCP: HR=0.47 (95%CI=[0.34; 0.66])

In summary,

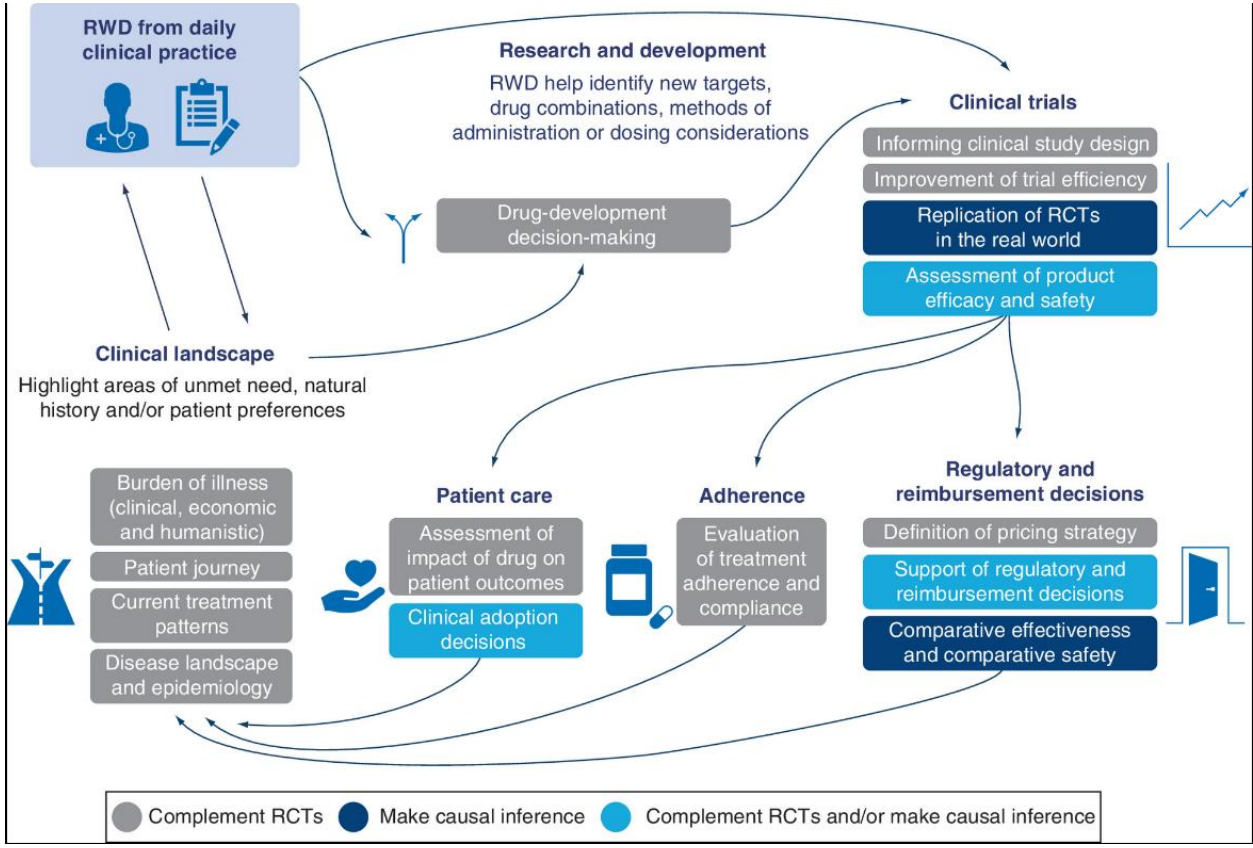
- The use of RWD to complement or replace RCTs when they are not feasible is of great interest (rare cancers)



Elson et al JCER 2021

In summary,

- The use of RWD to complement or replace RCTs when they are not feasible is of great interest (rare cancers)
- But, their use may present biases, potential confounding and pitfalls.



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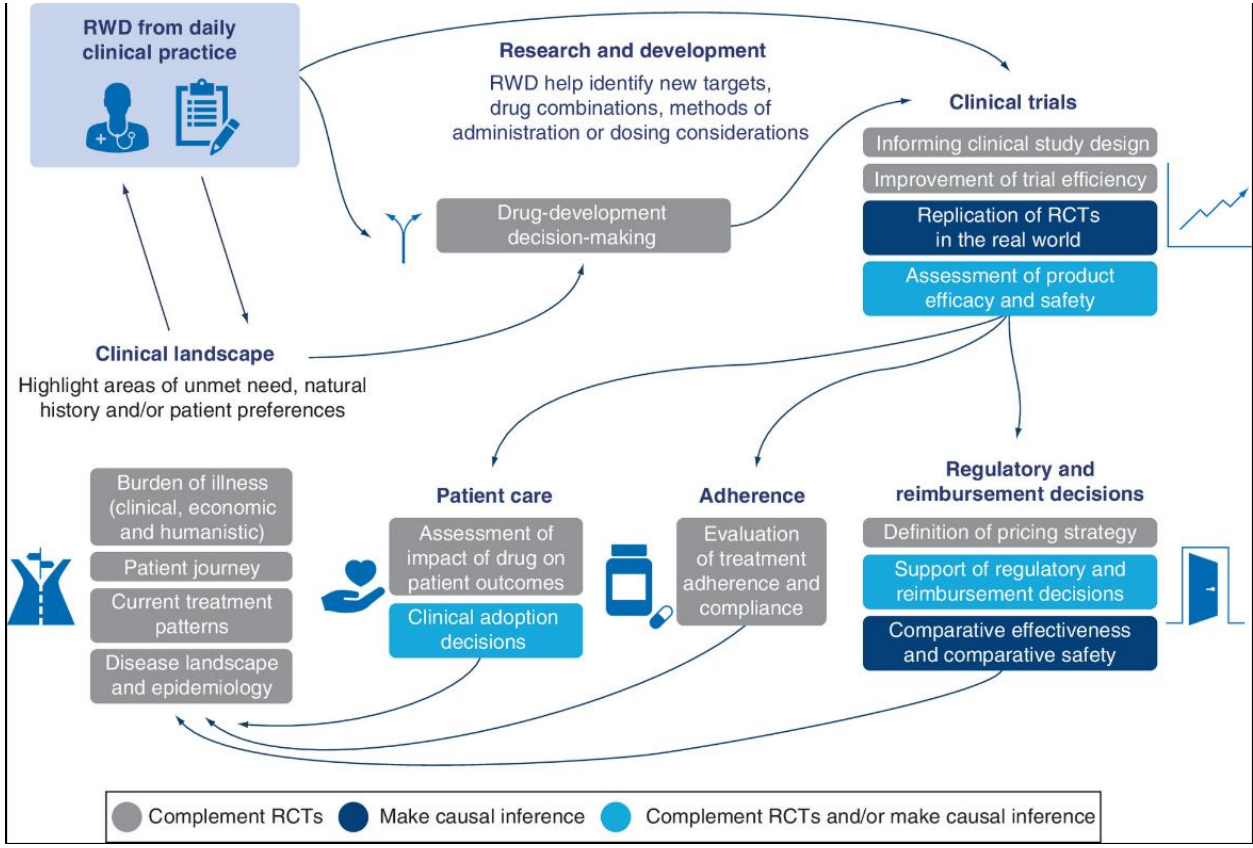
- But, robust process may help to minimize biases. This process would include considerations of data quality…



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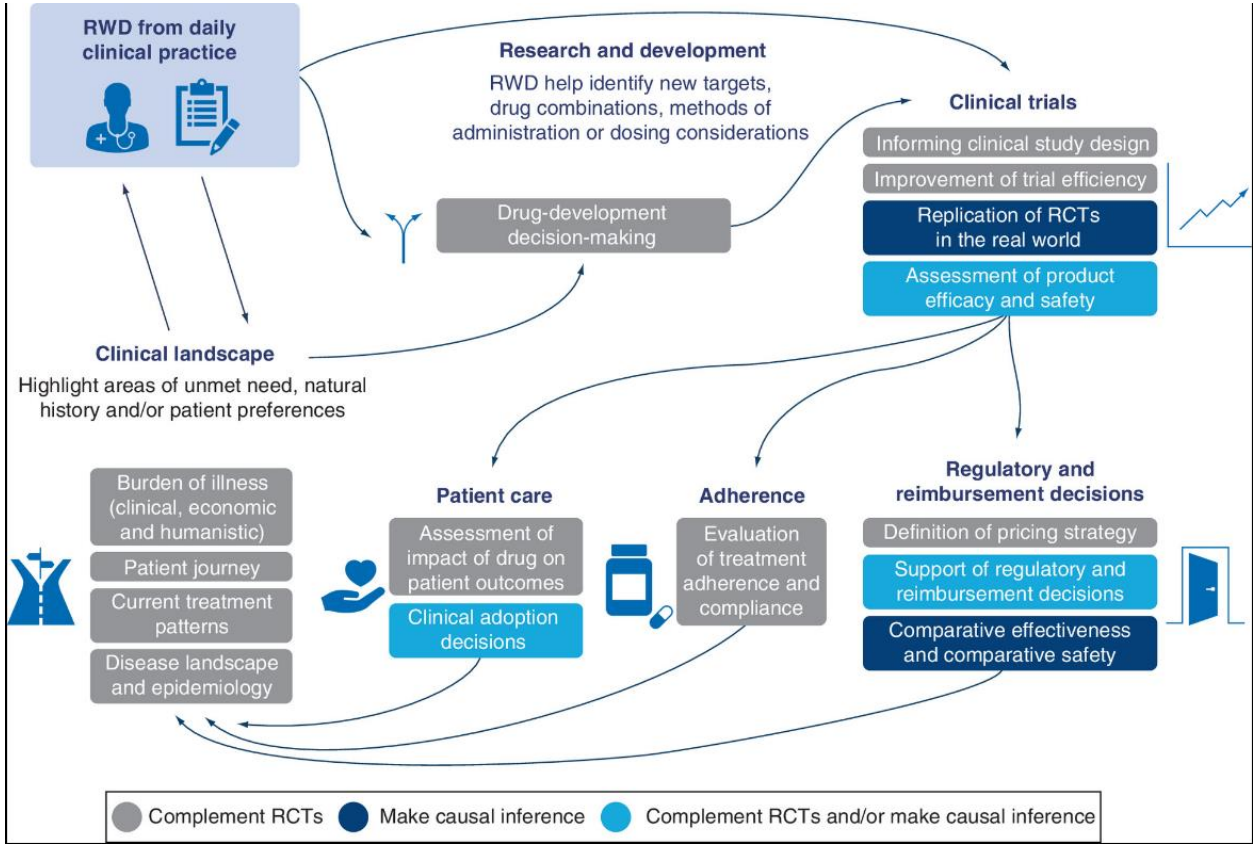
- But, their use may present biases, potential confounding and pitfalls.
- But, robust process may help to minimize biases. This process would include considerations of data quality…
- And, robustness assessments (sensitivity analyses, quantitative bias analyses) need to be conduct



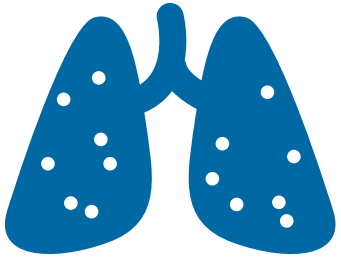
Elson et al JCER 2021

Use case: ROSLIC

- Medical context, guidelines and clinical trials
- ROSLIC study: an indirect treatment comparison study on French ROS1+ NSCLC patients
- Key messages and food for thought

NSCLC is an aggressive disease that represents a significant burden for the patient

Lung cancer is associated with significant impairment in quality of life that is reported to be higher than with other malignancies[1]



ROS1+ disease accounts for a small proportion of lung cancer cases, but many patients present with advanced-stage disease[2]

Central nervous system (CNS) metastases are common in advanced *ROS1+* NSCLC[3] and present a significant burden for patients[3,4]

1. Polanski, et al. Onco Targets Ther 2016; 2. Bergethon, et al. J Clin Oncol 2012;
3. Patil, et al. J Thorac Oncol 2018; 4. Johung, et al. J Clin Oncol 2016

Entrectinib clinical trials

Entrectinib is an oral, potent and selective ROS1 / TRK / ALK tyrosine kinase inhibitor that is CNS active[1,2]

ALKA-372-001 EudraCT 2012-000148-88
STARTRK-1 NCT02097810
STARTRK-2 NCT02568267
BFAST NCT03178552
MO41552 NCT04603807

Pooling of adult patients with locally advanced or metastatic NSCLC
From ALKA, STARTRK-1, and STARTRK-2

used to support entrectinib for dossier reimbursement along with indirect treatment comparisons

1. Rolfo, et al. Expert Opin Investig Drugs 2015; 2. Ahn, et al. WCLC 2017 (Abs. OA14.06);
3. Drilon, et al. Cancer Discov 2017; 4. Drilon, et al. Lancet Oncol 2020
5. Doebele, et al. Lancet Oncol 2020; 6. Rolfo, et al. ASCO 2020
7 Gadgeel, et al. ESMO 20195. 8. ClinicalTrials.gov NCT04603807.

ROSLIC study: an indirect treatment comparison study on French ROS1+ mNSCLC patients

- Partnership: Unicancer and Roche
- CROs: IQVIA and Horiana

➢ **Need to have comparative data on comparators recognized by the HAS**

- *Mainly chemotherapies*[1]

➢ **Need for comparative data on ROS1+ mNSCLC French patients**

1. HAS. Commission de la transparence - Avis XALKORI - 13 mai 2020.

ROSLIC study: objectives and study design

- **Primary objective:**

  Indirect comparisons of the **PFS** on patients treated in real-life setting with recognized French Health Technology Assessment (HTA) comparators (according to HAS opinion[1]) versus **entrectinib**

  - in first line
  - in second line

  for ROS1+ mNSCLC, using Matching-Adjusted Indirect Comparisons (MAIC).

1. HAS. Commission de la transparence - Avis XALKORI - 13 mai 2020; 2. Dziadziuszko, et al. J Clin Oncol 2021.

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  - in first line
  - in second line

  for ROS1+ mNSCLC, using Matching-Adjusted Indirect Comparisons (MAIC).

- **Design - Secondary data use of:**
  - **Combined** aggregated data of **3 Clinical Trials[2]:**

    Subpopulation of ROS1+ mNSCLC patients treated with entrectinib in three pooled CTs (ALKA-372-001, STARTRK-1 and STARTRK-2 studies)
    ⇒ **the experimental arm**.

  - **Individual Patient Data** from a French cohort:

    Subpopulation of ROS1+ mNSCLC patients in the ESME cohort, from **October 2017 to 30/06/2020**
    ⇒ **the comparator arm**.

1. HAS. Commission de la transparence - Avis XALKORI - 13 mai 2020; 2. Dziadziuszko, et al. J Clin Oncol 2021.

ROSLIC study: study populations

Entrectinib[1]
(n=124)

- **1L entrectinib population** (n=60)
- **2L entrectinib population** (n=64)

Recognized French HTA Comparators[2] (ESME)
(n=60)

- Patients aged ≥18 years, histological confirmation of mNSCLC, ROS1+,
- Naïve of ROS1 inhibitor treatment at index date

1L population
(n=30)

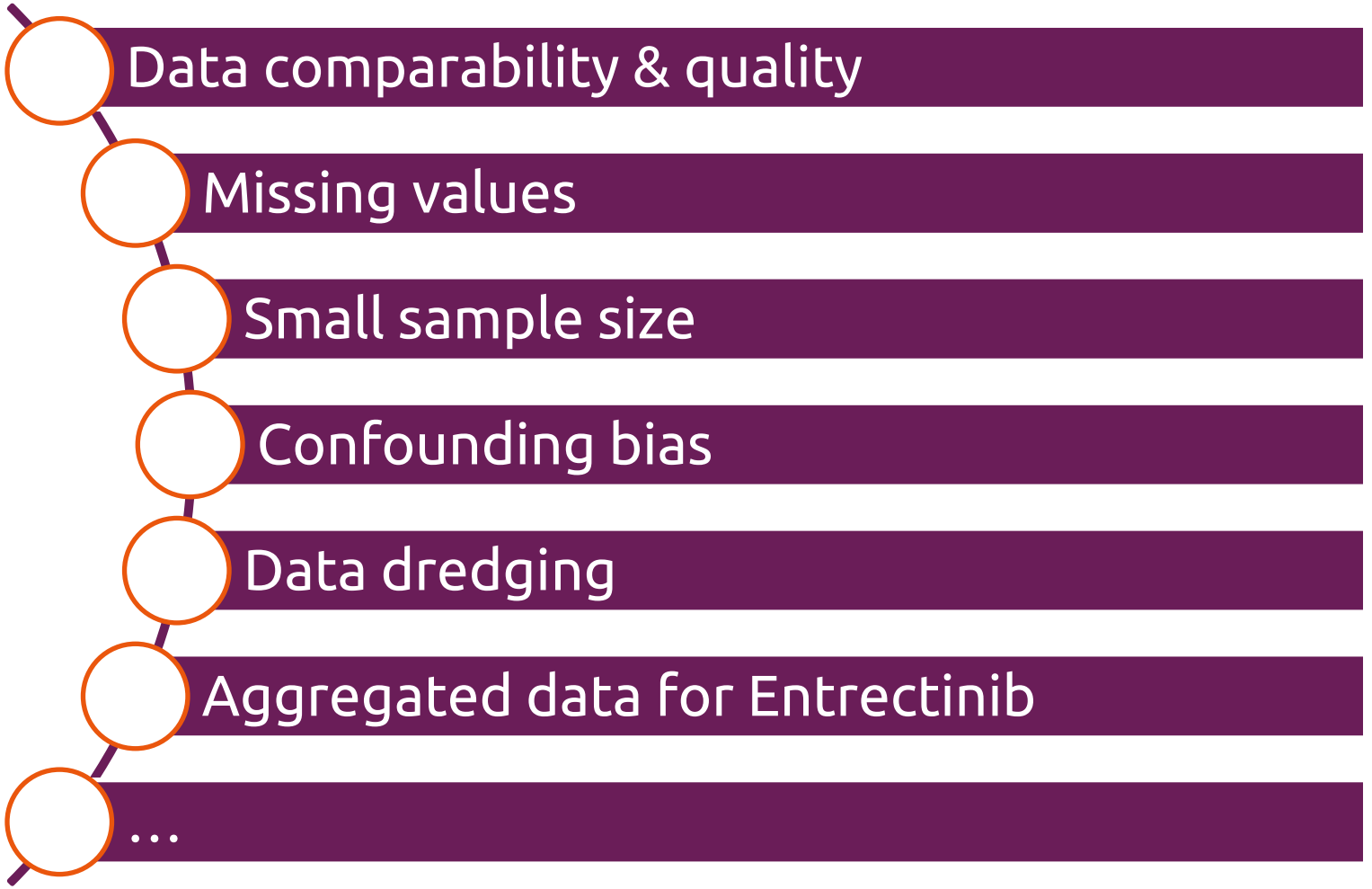
- chemotherapy alone or in combination: *pemetrexed / gemcitabine / docetaxel / vinorelbine / cisplatine* ***+/-*** *bevacizumab*

2L population
(n=30)

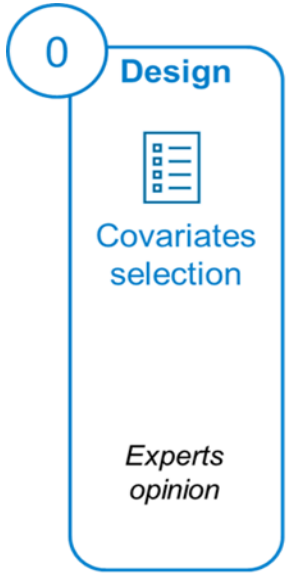
- chemotherapy alone or in combination: *pemetrexed / gemcitabine / docetaxel / vinorelbine / cisplatine;*
- ROS1 inhibitor: crizotinib

1.Dziadziuszko, et al. J Clin Oncol 2021. 2. HAS. Commission de la transparence - Avis XALKORI - 13 mai 2020.

ROSLIC study: many challenges to overcome



ROSLIC study: overview of the 3 steps methodology



C. Esnault et al. ISCB 43 Congress (2022)

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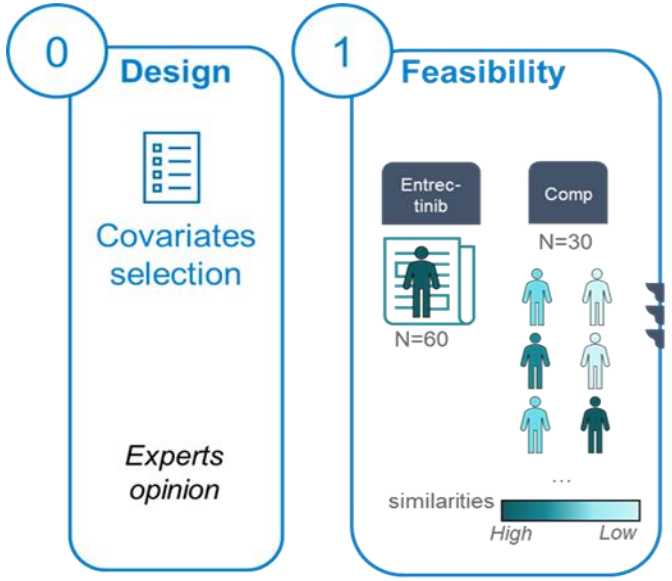

This study was conducted in 3 phases (go/no go):

1. feasibility assessment,

C. Esnault et al. ISCB 43 Congress (2022)

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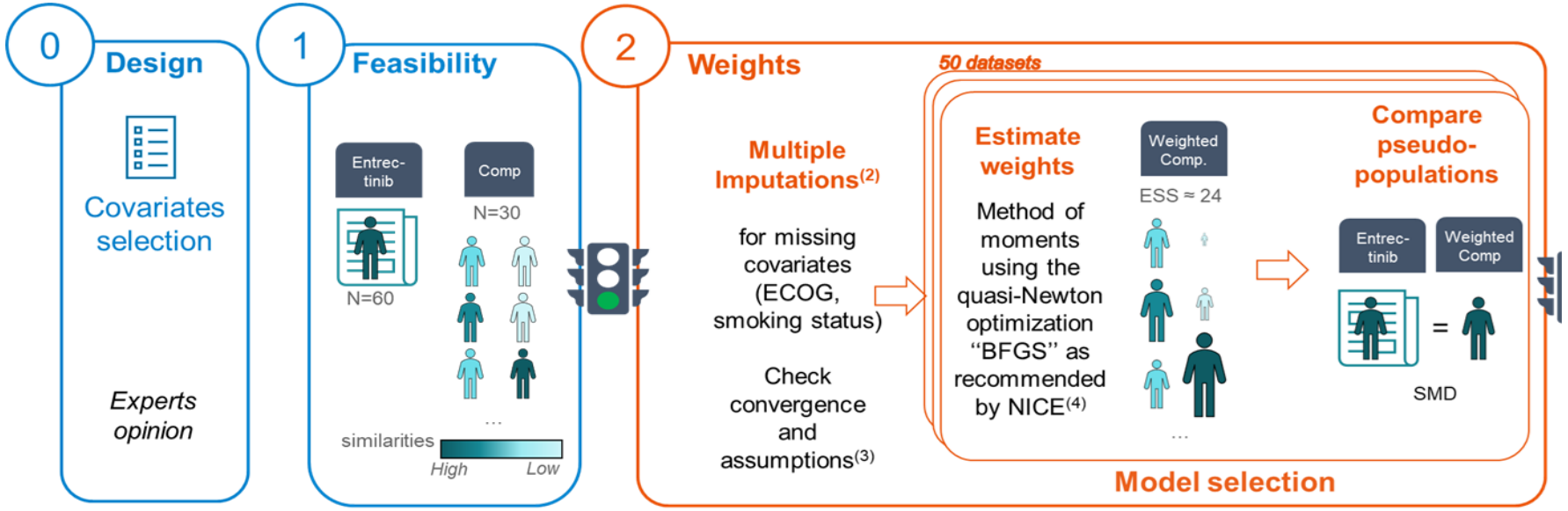
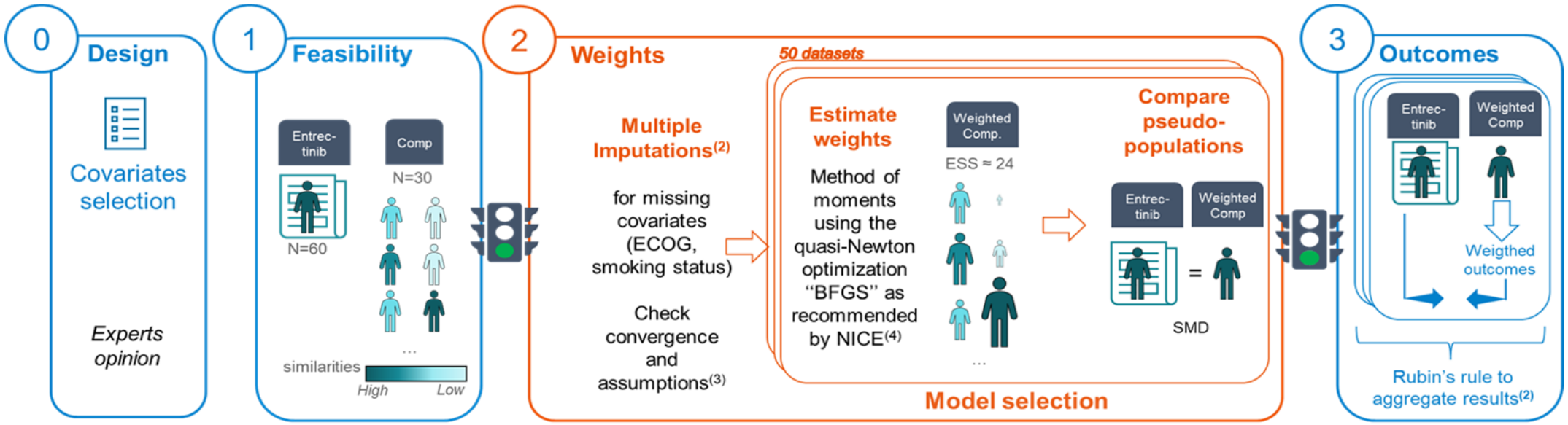


This study was conducted in 3 phases (go/no go):

1. feasibility assessment,
2. estimation of weights for the comparator arm (Comp.)

- ➢ with predefined steps for selecting the best model that calculates the weights, for each imputed dataset, in a small sample size setting with multiple imputations
- ➢ It also provides a **reading grid of the number of actions that were necessary** to reach the final model ("data dredging")

ROSLIC study: overview of the 3 steps methodology



This study was conducted in 3 phases (go/no go):

1. feasibility assessment,

2. estimation of weights for the comparator arm (Comp.)

- with predefined steps for selecting the best model that calculates the weights, for each imputed dataset, in a small sample size setting with multiple imputations
- It also provides a **reading grid of the number of actions that were necessary** to reach the final model ("data dredging")

and 3. outcome and inference analyses, **including sensitivity analysis**

C. Esnault et al. ISCB 43 Congress (2022)

A transparent and robust methodological approach to ease acceptability in a small sample size setting by avoiding data dredging

A WORKFLOW TO PERFORM MATCHING-ADJUSTED INDIRECT COMPARISONS WITH MULTIPLE IMPUTATION OF MISSING DATA ILLUSTRATED ON AGGREGATED SINGLE-ARM TRIALS AND THE ESME DATABASE

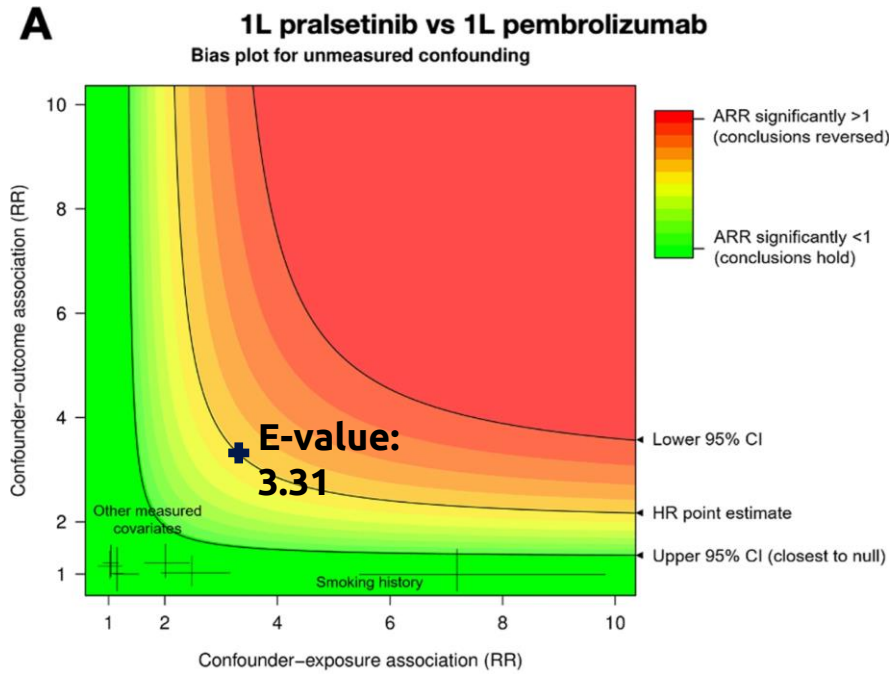
Cyril Esnault, Vanessa Barbet, Thomas Filleron, Gaëlle Chenuc, Maurice Pérol, Didier Debieuvre, Nicolas Girard, Xavier Quantin, Katia Thokagevistk, Gaëtane Simon, Louise Baschet

ISCB43 Congress (2022)

Ongoing step: quantitative Bias Analysis

Examples from previous papers

Bias plots showing unmeasured confounding for comparisons between the 1 L pralsetinib trial cohort and 1 L pembrolizumab cohort[1]



1. Popat, S., Liu, S.V., Scheuer, N. et al. Nat Commun (2022);

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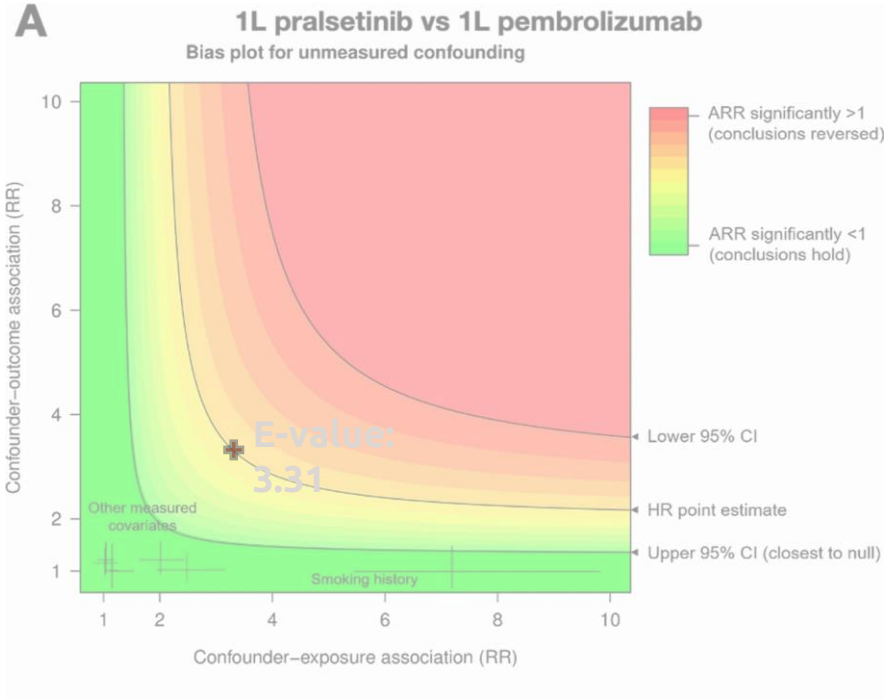
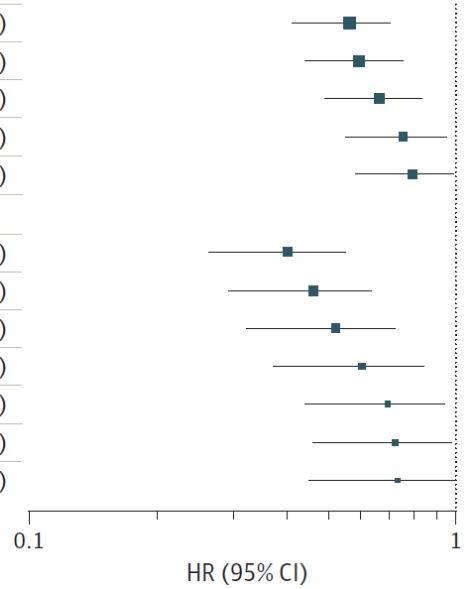


Tipping Point Analysis for Missing Eastern Cooperative Oncology Group (ECOG) Performance Status[2]

Trial-RWD	HR (95% CI)
δ=1	0.56 (0.41-0.70)
0	0.59 (0.44-0.75)
-1	0.66 (0.49-0.83)
-2	0.75 (0.55-0.95)
-3	0.79 (0.58-0.99)
RWD-RWD	
1	0.40 (0.26-0.55)
0	0.46 (0.29-0.63)
-1	0.52 (0.32-0.72)
-2	0.60 (0.37-0.84)
-3	0.69 (0.44-0.94)
-4	0.72 (0.46-0.98)
-5	0.73 (0.45-1.00)



Negative values of δ imply exponentially increasing odds of patients having poorer ECOG PS than expected under missing at random given their covariates. Sufficient balance for the trial data vs RWD comparison was not achieved beyond δ = −2.

1. Popat, S., Liu, S.V., Scheuer, N. et al. Nat Commun (2022);
2. Wilkinson S, Gupta A, Scheuer N, et al. JAMA Netw Open. (2021)

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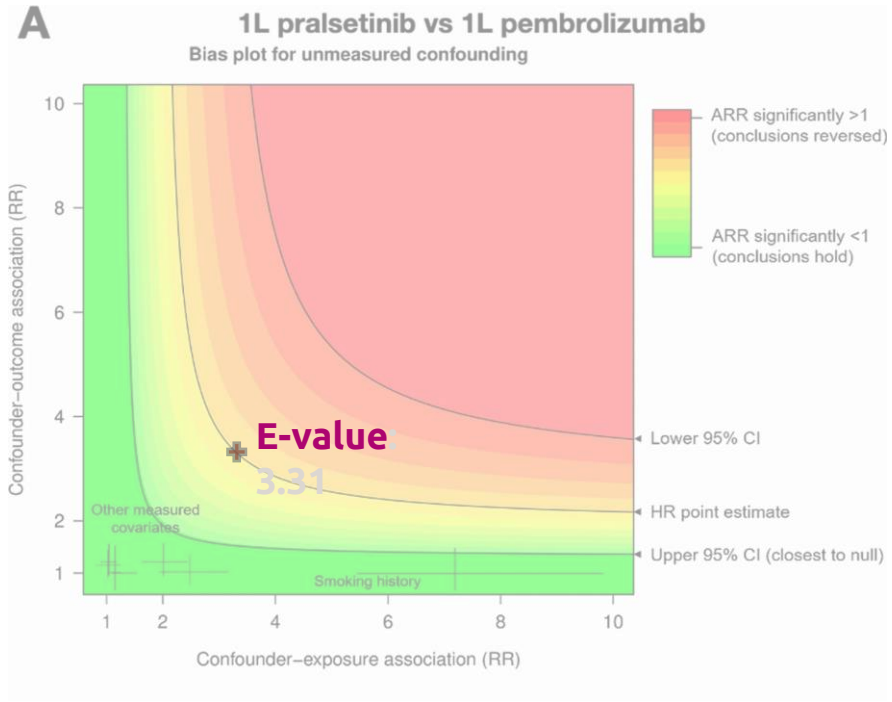

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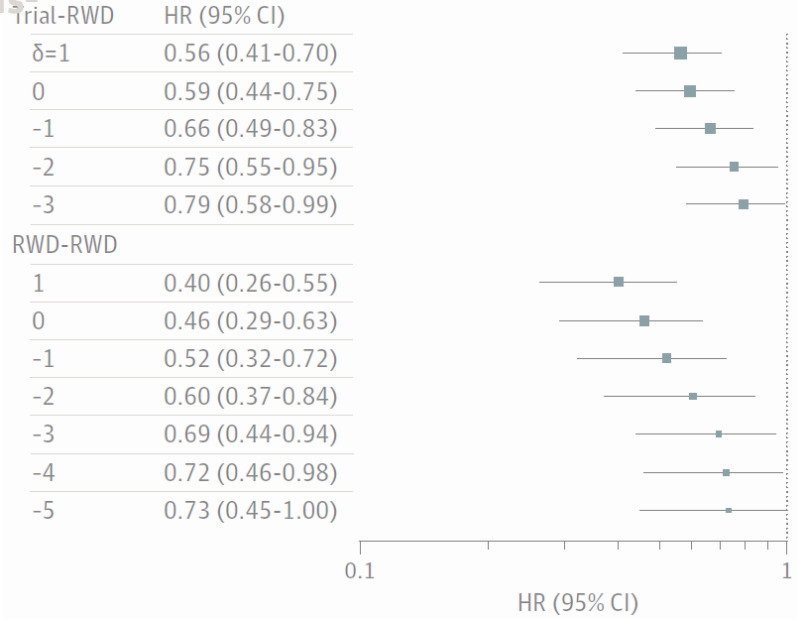

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QBA adapted to the context of the ROSLIC study: MAIC, few patients, multiple imputation of missing data, …

1. Popat, S., Liu, S.V., Scheuer, N. et al. Nat Commun (2022);
2. Wilkinson S, Gupta A, Scheuer N, et al. JAMA Netw Open. (2021)

Key messages

<u>ROSLIC use case:</u> Possible to compare aggregated clinical trials versus Real-World Standard of Care in the French setting with **strengths** and **weaknesses**

The perfect indirect comparison does not exist (“RCT-like”)

Strength in numbers!

Possible if…

- Selecting the good cohorts (FR / EU?) for data quality
- Applying adequate methodology