Strategies to Overcome Challenges of Eligibility Criteria for Historical Data as External Control Arm Source

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EUROPEAN FEDERATION OF STATISTICIANS IN THE PHARMACEUTICAL INDUSTRY
Representing Statistical Associations in Europe

Identifying the challenges of eligibility criteria and prioritizing trade-offs

Explicit / “visible”

- Inclusion / exclusion criteria
- Confounding factors

Implicit / “Hidden”

- Inclusion / exclusion criteria
- Confounding factors

Identifying the challenges of eligibility criteria and prioritizing trade-offs

Explicit / “visible”

Challenges for comparability

- Availability of I/E criteria
- Disease severity beyond “hard” measurements
- Baseline definition relying on stable condition / underlying therapy
- Other prognostic factors
- Changes in standard of care
  Diagnosis / Definitions / Treatment / Supportive care

Identifying the challenges of eligibility criteria and prioritizing trade-offs

Implicit / “Hidden”

Considerations influencing comparability

- Differences in clinical practice
  - Tertiary centers vs community centers
  - Post-discharge care (rehab)
  - Regional guidelines (hypertension)
- Disease severity assessment
  - Methods of assessment
  - Hospital admission criteria

Mitigating challenges with prospective data collection

Addressed challenges

- ✓ Prospectively defined I/E criteria
- ✓ Standardized and longitudinal outcome assessments
- ✓ Imaging and other biomarkers

Remaining challenges

- ❖ Concomitant medications
- ❖ Dose modifications
- ❖ Changes in standard of care
- ❖ Residual confounding

Time Period ⇔ Geography

Confounding factors ⇔ Sample size

Imaging and biomarkers ⇔ Sample size

ADNI
Alzheimer's Disease Neuroimaging Initiative

C-Path Institute Duchenne Natural History Study

CITIZEN

Mitigating challenges with RCT data

Addressed challenges

- ✓ Prospectively defined I/E criteria
- ✓ Standardized and longitudinal outcome assessments
- ✓ Imaging and other biomarkers
- ✓ Specific criteria (e.g. liver biopsy in MASH)
- ✓ Baseline measures
- ✓ Concomitant medications
- ✓ Intercurrent events

Remaining challenges

- ❖ Changes in standard of care
- ❖ Residual confounding

Time Period ⇔ Geography

Critical Path for Alzheimer's Disease

Integrated Parkinson's Database

Cystic Fibrosis External Control Repository

The Forum for Collaborative Research MASH Placebo Database

Further steps to mitigate risk of bias

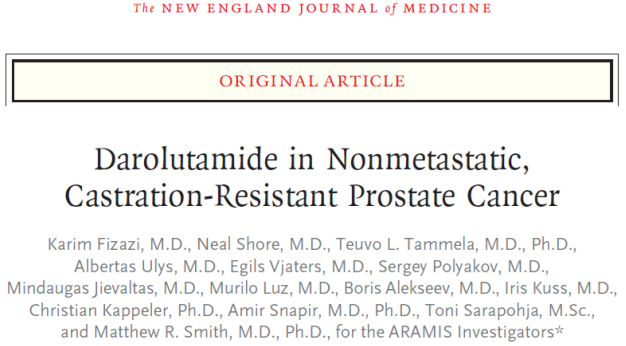
- Considering “hidden” factors in the process of historical data selection
- Identifying biases that can and can not be mitigated by statistical methods
- Defining and applying the same I/E to historical data by independent / blinded team
- Pre-defining SAP with pre-planned modifications
  - Anticipating challenges (e.g. missing confounding factors)
  - Pre-specifying actions (e.g. dropping some I/E criteria / confounding in prespecified order)
  - Pre-specifying sensitivity analysis
- Contextualizing findings
  - Other data and Literature
  - Meta-analytic prior accounting for heterogeneity
  - Evaluating sensitivity across the range of “skepticism”
- Collaborating on public-private initiatives to create high-quality databases

Post Approval Commitment Study: Single Arm Trial in China

Alfredo Farjat (Bayer)

Acknowledgment to Marie Aude Le Beurre

Clinical and Regulatory Context



Darolutamide Pivotal Trial and Post Approval Commitment (PAC) Study in China

- **ARAMIS**: randomized, double-blinded, placebo-controlled phase III study to evaluate efficacy and safety of darolutamide versus placebo in addition to standard androgen deprivation therapy (ADT) for participants with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC)
- **Primary endpoint**: metastasis free survival (MFS)
- **Recruitment / cutoff primary analysis**: from Sept 2014 to Feb 2018 / Sept 2018
- **Approval in US and EU**: FDA in July 2019, EMA in March 2020
- **Limitation**: pivotal trial did not include Chinese participants
- **Challenge**: extend regulatory approval to Chinese patients
- **Approval in China**: the center of drug evaluation (CDE) of the National Medical Products Administration (NMPA) **granted conditional approval** for darolutamide based on the findings of ARAMIS trial, contingent upon the provision of evidence pertaining to Chinese subjects

Original Design – RCT in China

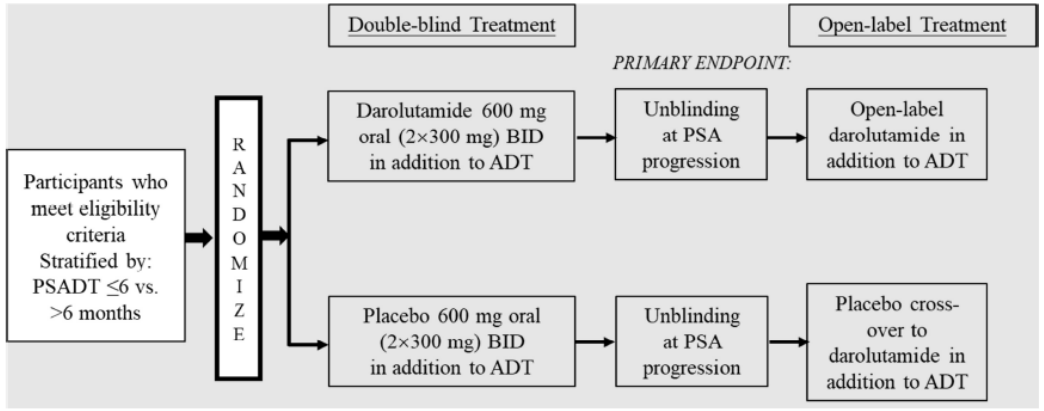
Protocol as of May 2020

Design: randomized, double-blinded, placebo-controlled Phase 2 trial of darolutamide vs placebo in addition to standard androgen deprivation therapy (ADT) for participants with high-risk nmCRPC, **N≈102 pts**

Primary endpoint: time to prostate specific antigen (TTPSA) progression

Expected follow-up: 36 months - then open-label/cross-over

Figure 4–1 Study design (before primary completion)* [a] [b]



* Participants who are ongoing with study intervention (treatment) at primary completion will be unblinded at that time.
[a] Participants will be randomized 2:1 active treatment: placebo
[b] Participants receiving darolutamide at the time of PSA progression will only continue open-label darolutamide if, in the opinion of their Investigator, they are still clinically benefitting from treatment.
Abbreviations: ADT=Androgen deprivation therapy, BID=Twice a day, PSA=Prostate-specific antigen, PSADT=Prostate-specific antigen doubling time

Recruitment rate was very low because of the placebo arm

There were other comparable drugs available in the Chinese market

Bayer proposes a modified study design (single-arm trial (SAT)) and recommends **creating external comparator arm from the ARAMIS** patient population.

Proposal: Single Arm Trial (SAT) in China

Protocol Amendment 3 as of July 2023

Design: single-arm, open-label, Phase 2 study of darolutamide in addition to standard androgen deprivation therapy (ADT) for participants with high-risk nmCRPC, **N≈70 pts**

Primary endpoint: prostate-specific antigen (PSA) response rate of ≥50% decline from baseline

Expected follow-up: 36 months

External control arm: created by selecting patients via propensity score matching (PSM) from the ARAMIS placebo arm (N=554)

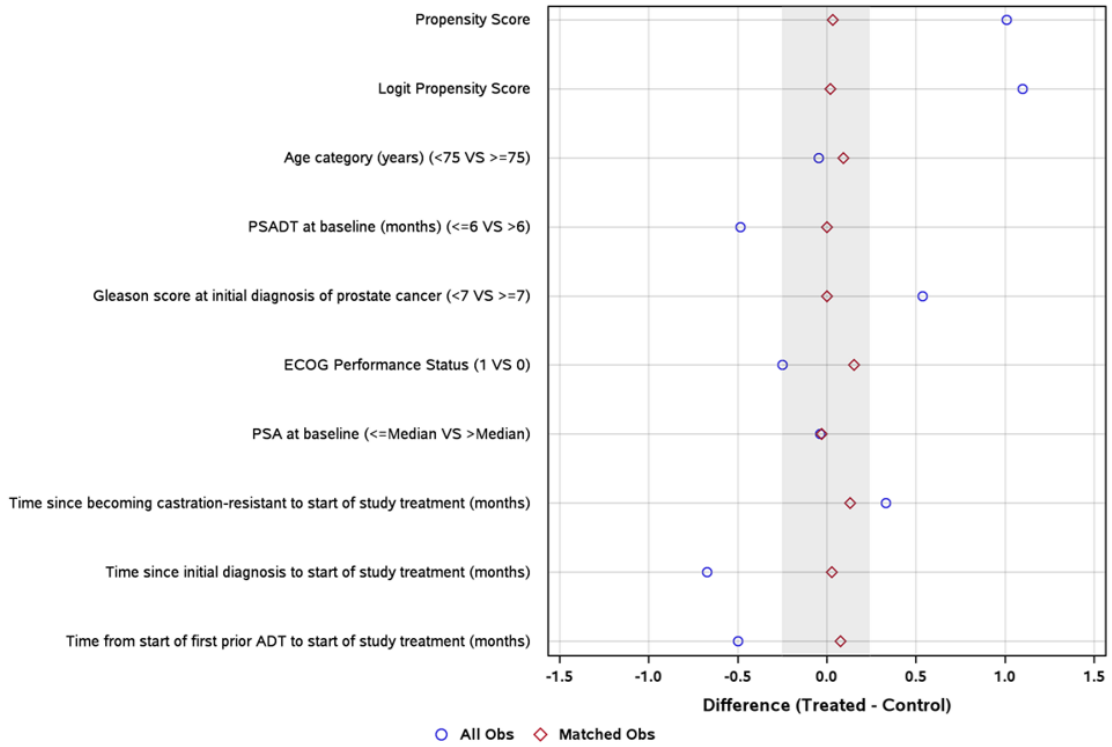
Recruitment / cutoff primary analysis: from Nov 2021 to Feb 2024 / Dec 2024

Recruitment rate improved considerably allowing to complete the study within the agreed time

Matched Sample to ARAMIS Placebo Arm

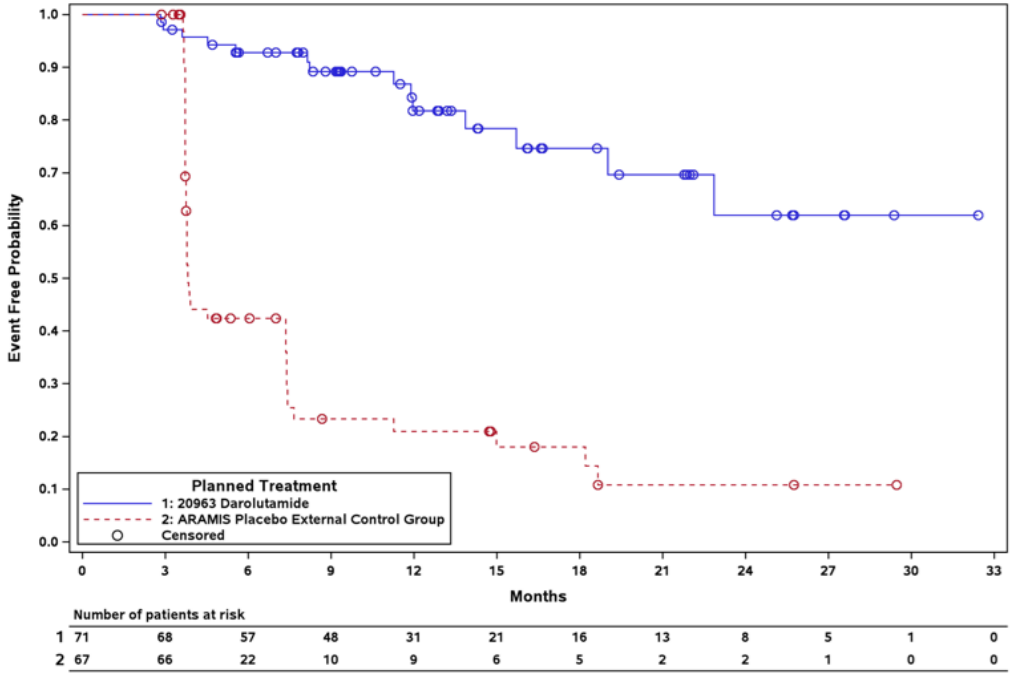
Balance of variables and TTPSA progression

Standardized Mean Difference
Darolutamide (N=71) vs ARAMIS placebo arm (N=67)



After propensity score matching (PSM) the baseline covariates between the darolutamide group and the ARAMIS placebo external control are successfully balanced, helping to control for confounding

Kaplan-Meier curves of TTPSA progression
Darolutamide (N=71) vs ARAMIS placebo arm (N=67)



After PSM, the KM curves show a consistent treatment effect on TTPSA progression for the darolutamide group compared to the ARAMIS placebo external control group

Key Takeaways

Outcomes

- Efficacy of darolutamide in Chinese patients was demonstrated using a single-arm trial (SAT) and the ARAMIS external control arm
- The CDE of the NMPA granted approval to darolutamide for the treatment of patients with nmCRPC in China in **September of 2025**

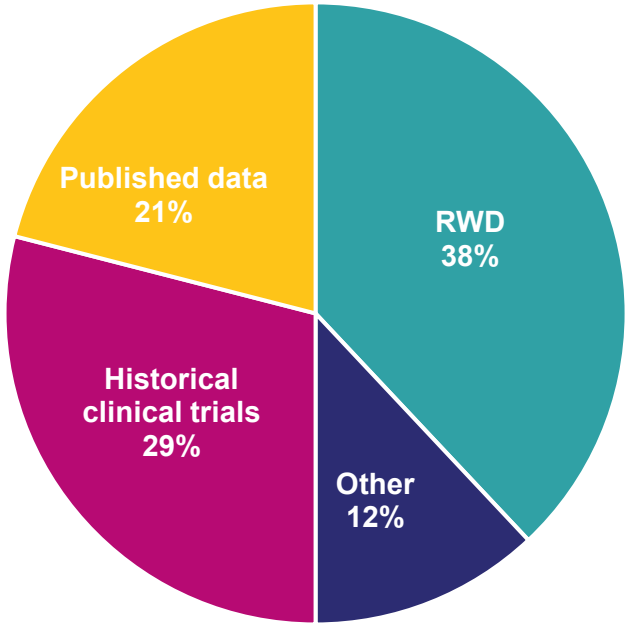
Strategies employed to mitigate risk of bias

- Identical eligibility criteria between the SAT and external group
- Variables, endpoints, and visits were aligned between the SAT and the external control
- A set of prognostic factors was identified
- PSM was used to create an external control arm from ARAMIS placebo arm
- Blinding of outcome during matching process was ensured
- Balance of essential patient baseline characteristics was achieved
- Substantial overlap between propensity score distributions
- Sensitivity analysis regarding geographic exchangeability was performed

BACK UP

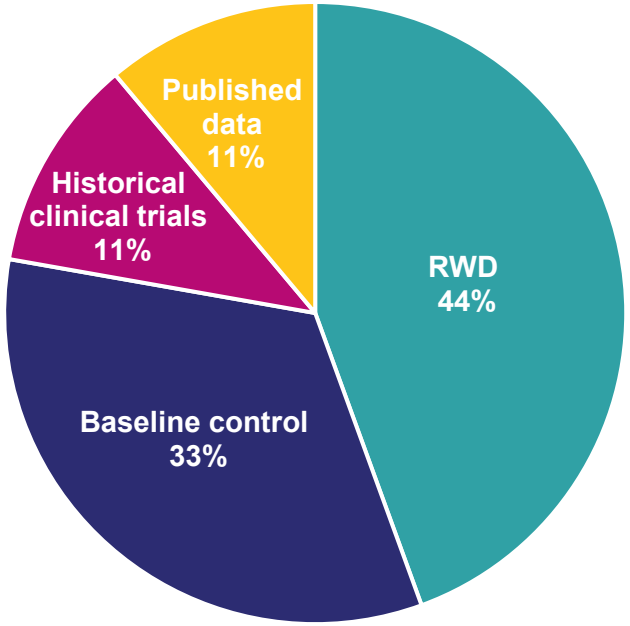
Data source for External Control Arms

Oncology



Based on analysis of FDA approvals 2000-2019 (1)

Non-oncology



Based on analysis of EMA approvals 2016-2021 (2)

- Oncology, neurology and rare disease accounts for majority of ECA cases
- RWD and especially natural history data have been important data source of ECA
- Collaborative projects enable creation of prospectively collected RWD and RCTs databases

1. Jahanshani et al. The use of external controls in FDA regulatory decision-making.Ther Innov Regul Sci 2021 2) Wang et al. Current perspectives for external control arms in oncology clinical trials: Analysis of EMA approvals 2016-2021. J Cancer Policy 2023