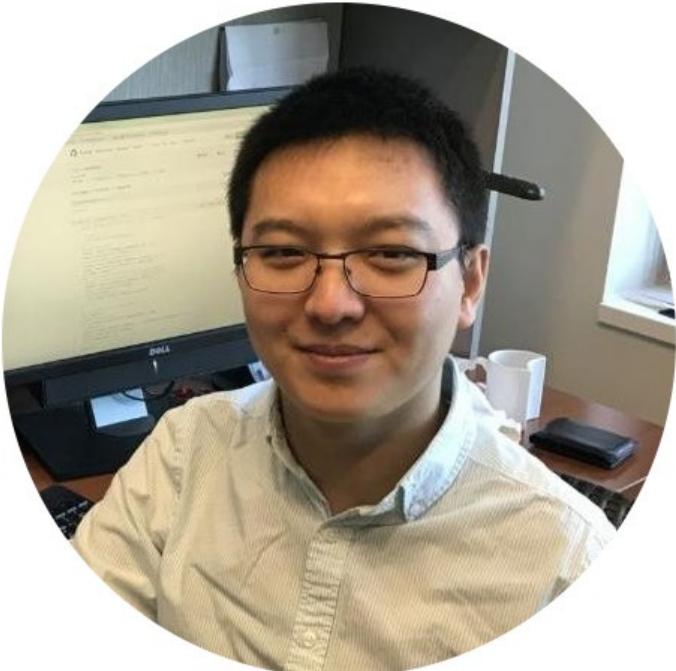


Speaker: Qing Li





Utilizing RWD and RWE in clinical development

July.23.2021

Fifth Boston Pharmaceutical Symposium
Qing Li, Takeda Pharmaceutical

Disclaimers

- Qing Li is the employee of Takeda. He is holding the respective company stocks.
- This presentation reflects the views of the authors and should not be constructed to represent Takeda's views or opinions.
- All the data presented in this seminar are based on publications from FDA review document, medical journal, ODAC meeting press release and others.

Background: Traditional Drug Development Diagram

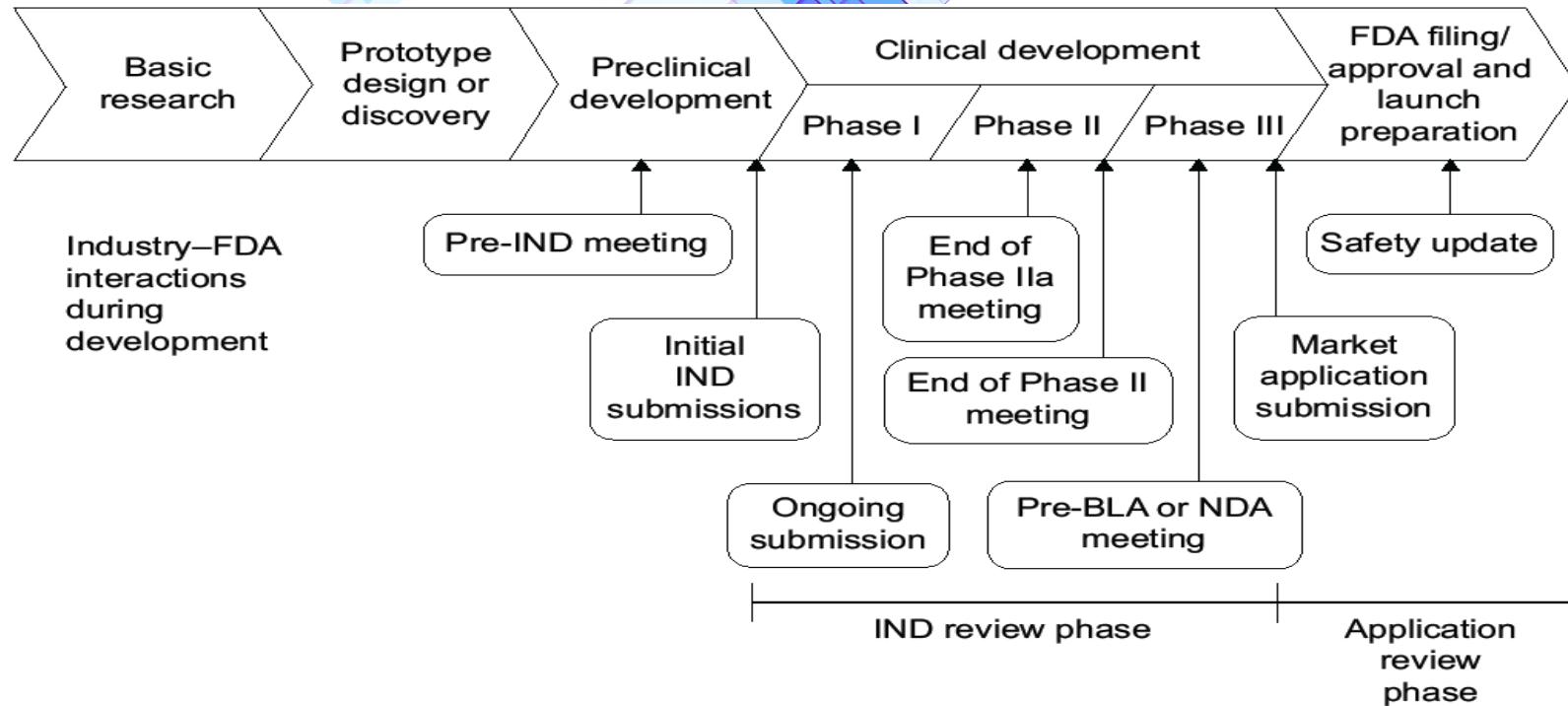


Figure 1 Drug development process.

Abbreviations: BLA, Biologics License Application; FDA, US Food and Drug Administration; NDA, New Drug Application; IND, Investigational New Drug.

Reference: Khorasani AA, Weaver J, Salvador-Morales C. Closing the gap: accelerating the translational process in nanomedicine by proposing standardized characterization techniques. *Int J Nanomedicine*. 2014;9(1):5729-5751 <https://doi.org/10.2147/IJN.S72479>

How to improve the drug development

- Traditional three phase trial approach lacks flexibility and speed to develop complex therapies in today's competitive, value-based markets
- The costs and risks of drug development are high: In 2014, total sponsor cost per new drug approved in USA increased by > \$2.5 billion over 15 years, reflecting a 145% increase
- Lack of external validity and generalizability
- Gaps between efficacy and effectiveness

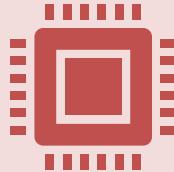
How can Real World Evidence increase the potential for clinical & commercial success?



Background: Comparison between RWD and RCT

	RCT	RWD
Purpose	Efficacy/safety	Effectiveness/safety
Setting	Research	Real world
Population	Homogeneous	Heterogeneous
Population size	Small - moderate	Large - huge
Patient follow-up	Fixed	Variable
Treatment	Fixed	Variable
Attending physician	Investigator	Practitioner
Costs	High	Low
Generalizability	Low - moderate	Moderate - high
Control for bias	Design and conduct	Analysis

What is RWD/RWE?



Real world data (RWD) are data relating to patient health status and/or the delivery of health care collected from a variety of sources

- Electronic health record (EHR)
- Hospital/insurance claims data
- Data from observational studies
- Patient reported outcome
- Wearable devices



RWE is the *clinical evidence* about the usage and potential benefits or risks of an intervention derived from analysis of RWD

- Observational studies
- Early Access Programmes
- Post-authorization safety studies
- Pragmatic clinical trials
- Registry studies

RWD/RWE Data Sources



Reference: <https://www.healthcatalyst.com/insights/real-world-data-chief-driver-drug-development>

RWD/RWE Data Sources



GE Healthcare



Opportunities: Healthcare Decision-Making Relies on RWD

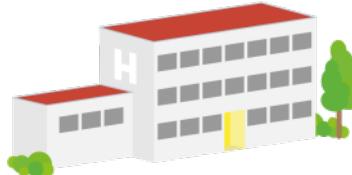
- Healthcare decision-makers are interested in the evidence supporting their decisions
- Understanding healthcare decision-maker perspectives is key to generating the right evidence

Is this the best treatment for my patients?



Healthcare professional

How does this treatment affect mortality?



Hospital

Is this treatment cost-effective?



Payer

Does this treatment work? How safe is it?



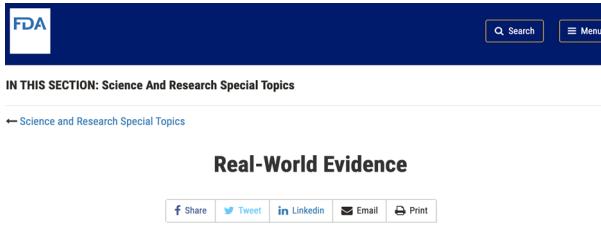
Regulator

What treatment is best for me?



Patient

Regulatory Perspectives: Regulators are encouraging the use of RWE



The screenshot shows the FDA's "Real-World Evidence" page. At the top, there's a navigation bar with the FDA logo, a search bar, and a menu icon. Below it, a section titled "IN THIS SECTION: Science And Research Special Topics" lists "Science and Research Special Topics". The main content area is titled "Real-World Evidence" and features a sub-section: "Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions." It includes a bulleted list of points and social sharing icons for Facebook, Twitter, LinkedIn, Email, and Print.

Real-world data (RWD) and real-world evidence (RWE) are playing an increasing role in health care decisions.

- FDA uses RWD and RWE to monitor postmarket safety and adverse events and to make regulatory decisions.
- The health care community is using these data to support coverage decisions and to develop guidelines and decision support tools for use in clinical practice.
- Medical product developers are using RWD and RWE to support clinical trial designs (e.g., large simple trials, pragmatic clinical trials) and observational studies to generate innovative, new treatment approaches.

Increasing Use of Real-World Data to Help Improve Cancer Care

In April 2019, [↗] Ibrance® (palbociclib) was approved for men with HR+, HER2- metastatic breast cancer. While the U.S. Food and Drug Administration's (FDA) decision was based largely on prior efficacy data from randomized controlled studies in women with metastatic breast cancer, such as the PALOMA-2 trial, Pfizer's supplemental regulatory submission for male breast cancer primarily included real-world evidence.



The screenshot shows the European Medicines Agency (EMA) website. At the top, there's a navigation bar with the EMA logo, a search bar, and a menu icon. Below it, a section lists various regulatory and committee areas. The main content area is titled "Global regulatory workshop on COVID-19 real-world evidence and observational studies" and includes a "Share" button, a date ("News 31/07/2020"), and a summary text about the workshop.

Global regulatory workshop on COVID-19 real-world evidence and observational studies ↗ Share

News 31/07/2020

Vaccines surveillance and vigilance, collaboration on pregnancy studies and building international patient cohorts were the main topics discussed during the 3rd workshop on observational studies of real-world data in the context of COVID-19. The workshop, organised under the umbrella of the International Coalition of Medicines Regulatory Authorities (ICMRA), was co-chaired by Health Canada and the European Medicines Agency (EMA) and took place on 22 July 2020. The main findings of the workshop are summarised in a report [↗](#).

NICE Partners with Flatiron Health to Develop Real-World Evidence Research Methodologies

Collaboration will help NICE expand use of real-world data in service of better outcomes for UK cancer patients

July 14, 2020 03:00 AM Eastern Daylight Time

MANCHESTER, England & NEW YORK--(BUSINESS WIRE)--The National Institute for Health and Care Excellence (NICE, www.nice.org.uk) is partnering with Flatiron Health (www.flatiron.com), an oncology research and technology company, to explore how real-world evidence (RWE) can inform the clinical and cost effectiveness of health technologies.

"We are very proud to partner with NICE to learn together, to continue to contribute to standards development and ensure that patient experiences inform research and drive better outcomes."

↗ Tweet this

Flatiron Health and NICE experts will together conduct research that leverages Flatiron expertise and evidence generated from Flatiron's electronic health record (EHR)-derived database; no individual patient data will be shared. An initial research project already underway will compare survival estimates from clinical trials to survival data observed in actual patient records to evaluate opportunities to reduce uncertainty in the estimation of long-term outcomes.

NICE provides guidance and standards about health technologies and clinical practices to England's National Health Service, and is a world leader in the development of evidence-based guidelines to improve health and social care.

FDA developing guidance for RWE



FRAMEWORK FOR FDA'S **REAL-WORLD EVIDENCE PROGRAM**

December 2018
www.fda.gov

Scope of RWE programme under 21st Century Cures Act

Current use of RWD for evidence generation

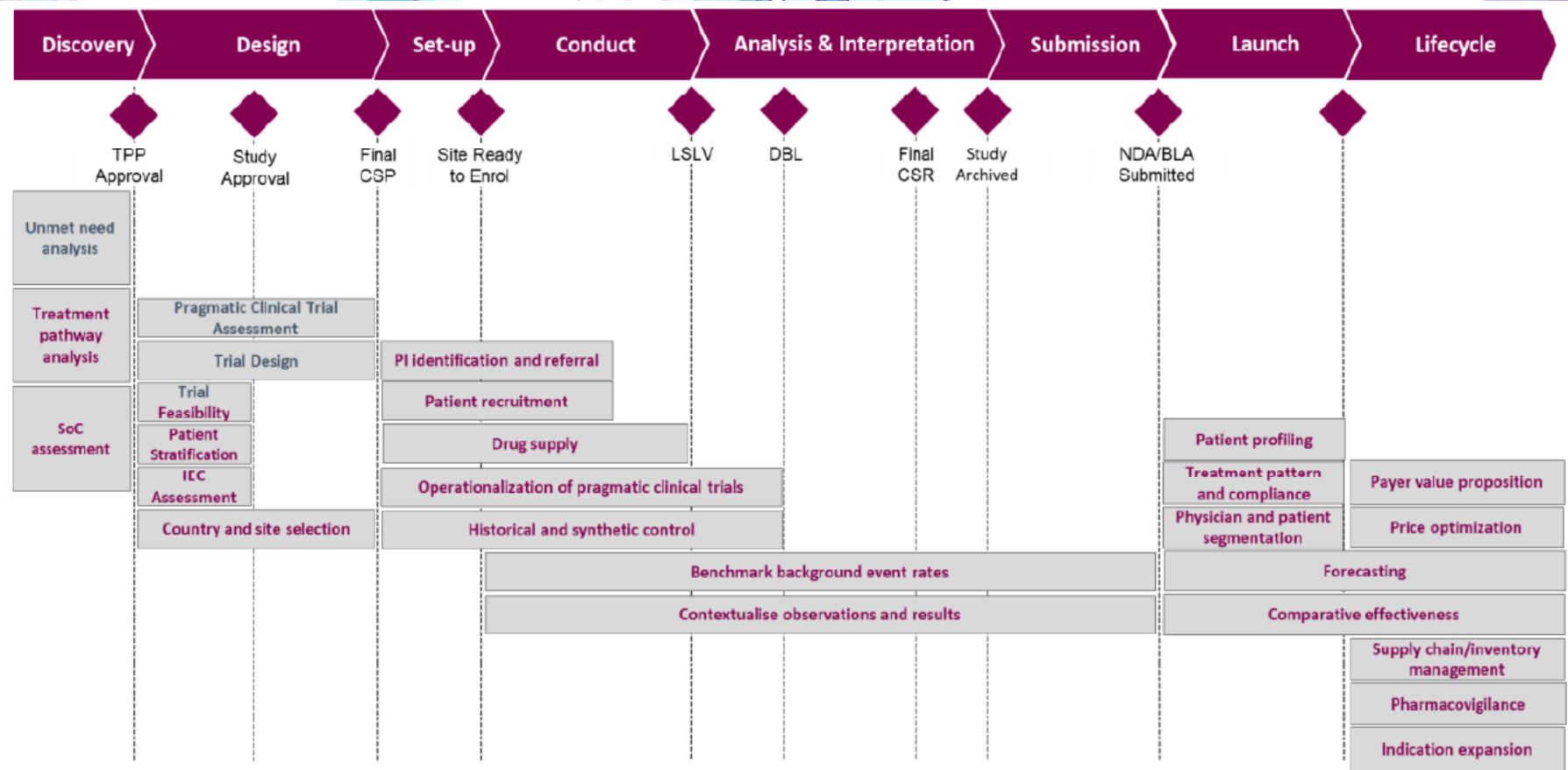
- Generating evidence regarding safety and effectiveness
- Supporting FDA's regulatory decisions of effectiveness
- Trial Designs using RWD to generate evidence

Framework for evaluating RWD/RWE for use in regulatory decisions

- Using trials/studies with RWD/RWE effectiveness
- Assessing fitness of RWD for regulatory use
- Potential for study designs to support effectiveness
- Regulatory considerations for study designs using RWD
- Data standards

Implications broader than FDA: workstreams ISPOR/ICPE on best practices, RWE-duplicate or REPEAT projects

Opportunities: RWD/RWE in Drug Development Life Cycle



Regulatory Approvals based on the Use of RWD/RWE

Regulatory Body/ies	Generic name (trade name)	Year of approval	Regulatory Body/ies	Generic name (trade name)	Year of RWD submission
EMA	<i>Alipogene tiparvovec</i> (<i>Glybera</i>)	2012** (⊖ 2017)	EMA	<i>Eculizumab</i> (<i>Soliris</i>)	2012
EMA	<i>Cholic acid</i> (<i>Orphacol</i>)	2013**	EMA	<i>Etravirine</i> (<i>Intelence</i>)*	2019
EMA	<i>Zalmoxis</i>	2016* (⊖ 2019)	US FDA	<i>Sapien TAVR device</i>	2017
EMA	<i>Stimvelis</i>	2016	US FDA	<i>Palbociclib</i> (<i>Ilbrance</i>)	2018
EMA	<i>Tisagenlecleucel</i> (<i>Kymriah</i>)	2018	US FDA	<i>Etravirine</i> (<i>Intelence</i>)*	2018
EMA	<i>Axicabtagene ciloleucel</i> (<i>Yescarta</i>)	2018	EMA, US FDA	<i>Paliperidone palmitate</i> (<i>Invega Sustenna</i>)	2014
FDA	<i>Glucarpidase</i> (<i>Voraxaze</i>)	2012	EMA, US FDA	<i>Alglucosidase alfa</i> (<i>Myozyme</i>)**	2014
FDA	<i>Elosulfase alfa</i> (<i>Vimizim</i>)	2014	EMA, US FDA	<i>Nusinersen</i> (<i>Spinraza</i>)**	2017
FDA	<i>Uridine triacetate</i> (<i>Vistogard</i>)	2015	EMA, US FDA	<i>Blinatumomab</i> (<i>Blinacyto</i>)**	2017
FDA	<i>Cholic acid</i> (<i>Cholbam</i>)	2015	EMA, US FDA	<i>Fosamprenavir</i> (<i>Lexiva/Telzir</i>)	2018
EMA, FDA	<i>Lepirudin</i> (<i>Refludan</i>)	1998, (⊖ EMA, 2012)			
EMA, FDA	<i>Alglucosidase alfa</i> (<i>Myozyme/Lumizyme</i>)	2006			
EMA, FDA	<i>Cerliponase alfa</i> (<i>Brineura</i>)	2017			
EMA, FDA	<i>Blinatumomab</i> (<i>Blinacyto</i>)	2015, 2014			
EMA, FDA, Health Canada	<i>Caraglumic acid</i> (<i>Carbaglu</i>)	2003**, 2010, 2015			
EMA, FDA, Health Canada, Japan PMDA	<i>Nusinersen</i> (<i>Spinraza</i>)	2017, 2016, 2016, 2017			
EMA, FDA, Health Canada, Japan PMDA	<i>Avelumab</i> (<i>Bavencio</i>)	2017			

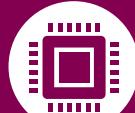
Table 2. Bolislis, Winona R., Myriam Fay, and Thomas C. Kühler. "Use of real-world data for new drug applications and line extensions." *Clinical Therapeutics* (2020).

Challenges of Successful Use of RWD/RWE



Data

- Data Access and Quality
- Lack of tools for data sharing, transfer and communication



Technology

- Technological Barriers
- Scalable platforms with analytics, potentially connecting different data sources
- Tech-enabled privacy and governance – ensure compliance



Capabilities

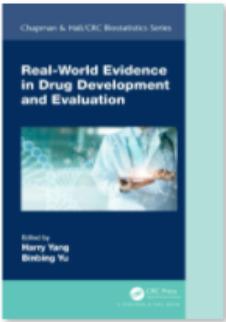
- Methodological challenges
- Lack of talents: data scientists and statisticians



Regulatory

- Regulatory risk
- Constantly changing landscape

Reference book



Book

Real-World Evidence in Drug Development and Evaluation

By Harry Yang, Binbing Yu

Edition	1st Edition
First Published	2021
eBook Published	11 February 2021
Pub. Location	Boca Raton
Imprint	Chapman and Hall/CRC
DOI	https://doi.org/10.1201/9780429398674
Pages	190
eBook ISBN	9780429398674
Subjects	Bioscience, Mathematics & Statistics, Medicine, Dentistry, Nursing & Allied Health

- This seminar will focus on chapter 4 – clinical development.
- Additional topics in this book: RWE utility, RWE in safety analysis, causal inference for RWE, cancer registry, coverage & payment, HTA, AI, deep learning

Contents

1. Utilize synthetic control arm to support a single arm study
2. Utilize natural history study for rare disease development
3. Utilize RWD/historical data for label expansion
4. Practical considerations of using RWD/historical data in the clinical development

1. Synthetic control to support single arm study



Patients

- Assign patients with life-threatening diseases to interventions, minimizing their exposure to ineffective controls or SoC
- Can raise patients' awareness and encourage their participation in clinical trials



Investigators

- Save time and costs as fewer patients are recruited, and redundant controls are removed
- Make trials more flexible and resilient when facing uncertainty



Regulators

- Promote innovation and drive down the number of patients required to be enrolled for ineffective controls
- Fast-track the regulatory review process for treatments that address life-threatening diseases

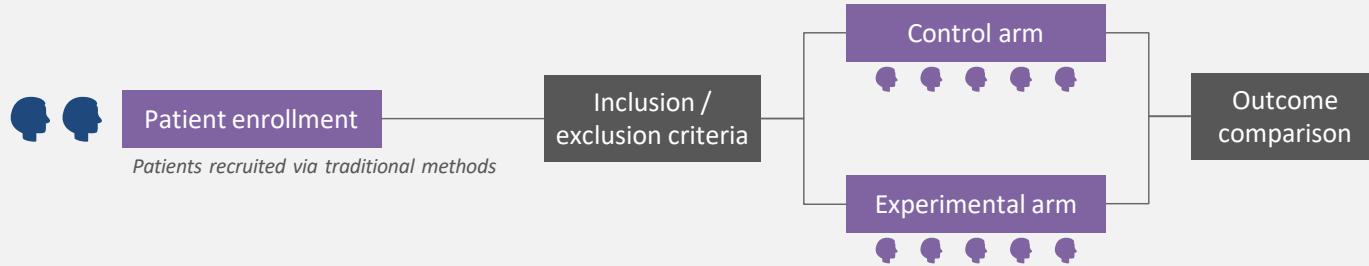


Market access

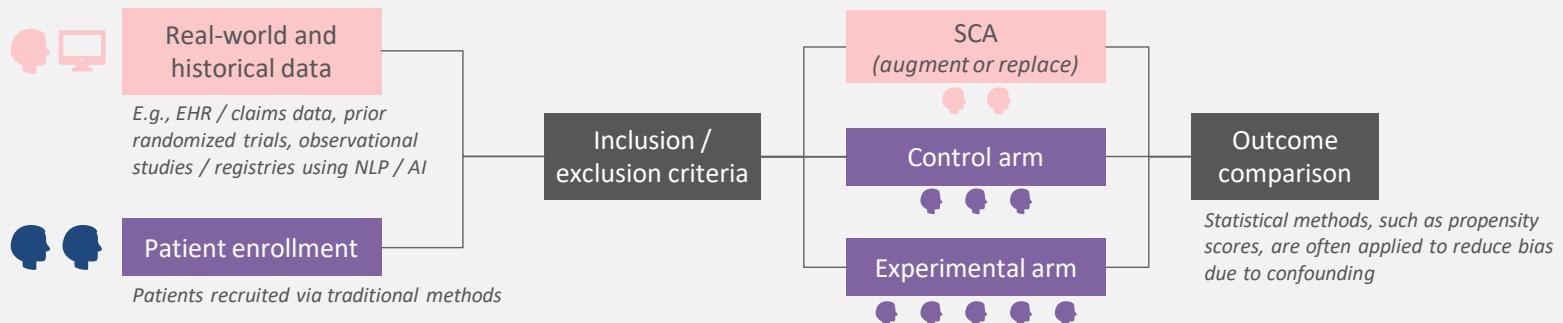
- Enable additional analyses based on the same or similar external data set approved by regulators
- Leverage external data to derive drug-specific information (e.g., indication, endpoint selection, safety, and efficacy) to guide drug repurposing and label expansion

Synthetic control arm designs

Traditional randomized control trial (RCT)

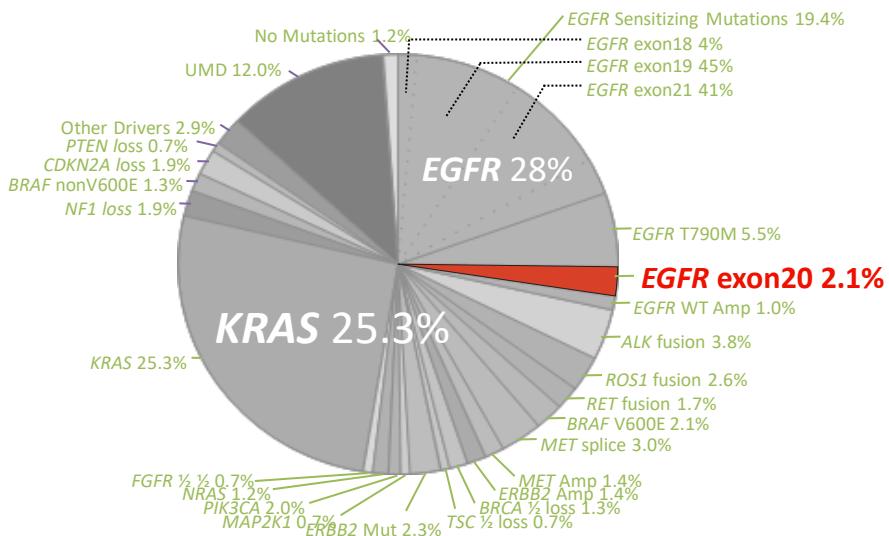


Synthetic control arm (SCA)

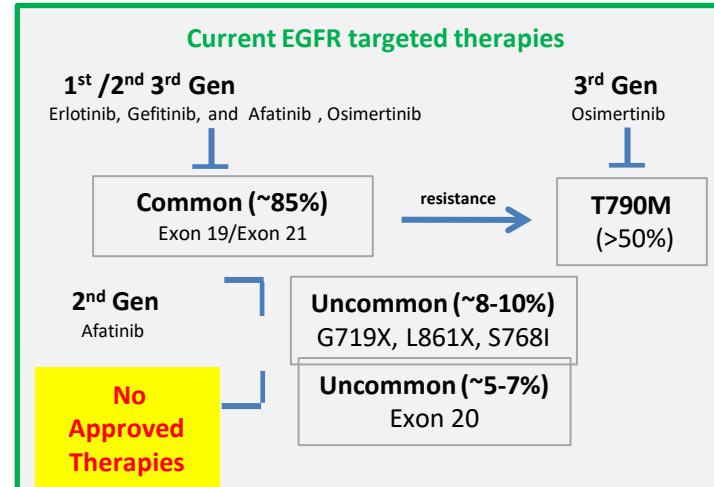


Example: non-small cell lung cancer (NSCLC)

NSCLC (GENETIC SUB POPULATIONS)⁶

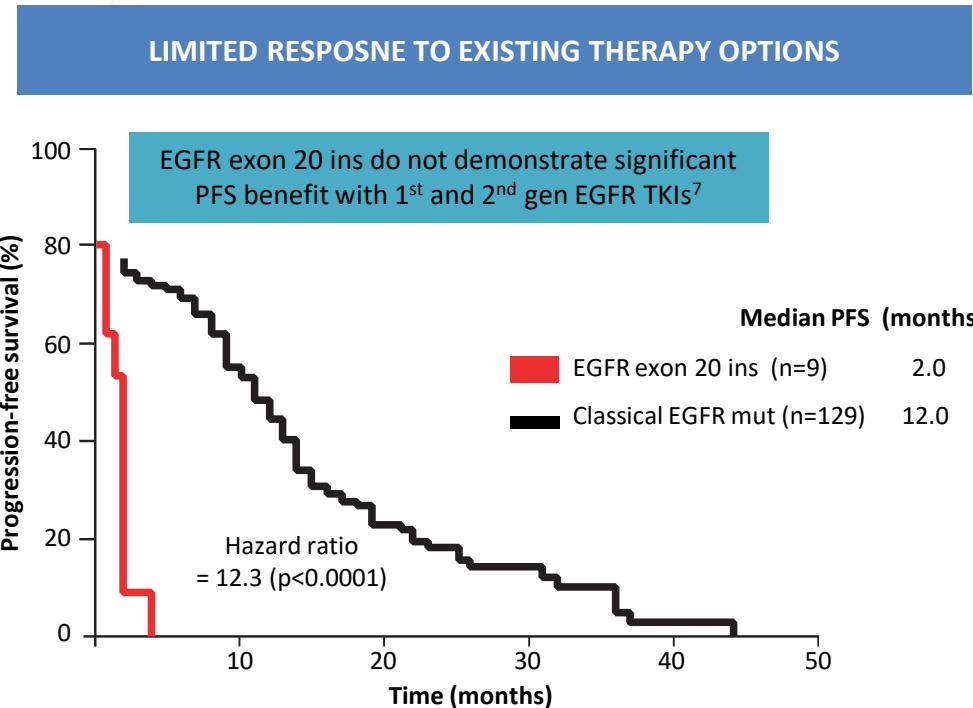


EGFR EXON 20 INSERTION MUTATIONS



Unmet medical needs

- Unmet medical needs:
 - no drugs approved
 - Patients are waiting
- Traditional registrational path is too long
- A single arm registrational trial with SCA has the potential to accelerate the drug development



Baseline characteristics

Table 1. Baseline Characteristics

	TAK-788 n=28	RWD n=71	
	Unweighted		Weighted
Age, mean (SD), y	62.1 (10.75)	64.9 (10.59)	62.0 (6.58)
Male, n (%)	7 (25)	33 (46.48)	25.68%
Race, n (%)			
Asian	5 (17.86)	7 (9.86)	16.62%
Non-Asian	23 (82.14)	64 (90.14)	83.38%
Smoking status, n (%)			
Never	17 (60.71)	39 (54.93)	62.59%
Former	11 (39.29)	32 (45.07)	37.41%
Presence of brain metastasis, n (%)	12 (42.86)	24 (33.80)	45.43%
ECOG, n (%)			
0	6 (21.43)	14 (19.72)	21.20%
1	22 (78.57)	19 (26.76)	23.94%
2	0	4 (5.63)	3.39%
3	0	3 (4.23)	3.81%
4	0	0	0
Missing	0	31 (43.66)	47.66%
No. of prior regimens, median (range)	3 (1, 7)	1 (1, 1)	1 (1, 1)
Prior chemotherapy exposure, n (%)	28 (100)	59 (83.10)	86.64%

1. Horn, Leora, Huamao Mark Lin, Sukhmani Kaur Padda, Charu Aggarwal, Caroline Elizabeth McCoach, Yanyan Zhu, Yu Yin et al. "Indirect comparison of TAK-788 vs real-world data outcomes in refractory non-small cell lung cancer (NSCLC) with EGFR exon 20 insertions." ASCO (2020): 9580-9580.

TAK-788 example

Context



Target disease

- Patients with locally advanced or metastatic NSCLC¹ with EGFR² exon 20 insertion mutations
- **Currently approved EGFR TKIs³ are ineffective** in patients that have NSCLC with EGFR exon 20 insertion



Drug fact

- TAK-788 is an EGFR TKI with potent and selective preclinical inhibitory activity against EGFR exon 20 insertions
- **TAK-788 has demonstrated preliminary efficacy in a single-arm Phase 1/2 trial** for patients who have been previously treated

Trial flow

Treatment arm

Ongoing enrollment of PTs⁴ with NSCLC-EGFR exon 20

PTs treated with TAK-788 as second-line treatment

28 treated PTs selected

SCA based on RWD

RWD derived primarily from Flatiron Health's EHR⁵

PTs received second-line treatment

71 external PTs from RWD

Treatment effect estimation
based on IPTW⁶

7.33-mo. median PFS⁷
43% ORR⁸

3.45-mo. median PFS
13% ORR

1. NSCLC: Non–small-cell lung cancer; 2. EGFR - Epidermal growth factor receptor; 3. TKI - Tyrosine kinase inhibitors; 4. PT – Patient; 5. EHR – Electronic health record; 6. IPTW – Inverse probability treatment weighting; 7. PFS – Progression free survival (with 95% confidence interval); 8. ORR – Objective response rate
Source: Horn, et al. "Indirect comparison of TAK-788 vs real-world data outcomes in refractory NSCLC with EGFR exon 20 insertions," J. Clin. Oncol. (2020)

Bavencio example

Context



Target disease

- Patients with metastatic MCC¹, an aggressive skin cancer
- MCC is a rare disease with short survival time, therefore **traditional randomized trials with control arms were not feasible for patients with urgent unmet medical needs**



Drug fact



- Bavencio (avelumab) is a human antibody specific for a protein called PD-L1
- It prevents tumor cells from using PD-L1 for protection against white blood cells

Trial flow

Single treatment arm

88 PTs² enrolled
in an open-label study

PTs treated with Bavencio

Outcomes measured by
ORR³ and DOR⁴

ORR: 33%
93% of PTs² have 6-mo. DOR⁴
75% of PTs have 12-mo. DOR

Historical data

686 PTs with MCC initially identified from iKnowMed⁵

14 PTs selected based on
disease subtypes and prior
treatment history

ORR: 28.6%
1.7-mo. median DOR
(95% CI⁶:0.5,3.0)

“Even though SCA only provided supportive evidence in this case, it played a critical role in fast-tracking Bavencio's regulatory approval”

1. MCC – Merkel cell carcinoma; 2. PT – Patient; 3. ORR - Objective response rate; 4. DOR - Duration of response; 5. iKnowMed is an interoperable EHR system for oncology practices;
6. CI – Confidence interval. Source: E. Schemmitt, "Case Study – Bavencio Merkel Cell Carcinoma," Cancer Drug Development Forum (2019); Takeda internal research

Summary

- In the second example, the matching procedure is only based on a few variables and a small number of patients from registry data.
- This synthetic control arm is only considered as supportive evidence given the limitation of the historical data.
- Even so, for a serious and life-threatening disease for which there is no FDA-approved therapy and no known curative therapy, synthetic arm provides an objective reference level to compare with.
- The objective reference level depends on the specific disease and the number of lines of treatment a patient has received.
- The comparison of DOR offers supportive evidence, which is very important for a disease with such short DOR under the standard treatment.

2. Utilize natural history study for rare disease

- Rare disease: a disease or condition that “affects less than 200,000 persons in the United States” [FDA 2015b and 2019a]
 - There are approximately 7,000 recognized rare diseases.
 - Most rare diseases have no approved therapies.
- The natural history of a disease is traditionally defined as the course a disease takes **in the absence of intervention** in individuals with the disease, from the disease’s onset until either the disease’s resolution or the individual’s death.
- Purpose: identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease’s development and outcomes.
- Draft guidance: Rare Diseases: Natural History Studies for Drug Development. (FDA 2019a).

Why single arm+ natural history study

- Rare patient population with limited patients
- Ethical concern
- Feasibility

Case study: Strengsiq that used natural history studies to create the SCA Context



Target disease

- HPP¹ is a rare, genetic metabolic disease that affects bones and teeth
- Enrolling enough patients for the trial was challenging
- Effective SoC was unavailable



Drug fact

ALEXION®

- Strengsiq (Asfotase Alfa) is a tissue nonspecific alkaline phosphatase, supplied as an injection for subcutaneous administration
- SRENSIQ treats patients with perinatal, infantile, and juvenile onset HPP

Trial flow

Pooled single-arm trial

70 PTs² from pooled cohorts enrolled³

PTs treated with Strengsiq

Trial outcomes measured by OS⁴



HR⁵: 0.089

Natural history study

48 PTs with similar baseline char. selected from 4 studies

PTs received no treatment

Retrospective data collection on OS



Median OS: 271 days

The similar patient populations and clear comparison of endpoint measurements contributed to the successful approval

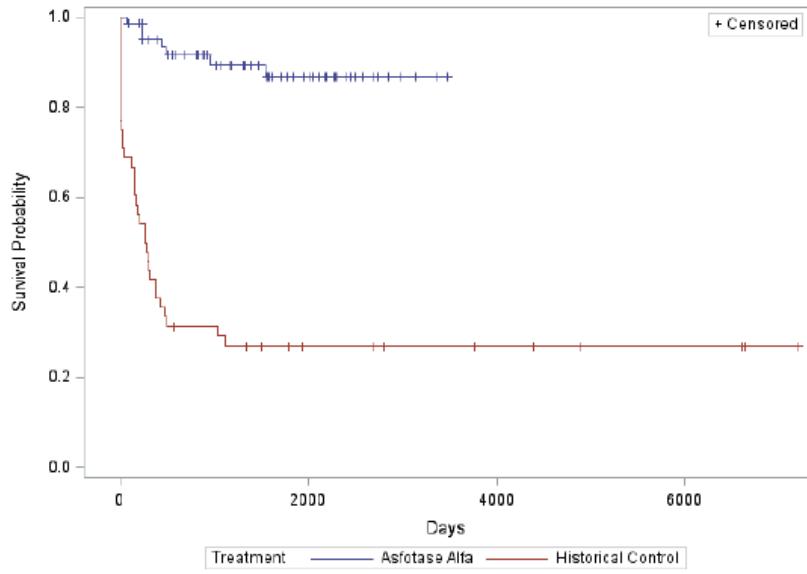
1. HPP – hypophosphatasia; 2. PT – Patient; 3. Two PTs not meeting the inclusion/exclusion criteria of the natural history study were excluded; 4. OS – Overall survival; 5. HR – Hazard ratio, e.g., a HR of 2 suggests the treated PTs may die twice the rate per unit time of the control group.

Source: Whyte, et al. "Asfotase alfa treatment improves survival for perinatal and infantile hypophosphatasia," J. Clin. Endocrinology (2016)

Treatment effect

- The primary endpoint was time to death, from birth up to the point of last contact (i.e., overall survival [OS]),
- The secondary endpoint was time to the start of invasive ventilator use or death (i.e., invasive ventilator-free survival).
- Both time-to-event endpoints were estimated
 - survival rates
 - median survival time
 - hazard ratio
 - Kaplan-Meier curve
 - log-rank test

Figure 1
Overall Survival – ENB-002-08/ENB-003-08 and ENB-010-10 vs. ENB-011-10
(All Qualified Enrolled/Extracted)



Source: Reviewer's Figure using SAS generated from ISE ADTTE dataset.

Summary (1)

- Successful Health Authority approval using an external control arm.
 - Endpoint
 - Both primary and secondary endpoints are objective survival endpoints.
 - Both endpoints show direct clinical benefits to the survival of patients, which indicate the robust clinical evidence.
 - Huge treatment effect
 - The huge treatment effects also can be seen in all summary statistics.
 - The huge treatment effects also enabled the conclusion to hold even if different sensitivity analyses were to be performed.
 - Similar patient population also contributed to the successful approval.

Summary (2)



- RWE does not lower the approval bar.
- Instead, RWE requires higher treatment effect.
- Limitations:
 - Weaker level of evidence: Because the study design with an external control arm is not as rigid as a randomized clinical trial, the use of a historical control is considered by the FDA as a weaker level of evidence.
 - Label: All previously presented inferential statistics (e.g., p-values) within this example are considered supportive and not confirmatory, and no inferential statistics should be presented within the final product labeling.

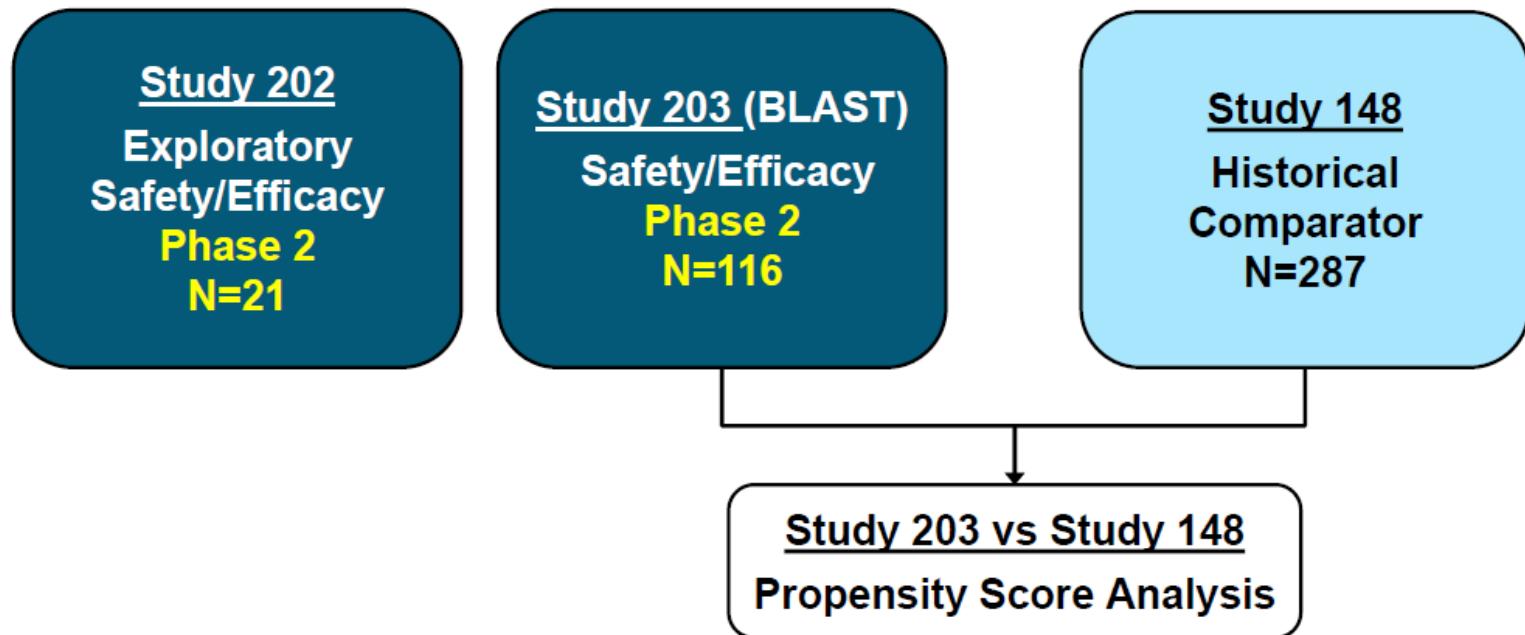
3. RWD/historical data for label expansion

- After the first NDA or BLA, a supplemental new drug application (sNDA) or supplemental Biologic License Application (sBLA) may also be applied to expand labels to more indications, patients, or regimens.
- Drug development
 - New patient populations
 - Different stages and/or disease subtypes
 - Combination treatment regimens
 - Off-label regimen for fully approval
- Using RWD/historical data as external control for label expansion is critical.

Blincyto regulatory history

Date	Milestone
2014 December	Accelerated Approval <ul style="list-style-type: none">• Ph- R/R B-cell precursor ALL• 1° Endpoint - hematologic complete remission (CR)• Approximately doubled CR rate vs. historical SOC control
2017 July	Full Approval <ul style="list-style-type: none">• R/R B-cell precursor ALL in adults and children• Broaden indication to include Ph+ R/R ALL• Confirmatory phase 3 trial demonstrated significant OS over chemotherapy• Reduction of leukemic burden (CR) correlated with OS
2017 September	sBLA submitted for MRD+ B-cell ALL

Study design



Study comparison

	Study 203	Study 148
Primary endpoint	Proportion of patients achieving complete MRD response (undetectable disease) after 1 cycle of blinatumomab	RFS and OS
Secondary endpoint	Hematologic relapse-free survival (RFS) among patients at 18 months	
Background	Investigators were uncomfortable with randomizing MRD+ patients who had already received 3+ blocks of intensive chemotherapy	Assessment of MRD response was not included because of the variability in treatment regimens after documentation of MRD positive status.

Inclusion criteria

- Select patients from both studies who share similar inclusion criteria
- Note here patients' number 116 → 73 in study 203

Study 203 (BLAST)

N=73

Study 148 (Historical Comparator)

N=182

- Ph B precursor ALL in CR after 3+ intensive chemotherapy blocks
- ≥ 18 years of age at MRD baseline date
- In first remission (CR1)
- MRD at $\geq 10^{-3}$

Propensity score model

- IPTW approach for propensity score adjustment was chosen for this analysis.
- This model was completed prior to the statisticians having access to the outcomes results.
- For each analysis set, the method that provided the best overall balance with respect to the baseline covariates and the fewest impactful statistical outlying values was chosen as the primary weighting method.
- Efficacy Endpoints: RFS and OS.

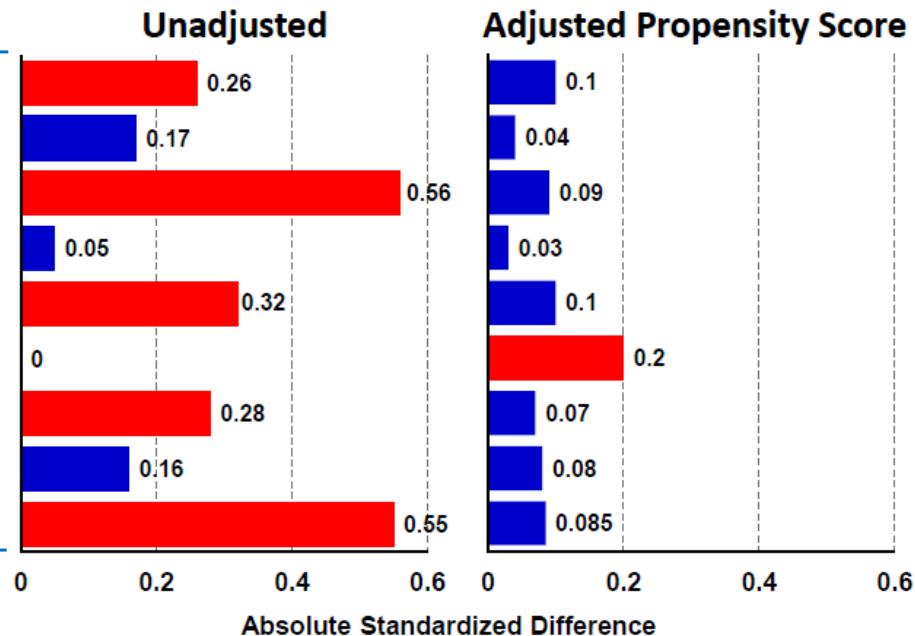
Baseline covariates

- The following prespecified covariates were identified as potentially important prognostic factors and were considered for the PS model
 - Age at primary diagnosis (years)
 - Sex (male, female)
 - Country (Germany, others)
 - Presence and type of any cytogenetic and molecular aberrations
 - Time from primary diagnosis to MRD baseline date (months)
 - Baseline MRD level
 - WBC at diagnosis ($\leq 30\,000/\mu\text{L}$, $> 30,000/\mu\text{L}$)
 - Type of prior chemotherapy (GMALL, other)
- Covariates were selected by a stepwise variable selection algorithm considering all main effects and 2-way interaction

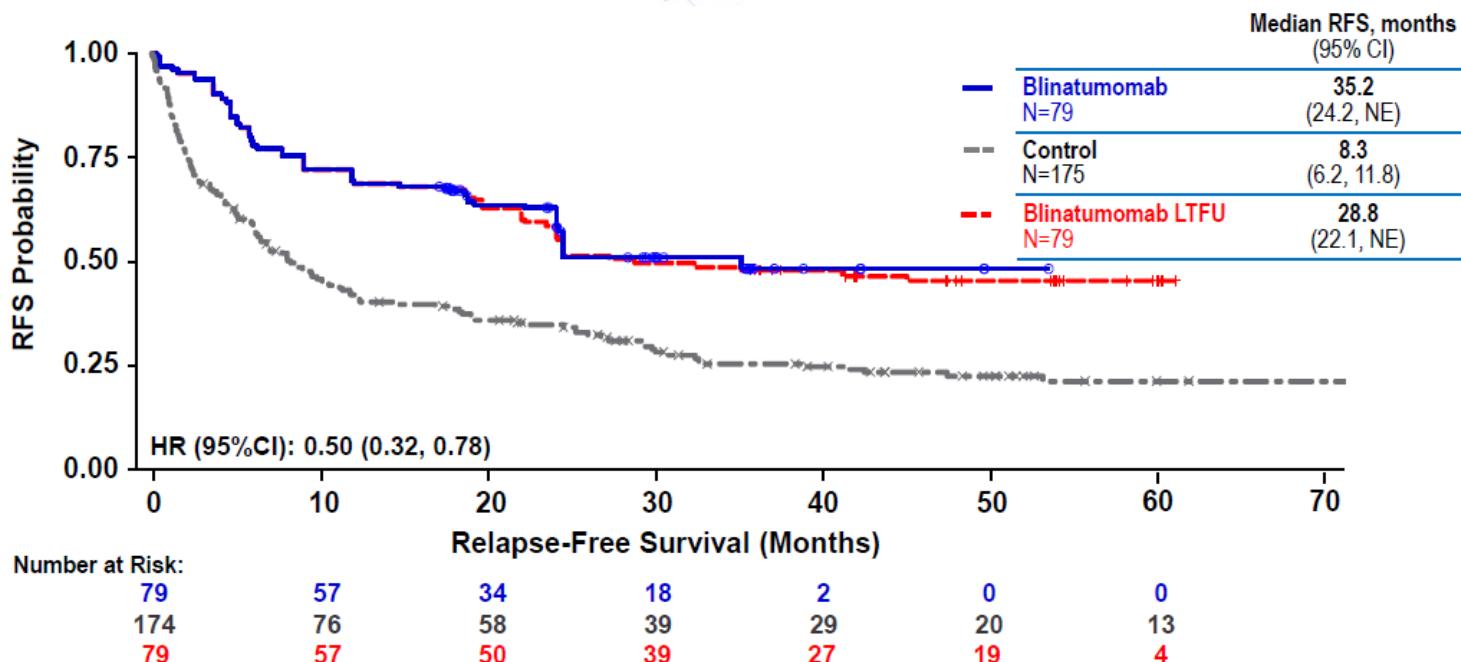
Covariates balance check

Baseline Covariates

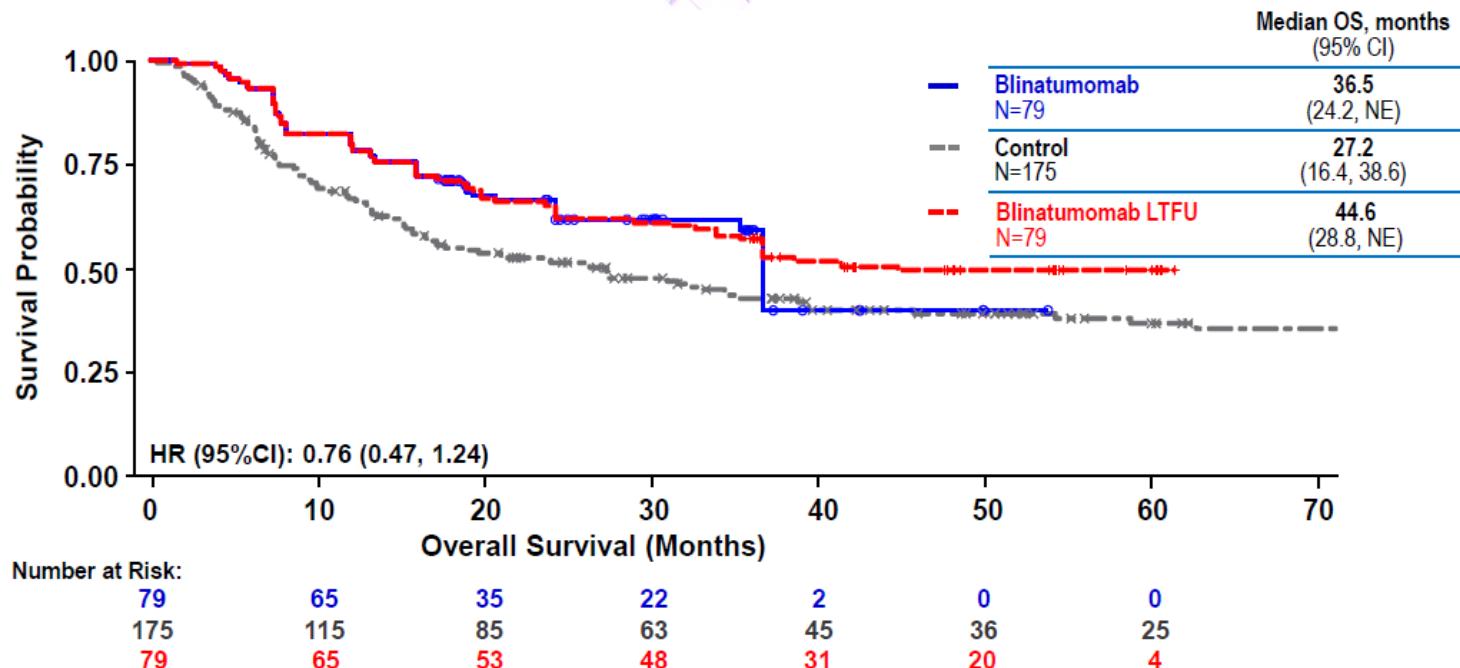
WBC at diagnosis (continuous, log10)
WBC at diagnosis ($> 30,000/\text{mm}^3$)
Time from diagnosis to baseline (months)
t(4;11) MLL-AF4 mutation (Yes)
Prior chemotherapy (GMALL)
Gender (Female)
Country (Not Germany)
MRD at Baseline (recoded)
Age at primary diagnosis (years)



RFS



OS



Sensitivity analysis

- Stabilized IPTW (sIPTW), trimmed IPTW and trimmed sIPTW were also considered.
- For primary analysis set:
 - Stabilized IPTW provided the best overall balance of baseline covariates, including age at primary diagnosis and the time from primary diagnosis to baseline MRD.
- Hematopoietic stem cell transplantation (HSCT) confounding effect

Exploratory Subgroup Analyses by HSCT (Y/N)



RFS

OS

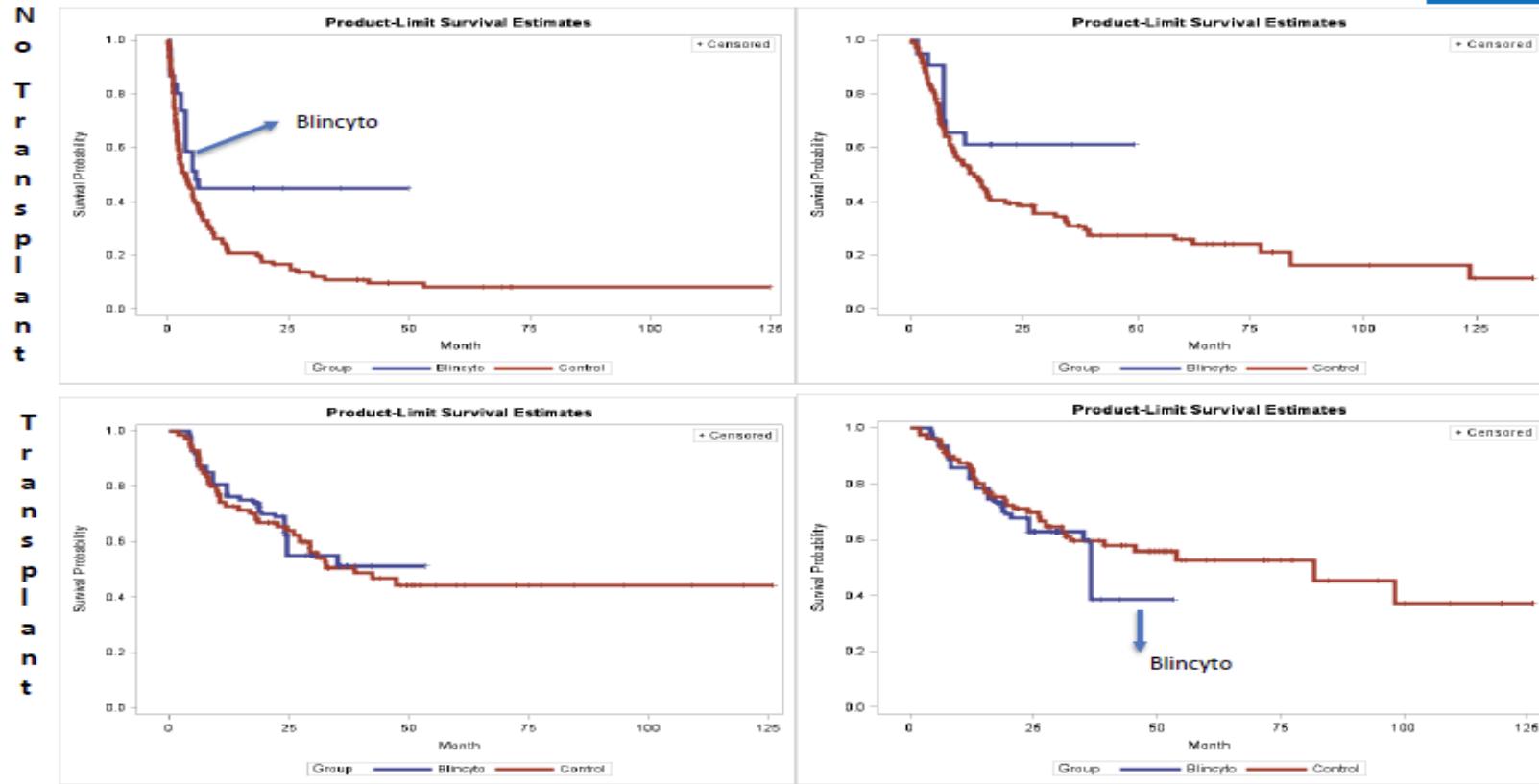


Figure 4: Kaplan Meier Curve of RFS After HSCT with Propensity-Score Adjustment

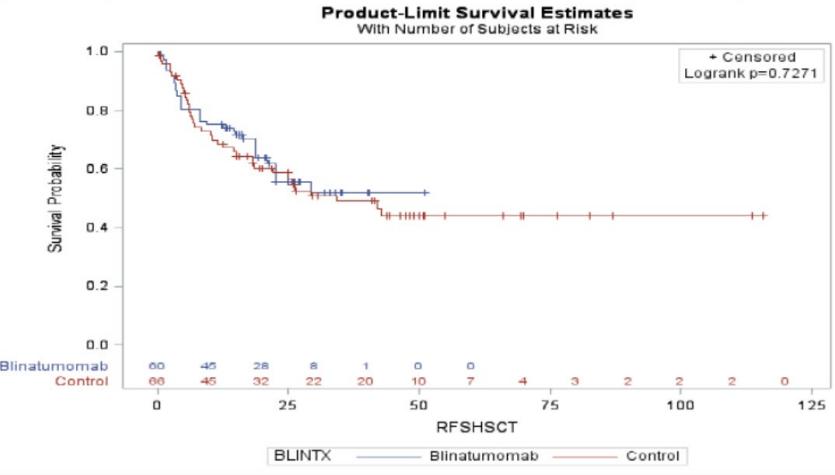
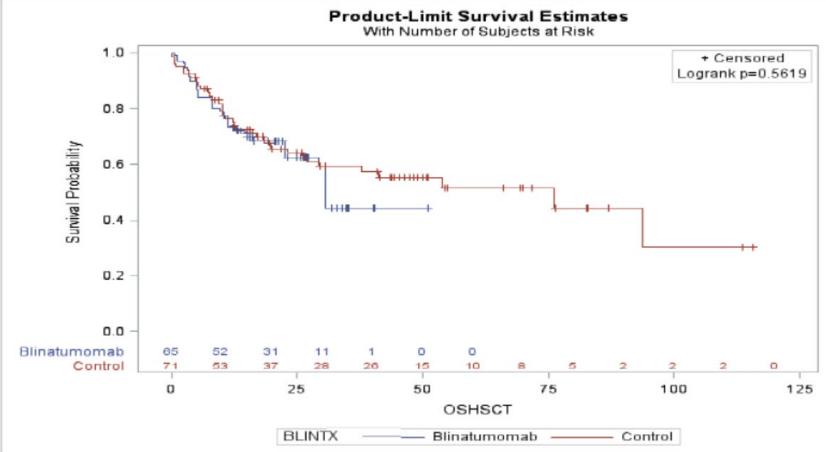


Figure 6: Kaplan Meier Curve of OS After HSCT with Propensity-Score Adjustment



Source: FDA analysis

- The Kaplan-Meier curves overlap over time
 - demonstrating there is no difference between the two treatment groups.
 - potential confounding of HSCT on the group comparison.
- Such confounding was further demonstrated by the significant study group by HSCT interaction when HSCT was defined as a time-dependent covariate based on the Cox proportional hazards model for both RFS and OS endpoints.

Results

- Propensity score analysis demonstrated
 - Significantly prolonged RFS
 - Positive OS trend compared to historical control
- However,
 - HSCT
 - Excluded patients
 - Substantial different follow up times
 - Subsequent therapy

Limitation details

- 35% of Blincyto patient data excluded
 - Patients in CR2 are included in current indication
 - Patients in CR2 of Study 203 removed to match historical control
- Confounding due to subsequent treatment
 - Study 203: 78% of Blincyto patients received HSCT
 - Study 148: 44% of control patients received HSCT
- Different median follow-up times
 - 8.2 months in Study 203
 - 18.4 months in Study 148
- Potential Confounding from HSCT

ODAC question

- 1. DISCUSSION: Study MT103-203 included patients with MRD > 0.1%. Do the available data support the cut-off of MRD > 0.1% as describing a subpopulation of patients with ALL in CR who have a need for pre-emptive therapy?
- 2. VOTE: Do the results of MT103-203 demonstrate that for patients with ALL in CR who have MRD > 0.1%, treatment with blinatumomab provides a potential benefit that outweighs the risks from the treatment?

Vote results

- Yes:8
- No:4
- Mach 7,2018

 U.S. FOOD & DRUG
ADMINISTRATION

A to Z Index

Search FD

≡ Home Food Drugs Medical Devices Radiation-Emitting Products Vaccines, Blood & Biologics Animal & Veteri

News & Events

Home > News & Events > Newsroom > Press Announcements

FDA News Release

FDA expands approval of Blincyto for treatment of a type of leukemia in patients who have a certain risk factor for relapse

[SHARE](#) [TWEET](#) [LINKEDIN](#) [PIN IT](#) [EMAIL](#) [PRINT](#)

For Immediate Release March 29, 2018

Release

The U.S. Food and Drug Administration granted accelerated approval to Blincyto (blinatumomab) to treat adults and children with B-cell precursor acute lymphoblastic leukemia (ALL) who are in remission but still have minimal residual disease (MRD). MRD refers to the presence of cancer cells below a level that can be seen under the microscope. In patients who have achieved remission after initial treatment for this

Summary



- RWD and historical data have the potential to support label expansion.
 - RWD/historical trial data could be useful if it could mimic the investigational drug arm
- Lesson learned
 - Exclude treated patients
 - Unmeasured or unknown covariates
 - Follow up time for time-to-event data
 - Substantial treatment effect

Seem easy, however

- XPOVIO (Selinexor) developed by Karyopharm Therapeutics was accelerated approved in 2018.
- However, the RWD part was not fully supported by FDA.
- Indication: relapse refractory multiple myeloma (RRMM)
- Primary endpoint: ORR 25.4% CI [18%, 34.1%]
- Secondary endpoint: DOR 4.4 months [0.8, 9]
- Disclaimer: all the following comments are from FDA multi-discipline review document and they did not reflect my personal opinion.



ODAC Briefing Document

NDA 212306
Selinexor

FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting
February 26, 2019

NDA 212306
Selinexor

Applicant: Karyopharm Therapeutics, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the Selinexor NDA to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Document submission timing

performed to generate evidence for regulatory decision-making. To enhance transparency and facilitate evaluation of validity, FDA requires submission of study protocols and statistical analysis plans (SAP) prior to study initiation. Pre-specification of study protocols and SAPs can preclude unplanned multiple testing and analyses, which may inflate Type I error probability and lead to spurious or un-reproducible findings. In support of NDA 212306 for selinexor, the Applicant submitted analyses using retrospectively collected electronic health record (EHR) data. However, neither the protocol or SAP for the selinexor RWD analysis was submitted to FDA prior to the conduct of the study. FDA was made aware of Study KS-50039 upon receiving the final study report on October 6, 2018.

Without having reviewed and consented to a protocol and SAP, FDA cannot be certain that the protocol and SAP were pre-specified and unchanged during the data selection and analyses. Further, upon receipt of the NDA and the RWD study, FDA requested the Applicant address several issues that presented challenges for comparison of the two study samples. These issues, and how the Applicant addressed them, are discussed in more detail below. The summary of FDA's information requests (IR) and the Applicant's response to FDA IRs are

Selection Criteria Issues

In the Applicant's original NDA submission, a total of 64 patients were selected from the Flatiron Health Analytic Database (FHAD). The inclusion and exclusion criteria used to identify patients for Part 2 of STORM and the FHAD analysis are compared side by side in Table 31 (see Appendix 13.5 for full eligibility criteria for STORM Part 2), and the selection steps used to identify the FHAD cohort are shown in Figure 6. Substantial differences in the inclusion and exclusion criteria for the STORM and FHAD cohorts are likely to result in selection bias, misclassification, and confounding. For example, the Applicant cited real-world OS of patients

Continue

STORM	FHAD
Inclusion Criteria	
<p>Histologically confirmed diagnosis, measurable disease and evidence of disease progression. Symptomatic MM based on IMWG guidelines.</p> <p>Measurable disease as defined by at least one of the following:</p> <ol style="list-style-type: none"> 1. Serum M-protein $\geq 0.5\text{g/dL}$ by serum electrophoresis (SPEP) or for IgA myeloma, by quantitative IgA; or 2. Urinary M-protein excretion at least $200\text{mg}/24\text{ hours}$; or 3. Serum Free Light Chain (FLC) whereby the involved light chain measures $\geq 10\text{ mg/dL}$ and with an abnormal light chain ratio. 	<ol style="list-style-type: none"> 1. International Classification of Diseases (ICD) diagnosis of MM (ICD-9 203.0x or ICD-10, C90.0x, C90). 2. 2+ documented clinical visits on or after 01/01/2011. 3. Pathology consistent with MM.
Patient must have received ≥ 3 anti-MM regimens including the following: an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib and a glucocorticoid.	Treatment with lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab (i.e. Penta-exposed).
N/A	Treatment initiation no more than 30 days before the start of structured activity (excludes patients with potentially missing structured Flatiron data).
Multiple myeloma refractory to the patient's most recent anti-MM regimen.	Documentation of having MM refractory to (1) at least 1 PI (bortezomib or carfilzomib), (2) at least 1 IMiD (lenalidomide or pomalidomide), and (3) daratumumab.
Laboratory data establishing: <ol style="list-style-type: none"> 1. Adequate hepatic functioning 2. Adequate renal functioning 3. Adequate hematopoietic function 	No similar criteria.
Exclusion Criteria	
Life expectancy < 4 months	No similar criteria.

Index date issue

The index dates were originally defined as follows:

- FHAD: the end date of the regimen for which the patient's MM may first be defined as penta-exposed. (Note, this date could be earlier than the date on which the patient's MM could be defined as triple-class refractory)
- STORM: the progression date of the last line of therapy prior to selinexor initiation
(Note, all STORM patients were penta-exposed, triple-class refractory)

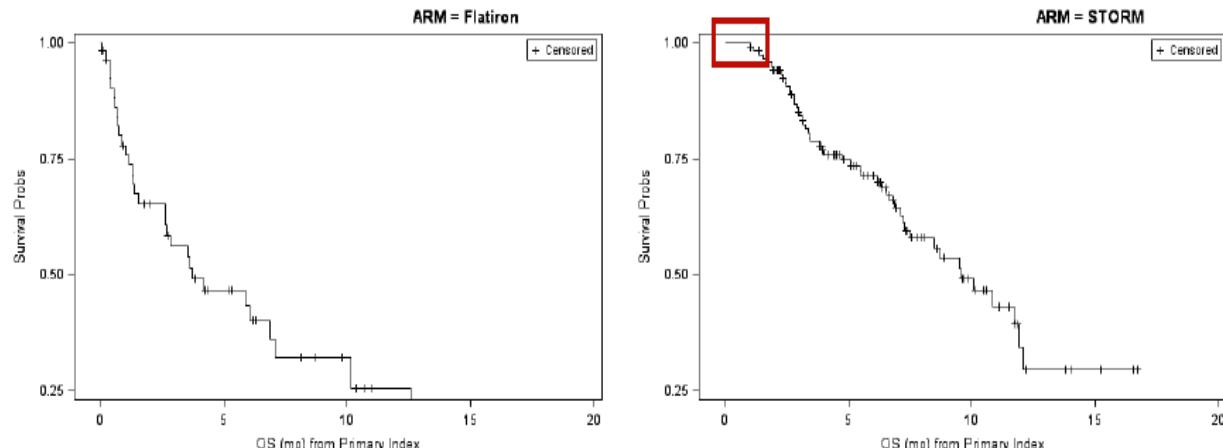
The index date to start assessment of overall survival, for both the STORM trial and FHAD, was the date upon which a patient failed his or her last treatment. Using this index date, some FHAD patients could have exhausted all treatment options and could not be indexed at their next treatment (note that 27/64 FHAD patients had no subsequent treatment and should have been excluded from the study). However, in STORM, all patients must survive until randomization (initiation of selinexor) by design. Thus, person-time between failure of the prior therapy and randomization is “immortal” by design in STORM. It is unknown how many

Continue

- For patients to be in the selinexor treatment arm, they are required to have lived long enough to enroll on the study.
- Even OS hazard ratio is 0.41 (0.26,0.65)

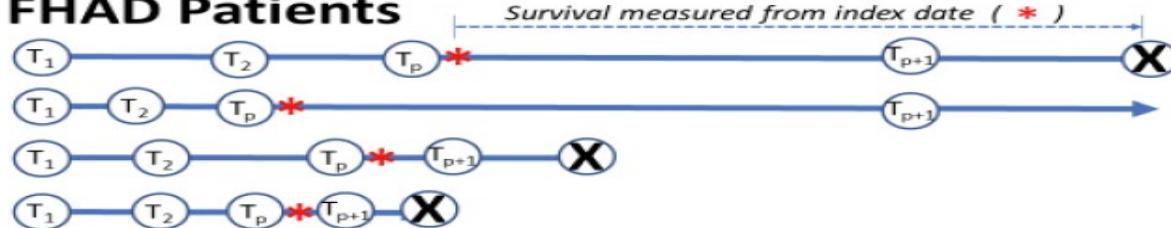
months of immortal time this represents on average. From the survival plot below (Figure 7), the first outcome/censoring event in the STORM trial appears to be at approximately 1.2 months. At this time, approximately 22% of the FHAD patients had died or been censored (highlighted in red in Figure 7).

Figure 7: Unadjusted OS by Study Population

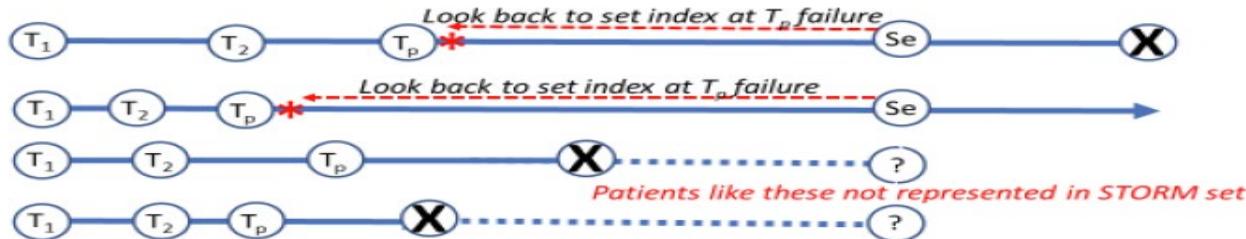


Note: Red box represents minimum level of immortal time bias.
(Source: FDA Analysis)

FHAD Patients



STORM Patients



(Source: FDA)

In Figure 8 (above), each line represents a hypothetical patient; the circles containing letters represent treatment regimens; T_p represents the treatment after which a patient may be considered triple-class refractory; X represents death. The index date is set at treatment T_p failure for all patients. To set the index date for patients in STORM according to the above definition, one must look back into the patients record to determine the failure date of the previous regimen. This requirement excludes patients who do not live long enough to enroll in STORM. In contrast, patients with short survival times are not systematically excluded from the FHAD set.

Comparability issue

Parameter	FHAD (N=64)	STORM (N=122)
<i>Age (years)</i>		
Mean (SD)	66.2 (9.3)	63.8 (9.3)
<i>Sex, n (%)</i>		
Male	33 (51.6)	71 (58.2)
Female	31 (48.4)	51 (41.8)
<i>Race, n (%)</i>		
White	38 (59.4)	78 (69.3)
Non-White	26 (40.6)	44 (36.1)
<i>Prior Therapy</i>		
Carfilzomib, pomalidomide, and daratumumab	34 (53.1)	117 (95.9)
Median number of prior regimens (min, max)	5 (2, 8)	7 (3, 18)
Daratumumab as last line prior to index date, n (%)	43 (67.2)	58 (47.5)
Exposed to anthracyclines prior to index date, n (%)	7 (10.9)	45 (36.9)
Exposed to alkylating agent prior to index date, n (%)	41 (64.1)	122 (100)
Stem cell transplant prior to index date, n (%)	38 (59.4)	102 (83.6)
<i>Immunoglobulin Subtype</i>		
IgA or IgM, n (%)	16 (25)	18 (14.8)
<i>ECOG Performance Status, n (%)</i>		
0	4 (6.3)	37 (30.3)
1	33 (51.6)	71 (58.2)

2	7 (10.9)	11 (9)
Missing	20 (31.3)	3 (2.5)
<i>R-ISS, n (%)</i>		
I	11 (17.2)	20 (16.4)
II/Unknown	50 (78.1)	79 (64.8)
III	3 (4.7)	23 (18.9)

Summary



- ODAC Opinion: “The RWD analyses of the [external comparator] population were **not prespecified** and have **major methodological issues**. The results of the [external comparator study] are difficult to interpret due to these limitations, and therefore, are **not acceptable** as supportive evidence for the NDA.
- Study protocol and statistical analysis plan was not submitted to the FDA for review **prior to the execution of the study**.
- Selection of the External Comparator Population: **Differences in the IC/EC** leading to selection bias as well as differences in data availability and misclassification of missing data.
- Operational Definitions of Data Fields: Definitions of key variables introduced bias into the analysis, **particularly the “index date.”**

4. Practical considerations of using RWD/historical data in the clinical development

- Patient populations/data
- Endpoints
- Propensity score methods
- Practical implementation flow
- Sensitivity analysis



Practical considerations of utilizing propensity score methods in clinical development using real-world and historical data

Qing Li*, Jianchang Lin, Andy Chi, Simon Davies

Statistical and Quantitative Sciences, Takeda Pharmaceuticals, 300 Massachusetts Ave, Cambridge, MA 02139, United States

ARTICLE INFO

Keywords:
Propensity score
Real-world-data (RWD)
Real-world-evidence (RWE)
Historical data
External control
Natural history study
Drug development

ABSTRACT

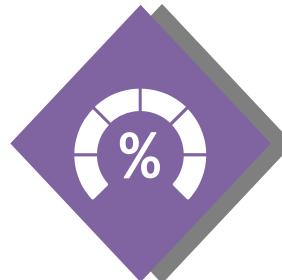
In recent years, with the rapid increase in the volume and accessibility of Real-World-Data (RWD) and Real-World-Evidence (RWE), we have seen the unprecedented opportunities for their use in drug clinical development and life-cycle management. RWD and RWE have demonstrated the significant potential to improve the design, planning, and execution of clinical development. Furthermore, they can feature in the designs as either a substitute or complement to traditional clinical trials. However, to utilize RWD and RWE appropriately and wisely, it is critical to apply rigorous statistical methodologies that enable the robustness of results to be characterized and ascertained. Several statistical methodologies including exact matching, propensity score methods, matching-adjusted indirect comparisons and meta-analysis have been proposed for analyzing RWD. Among them, propensity score method is one of the most commonly used methods for non-randomized trials with indirect comparison. Although massive methodologies and examples have been published and discussed since propensity score methods were introduced, systematic review and discussion of how to rigorously use propensity score methods in the practical clinical development is still deficient. This paper introduces commonly used and emerging propensity score methods with detailed discussions of their pros and cons. Three different case studies are presented to illustrate the practical considerations of utilizing propensity score methods in the study design.

Select comparable external data sources



- Identify external patient populations with baseline characteristics (sex, age, demographics, region, treatment history, etc.) similar to those of the treatment group
- Ensure reliable data accrual processes (e.g., data documentation, methods, time window, etc.) and valid quality control

Match outcome measures and endpoints



- Ensure the same outcome measures between SCAs and treatment arms
- Strategically choose endpoints and outcome measures (e.g., DOR¹ vs. ORR² in the Bavencio case³) that demonstrate meaningful clinical effects

1. DOR – Duration of response; 2. ORR – Objective response rate; 3. In the Bavencio case study, the similar ORRs were found between the treatment arm and the SCA. Nevertheless, the treatment arm resulted in a significantly higher DOR than the SCA.

The right study and right patient population

To mimic randomized trial and reduce bias, subjects in the two arms must have similar baseline characteristics

Selection must include the exact same

- ① Eligibility requirement
- ② Inclusion / exclusion criteria
- ③ Medical condition
- ④ Prior lines of treatment
- ⑤ Clinical endpoint evaluation
- ⑥ Disease severity, duration of illness
- ⑦ Any other aspect of the disease that could affect outcome and timing of outcomes



However, there are some key challenges in achieving this, so trial teams should plan ahead

- Limited availability of relevant historical studies and RWD¹ when considering all the selection factors
- Difficulty getting access to patient level data due to platform or privacy restrictions (especially in EU)
- Lower quality of data standardization for RWD and historical data compared to randomized clinical trials
 - e.g., inconsistent definition of baseline variables and endpoints

1. RWD – Real world data

Critical considerations for outcome measure and endpoint selection



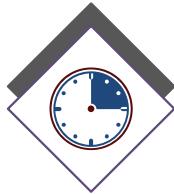
Ideally, select objective and robust endpoints (e.g., OS¹) for SCA studies

Time to event endpoint data (e.g., OS¹)



- Variability in follow-up times can affect the maturity of summary statistics
- Subsequent therapies can be confounding as they might prolong OS
- Inaccurate definition of index date or "time zero date" could induce a huge bias (e.g., for a first-line treatment setting, the index date should be the initiation of first-line treatments, while for a relapsed / refractory setting, the index date should be the start of second-line treatments)

Short-term surrogate endpoints (e.g., ORR², MRD-negative³)



- Require demonstrating strong correlation between short-term endpoint and long-term time to event endpoint
- Additionally, endpoints based on tumor assessment such as PFS⁴ or ORR may use different criteria or assessment schedule and will require adopting independent verification or judgment of the assessment for both arms to ensure consistency

Rare disease-specific endpoints (e.g., CLN2 rating scale⁵)



- Due to the limited knowledge of the disease, endpoints can evolve frequently and become difficult to standardize
- Endpoint discrepancies between studies and lack of standardization, such as functional score defined by a clinician, will require independent re-evaluation and additional sensitivity analysis

1. OS – Overall survival; 2. ORR - Objective response rate; 3. MRD - Minimal residual disease, MRD-negative meaning no disease was detected after treatment; 4. PFS - Progression-free survival; The CLN2 is structured so that a score of 3 indicates a normal condition, 2 is a slight or just noticeable abnormality, 1 is a severe abnormality, and 0 denotes a complete loss of functioning.

3 common types of statistical methods

for reducing sample bias between treatment and external control arms



Matching-adjusted indirect comparison (MAIC)

- Applicable to compare trials with IPD¹ to previously reported studies without IPD
- Assign weights to patients in trials with IPD such that their weighted mean baseline characteristics match those in published studies with only aggregate data

Propensity score (PS) methods

- Balance baseline covariates between treated and external control arms via PS when exact matching of every variable is not feasible
- Include three typical methods: PS matching, PS stratification, and IPTW²

Exact matching

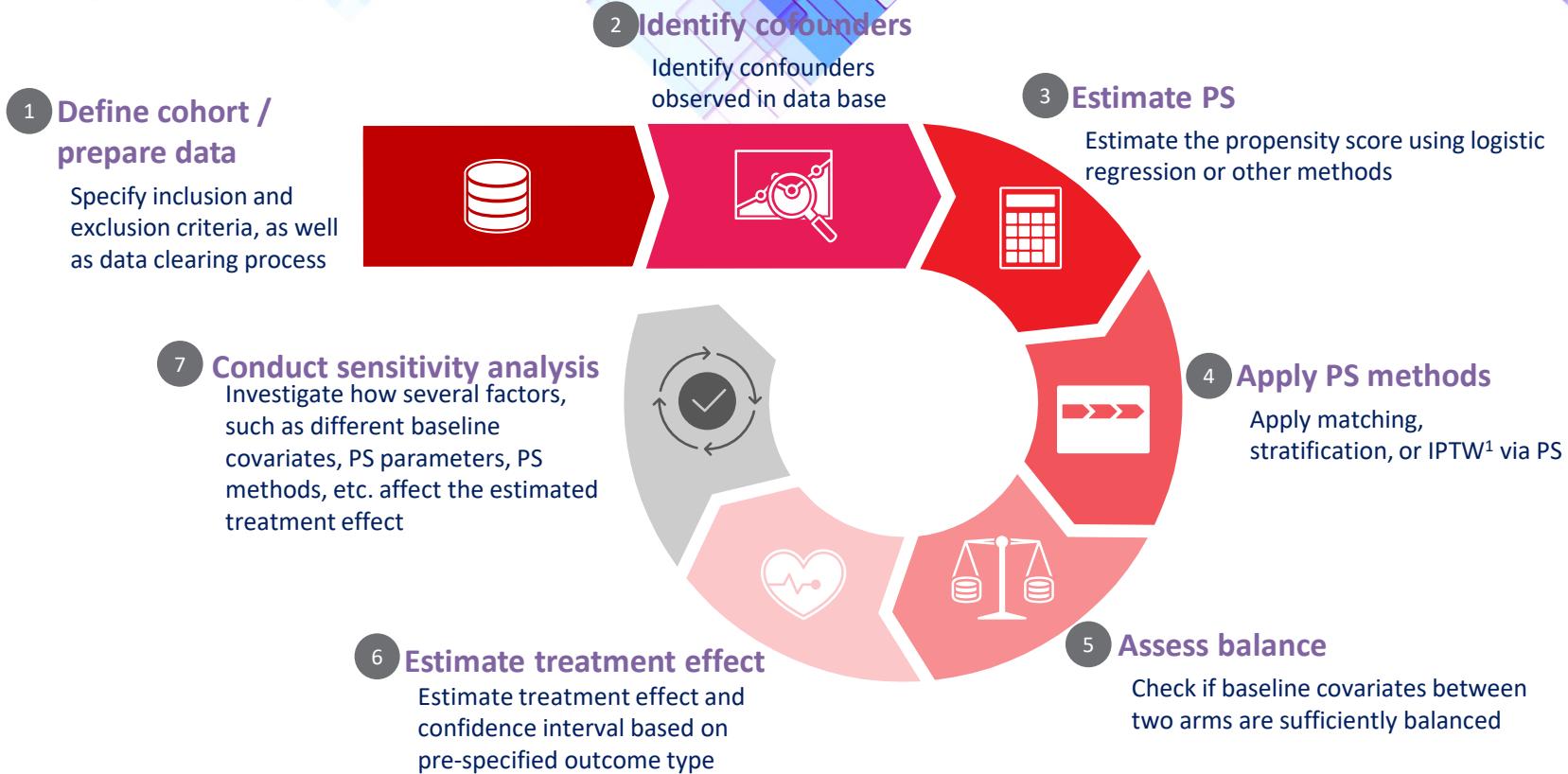
- Match subjects in the treated and control group based on a few matching variables
- Intuitive when the treated and external control group have highly similar baseline covariates, and the number of matching variables is small

1. IPD – Individual patient data; 2. IPTW – Inverse probability treatment weighting

Source: Q. Li, J. Lin, A. Chi, S. Davies, "Practical considerations of utilizing propensity score methods in clinical development using real-world and historical data," *Contemp. Clin. Trials* (2020);

Signorovitch, et al. "Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research," *Value in Health* (2012)

Propensity score (PS) analysis flow



1. IPTW – Inverse probability treatment weighting

Pros and cons of the three main types of PS methods



Matching

- ✓ **Pros**
- Select patients that are best matched in PS¹
 - Have intuitive concept that is easy to perform and interpret

- ✗ **Cons**
- May lead to selection bias when choosing only matched subjects
 - May require a large external patient group

★ **Ideal design**



Stratification

- Include all patients and provide an objective approach for analysis
- Does not require a large sample size for external patients

- Require the two groups' PS distributions fall within a reasonable range
- May result in unbalanced subjects within each stratum

- Create a SCA based on a large pool of external patients
- Construct a SCA from studies with a similar design and patient population as the treated arms



IPTW²

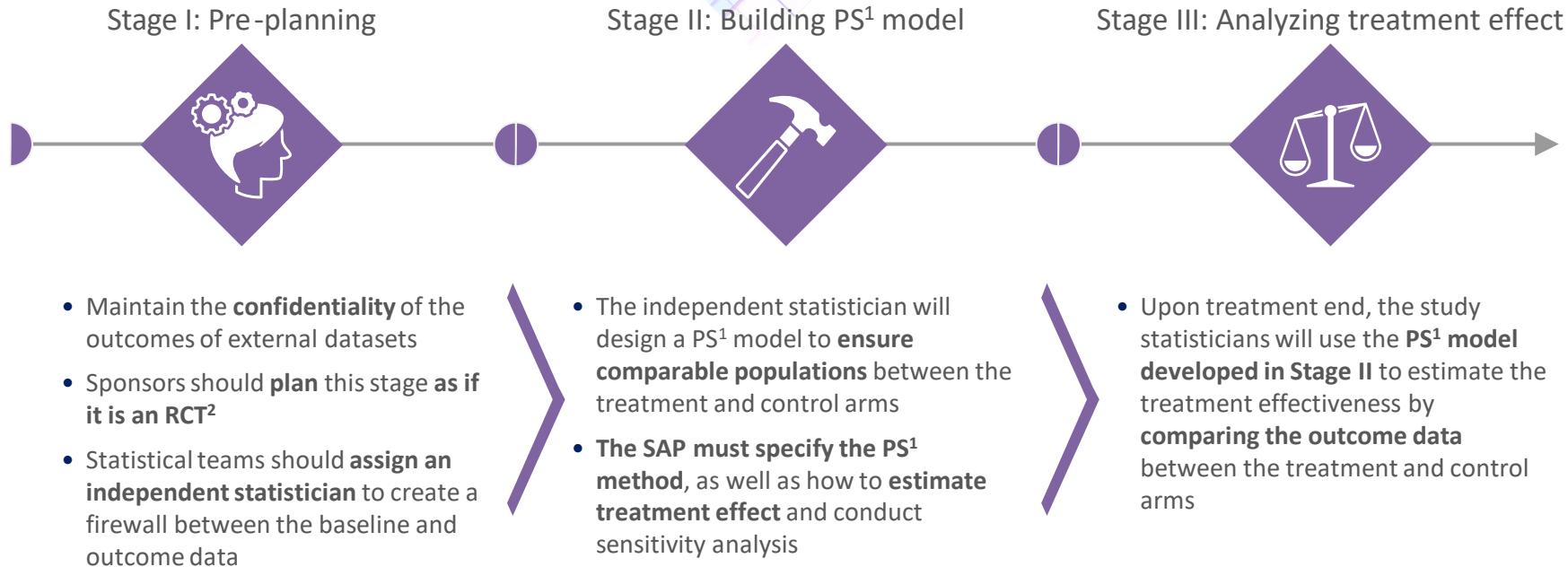
- Include all patients and provide an objective approach analysis
 - Less affected by the variation in sample size
-
- Not applicable to significantly divergent PS values as they affect treatment effect estimation
-
- Require homogeneous baseline covariates for all subjects (in both treated and external groups), where no significant outliers exist

1. PS – Propensity score; 2. IPTW – Inverse probability treatment weighting

Source: Q. Li, J. Lin, A. Chi, S. Davies, "Practical considerations of utilizing propensity score methods in clinical development using real-world and historical data," *Contemp. Clin. Trials* (2020);

Kristian, et al. "Synthetic and external controls in clinical trials—a primer for researchers," *Clinical Epidemiology* (2020)

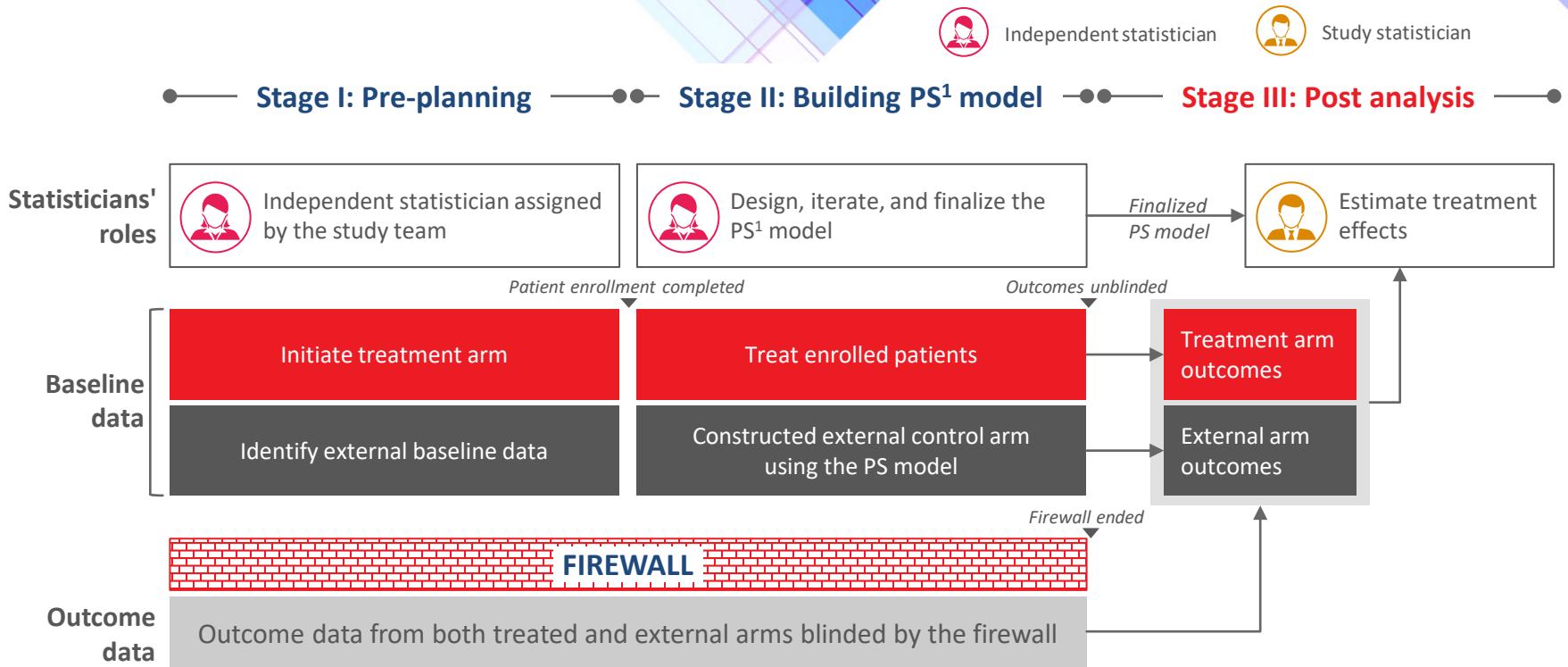
Implementation of PS methods



1. PS – Propensity score; 2. RCT – Randomized clinical trial; 3. SAP – Statistical analysis plan

Source: Q. Li, J. Lin, A. Chi, S. Davies, "Practical considerations of utilizing propensity score methods in clinical development using real-world and historical data," *Contemp. Clin. Trials* (2020)

Illustration of the implementation flow of methods



Sensitivity analysis

Why is sensitivity analysis necessary?

Incomplete baseline covariates

- Estimated treatment effects from a PS model are unbiased only if all relevant baseline covariates are considered



Missing values in baseline covariates

- The sample size of evaluable PS dataset is smaller than expected due to removing subjects with missing baseline covariate values



Different baseline covariates for calculating PS

- The choice of baseline covariates for calculating PS will affect downstream PS methods and final treatment effect estimation



Different PS methods

- Each PS method has its unique benefits and limitation (as discussed in the previous slide)



Different tuning parameters of PS methods

- Several critical tuning parameters can significantly impact the PS matching and stratification results²



How to drive the sensitivity analysis?

Analyze unmeasured baseline covariates

- Conduct sensitivity analysis on unmeasured baseline covariates to test the robustness of the estimated treatment effects

Assign new values to the baseline covariates

- Assign values to the baseline covariates¹ and reconstruct the PS model to conduct the analysis and compare the results

Add, change, or delete certain PS variables

- Re-calculate PS distribution after adding, changing, or deleting certain baseline covariates and examine their impact on results

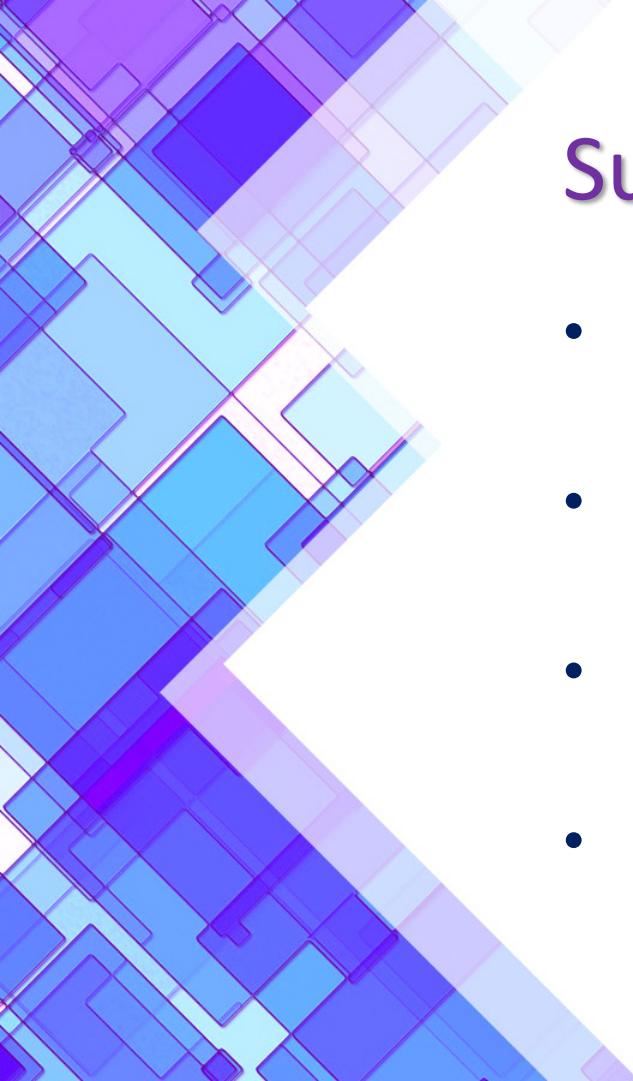
Benchmark with other PS methods

- Adopt other PS methods to conduct analysis with identical input data and probe how estimated treatment effects differ

Modify the parameters of the PS method

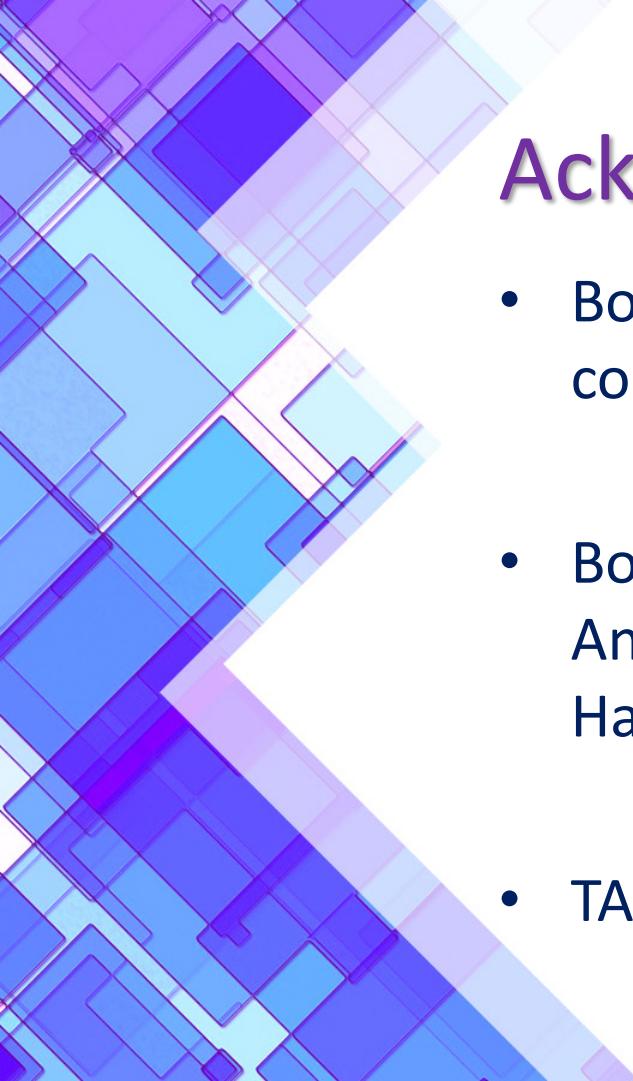
- Change the tuning parameters to examine the robustness of the model and its estimation of treatment effect

1. Methods to assign new values include using mean or median for continuous variables and randomly assigning responders using the distribution parameters calculated by the complete cases for categorical variables. 2. E.g., caliper distance in the optimized matching method, number of strata in propensity stratification



Summary

- RWD and historical data have been playing an important role in clinical development
- Turn valuable data into evidence still need careful considerations
- RWE has tremendous opportunities to accelerate and improve drug development
- Next RWD opportunities TA: gene/cell therapy, vaccine, CNS



Acknowledgement

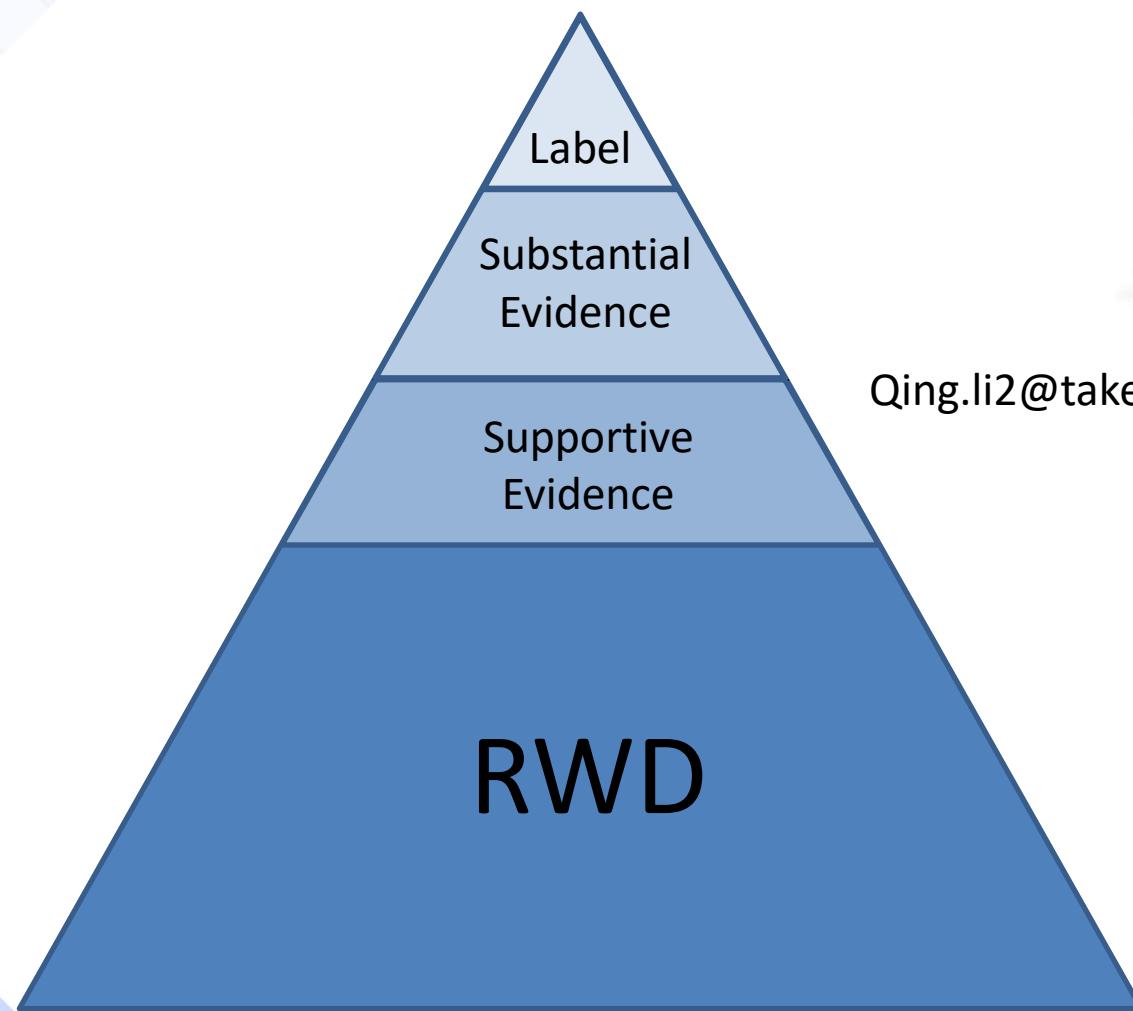
- Boston Pharmaceutical Symposium organizing committee: Kristin Baltrusaitis and Olga Vitek
- Book contributor and editors: Jianchang Lin, Andy Chi, Simon Davis, Gary Chen, BinBing Yu, Harry Yang, Bo Lu
- TAK-788 development team

Reference

- Food and Drug Administration [FDA]. 2014a. Guidance for industry: expedited programs for serious conditions – drugs and biologics. <https://www.fda.gov/media/86377/download>
- Food and Drug Administration [FDA]. 2014b. Guidance for industry: rare diseases: common issues in drug development. <https://www.fda.gov/media/119757/download>
- Food and Drug Administration [FDA]. 2015. Statistical review: application number 125513Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125513Orig1s000MedR.pdf
- Food and Drug Administration [FDA]. 2017a. FDA briefing document oncologic drugs advisory committee meeting: BLA 125557 S-013, Blincyto (blinatumomab). <https://www.fda.gov/media/111622/download> [AQ17]
- Food and Drug Administration [FDA]. 2017b. Multi-discipline review: application number 761049Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000MultidisciplineR.pdf
- Food and Drug Administration [FDA]. 2017c. Statistical review: application number 761052Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761052Orig1s000StatR.pdf
- Food and Drug Administration [FDA]. 2018a. Framework for FDA's real-world evidence program, 2018. <https://www.fda.gov/media/120060/download>

Reference

- Food and Drug Administration [FDA]. 2018b. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. <https://www.fda.gov/media/71195/download>
- Food and Drug Administration [FDA]. 2019a. Guidance for industry: rare diseases: natural history studies for drug development.<https://www.fda.gov/media/122425/download>
- Food and Drug Administration [FDA]. 2019b. Guidance for industry: submitting documents using real-world data and real-world evidence to FDA for drugs and biologics. <https://www.fda.gov/media/124795/download>
- Food and Drug Administration [FDA]. 2019. Statistical review: application number 212306Orig1s000 https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212306Orig1s000MultidisciplineR.pdf
- Horn, Leora, Huamao Mark Lin, Sukhmani Kaur Padda, Charu Aggarwal, Caroline Elizabeth McCoach, Yanyan Zhu, Yu Yin et al. "Indirect comparison of TAK-788 vs real-world data outcomes in refractory non-small cell lung cancer (NSCLC) with EGFR exon 20 insertions." ASCO (2020): 9580-9580.
- Huang, B., Tian, L., McCaw, Z. R., Luo, X., Talukder, E., Rothenberg, M., ... & Wei, L. J. (2020). Analysis of response data for assessing treatment effects in comparative clinical studies. *Annals of Internal Medicine*, 173(5), 368-374.
- Yang, H., & Yu, B. (Eds.). (2021). Real-world Evidence in Drug Development and Evaluation. CRC Press.
- Li, Q., Lin, J., Chi, A., & Davies, S. (2020). Practical considerations of utilizing propensity score methods in clinical development using real-world and historical data. *Contemporary Clinical Trials*, 106123. <https://doi.org/10.1016/j.cct.2020.106123>



Qing.li2@takeda.com