# The use of Historical Control Data to Assess the Benefits of New Therapies: A Case Study of Blinatumomab versus Standard Therapy of Adults relapsed/refractory Acute Lymphoblastic Leukaemia

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# Outline

- Background
- Historical control group
  - Sources of data, analysis methods, results
- Conclusion/discussion
  - Challenges, lessons learned,

# Background: ALL Disease

- Adult acute lymphoblastic leukemia (ALL):
  - Rare disease (~ 1-2/100,000 age-adjusted incidence rate among adults)
  - Large percentage of adult patients relapse after initial treatment
  - Very poor prognosis (1 year survival ~ 15% among relapsed/refractory (R/R) patients)
- Prognosis of R/R ALL is strongly impacted by:
  - Time to relapse (or duration of remission)
  - Number of previous relapses and salvage treatments
  - History of HSCT

# Background: ALL Treatment Options

- No established standard treatment for R/R ALL patients
- HSCT, considered a potentially curative option, is generally not available for older patients (> 60 years)
- Palliative care often the only treatment option for many adult R/R ALL patients:
  - intolerability to aggressive chemotherapy
  - lack of curative intent if HSCT unavailable
- Promising results for blinatumomab reported in initial Phase II trial – high remission rates in R/R ALL population –

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# Background: Challenge for a Phase 3 RCT

- **Rare disease** – recruitment, achieving sufficient sample size are challenging
- **Unmet medical need -** poor disease prognosis
- **Limited or no treatment options** – would be unethical to allocate patients to “standard of care”
- **Clinicians unwilling to participate** in these trials
- **Other design challenges with clinical trials**:
  - Subject retention
  - Cross-over
- **New therapy** – initial promise, might offer hope
- **Some control data better than no information –** To help put results into appropriate perspective/context

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# Potential Data Sources/ Data Availability that could help provide some context – Historical controls

- Several studies* reported data on clinical outcomes among adult patients with R/R ALL:
  - Appeared data were available and could be assembled into a larger study relatively quickly
- Summarizing the literature was limited because of significant variation on how data were reported:
  - Differences in treatment histories (e.g. # of prior salvage therapies)
  - Differences in patient subgroup categories: time to relapse, age etc.
- Need individual patients data

*Fielding et al Blood 2007; Gokbuget et al Blood 2012; O'Brien et al Cancer 2008; Oriol et al Haematologica 2010; Tavernier et al Leukemia 2007

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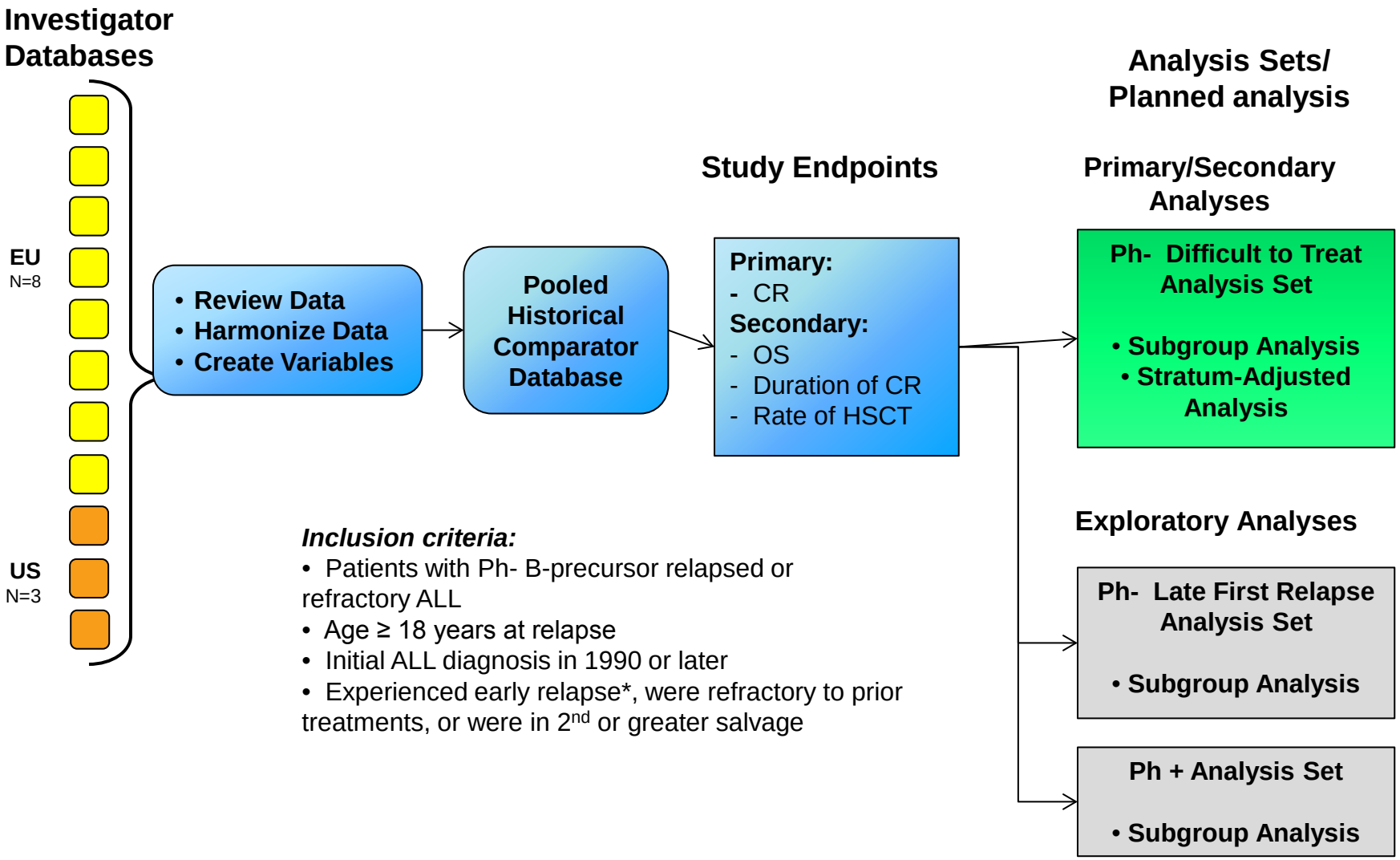
# Adult R/R ALL Historical Comparator Study: Study Schema



# Analysis approach

- Direct comparison of endpoints
  - Overall
  - By subgroups
  - Weighting endpoints on key characteristics to the clinical trial population
- Propensity score analyses

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# Results: Complete Remission as Defined by the Study Group (CRsg)

| Stratum | Age at Treatment | Prior lines of Treatment | n/N | Stratum % Observed | Stratum % Observed in Trial | CRsg Proportion (95% CI) |
|---|---|---|---|---|---|---|
| 1 | <35 | alloHSCT | 14/48 | 6.9% | 21.2% | 0.29 (0.17, 0.44) |
| 2 | <35 | In 1st salvage | 52/119 | 17.2% | 5.3% | 0.44 (0.35, 0.53) |
| 3 | <35 | In 2nd+ salvage | 27/150 | 21.6% | 21.2% | 0.18 (0.12, 0.25) |
| 4 | >=35 | alloHSCT | 11/41 | 5.9% | 12.7% | 0.27 (0.14, 0.43) |
| 5 | >=35 | In 1st salvage | 57/187 | 27.0% | 10.1% | 0.30 (0.24, 0.38) |
| 6 | >=35 | In 2nd+ salvage | 25/149 | 21.5% | 29.6% | 0.17 (0.11, 0.24) |
| **Weighted estimate for historical data** | | | | | | **0.24 (0.20, 0.27)** |
| | | | | | | |
| **Clinical trial data*** | | | | | | **0.43 (0.36, 0.50)[1]** |
| | | | | | | **0.33 (0.27, 0.41)[2]** |

n = number of patients achieving CRsg, N = number of patients evaluated for CRsg

- Topp et al. Lancet Oncology 2015;16:57-66.
- 1. CR/CRh* 2. CR

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# Results: Median Overall Survival

| Stratum | Age at Treatment | Prior lines of Treatment | N | Stratum % Observed | Stratum % Observed in Trial | Median OS (95% CI) |
|---|---|---|---|---|---|---|
| 1 | <35 | alloHSCT | 108 | 9.7% | 21.2% | 3.8 ( 2.9, 4.5) |
| 2 | <35 | In 1st salvage | 258 | 23.2% | 5.3% | 5.7 ( 4.9, 6.3) |
| 3 | <35 | In 2nd+ salvage | 161 | 14.5% | 21.2% | 2.9 ( 2.3, 4.0) |
| 4 | >=35 | alloHSCT | 79 | 7.1% | 12.7% | 4.0 ( 2.8, 4.7) |
| 5 | >=35 | In 1st salvage | 341 | 30.7% | 10.1% | 3.7 ( 3.2, 4.4) |
| 6 | >=35 | In 2nd+ salvage | 165 | 14.8% | 29.6% | 2.2 ( 1.7, 2.9) |
| **Weighted estimate of historical data** | | | | | | **3.3 ( 2.8, 3.6)** |
| | | | | | | |
| **Clinical trial data*** | | | | | | **6.1 (4.2, 7.5)** |

* Topp et al. Lancet Oncology 2015;16:57-66.

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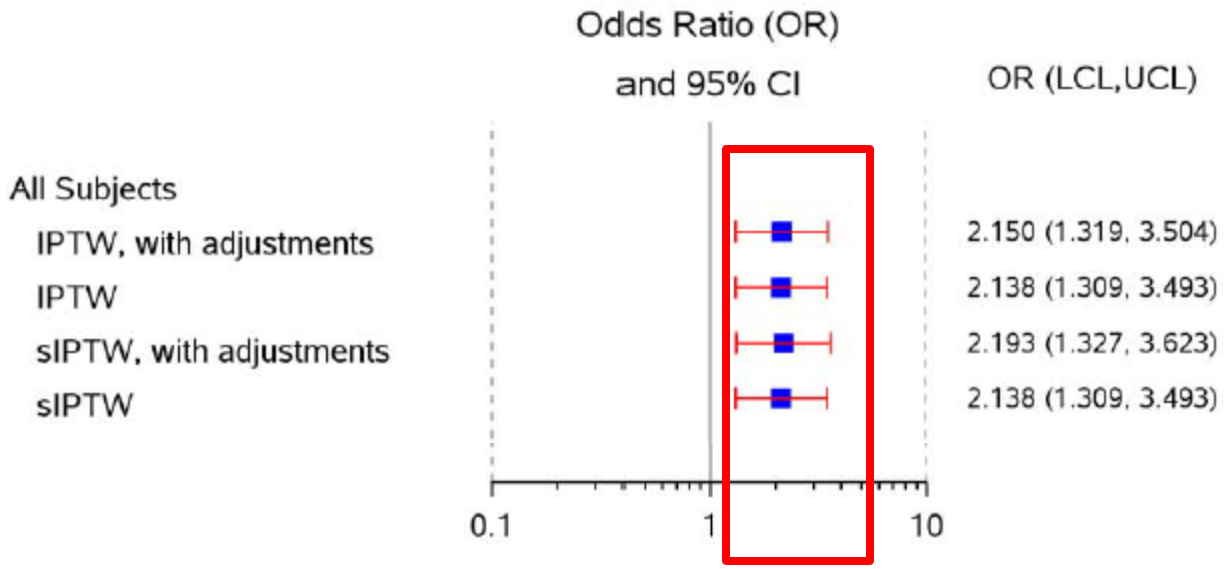
# Forest Plot of Odds Ratios for Analyses of Complete Remission




IPTW=Inverse probability of treatment weighting. sIPTW=Stabilized inverse probability of treatment weighting.

***Strong evidence of higher odds of CR in the trial (treated) population compared to the 'control' population***

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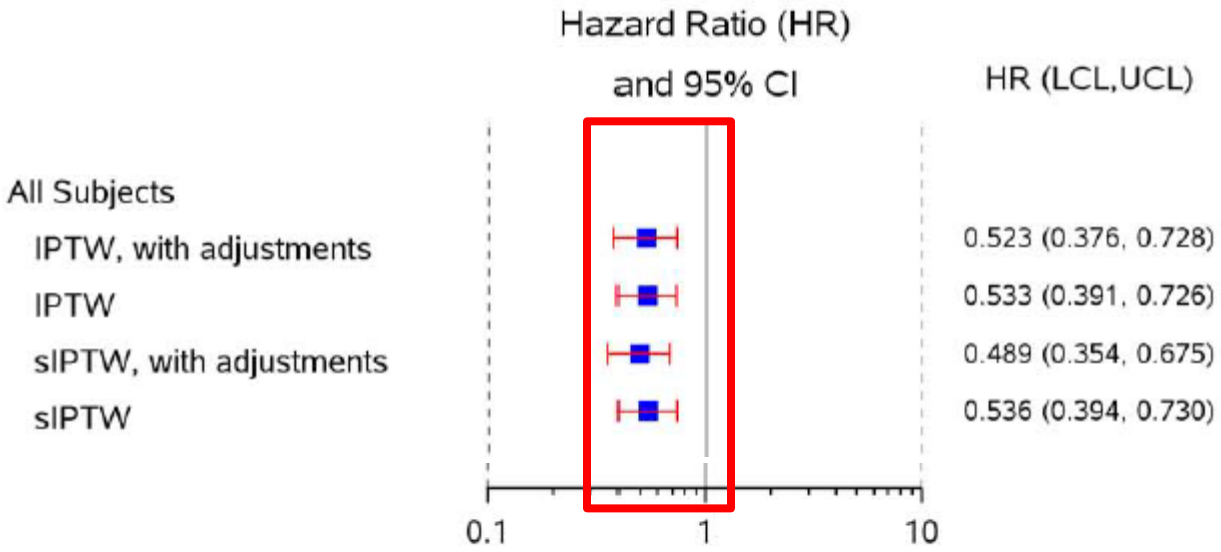
# Forest Plot of Hazard Ratios for Analyses of Overall Survival




IPTW=Inverse probability of treatment weighting. sIPTW=Stabilized inverse probability of treatment weighting.

***Strong evidence of smaller hazard of death in the trial (treated) population compared to the 'control' population***

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# In summary

- Faced with the challenge of an effective registrational phase 3 RCT, partly due to:
  - Rare disease, very poor prognosis, limited treatment options, clinician willingness to participate, etc…
- Systematically collected, carefully analyzed, historical individual R/R ALL patients data:
  - Showed strong and consistent benefit of treating R/R ALL patients with Blinatumomab compared to standard of care
- **Evidence was deemed important to help accelerated approval of Blinatumomab for adults R/R ALL by the FDA**
  - Among others, the robustness of the results and the importance of the effect size played key roles
  - Helped by the availability of good historical data and excellent collaboration between contributing investigators

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# In summary

- The TOWER study, a phase 3 randomized open label trial later confirmed these findings
  - An almost two-fold increased in median overall OS compared to SOC
- These results and their outcomes, further highlight the importance for all relevant stakeholders to continue to explore the potential role of the RWD in drug regulatory process.
  - Work was presented at a FDA symposium on how RWD can be used for faster regulatory approval
- In some situation, RWD can be used to enable faster delivery to the patients:
  - Considerable unmet medical need
  - New and very promising therapy
  - Clinicians unwilling to participate in these trials
  - Rare disease

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# Study Collaborators

- **Nicola Gokbuget*, Dieter Hoelzer**
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- **Hagop Kantarjian, Susan O'Brien**
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- **Jacob M Rowe**
  - Rambam Medical Center, Haifa, Israel
- **Victoria Chia, Aaron Katz, Michael Kelsh, Julia Steiglmaier**
  - Amgen

* Principal Investigator

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# Thank You!

# Back UP

# Particular Efforts to Minimize Bias

- At data collection stage – requested sites to provide all patients with R/R ALL – rather than having sites apply selection criteria
- Inclusion/exclusion criteria applied centrally across all data sets
- Study sites reflected centers of excellence for treatment of ALL
- Weighting, stratified, and propensity score analyses to make endpoints more comparable
- Variety of sensitivity analyses conducted in order to address assumptions

# Strength/Limitations of the approach

- Availability of and access to external control data
- Data definitions – outcomes, exposure, covariates
- Study biases:
  - Selection
  - Confounding
  - Immortal Time
- Treatment differences: across time, geographic regions
- Heterogeneity

# Propensity Score Analysis – Methods

- Propensity scores derived from logistic regression models considering available covariates
- Odds ratio (OR) for complete remission estimated from logistic regression models, using stabilized inverse probability treatment weighting (sIPTW)
- Hazard ratio (HR) for death estimated from Cox models, using inverse probability treatment weighting (IPTW)
- Sensitivity analysis conducted by:
  - Alternating weighting factors
  - Time period
  - Further model adjustments

# Propensity Score Analysis

- Aim to create balance in baseline covariates between patients treated with blinatumomab and patients treated with standard of care (historical comparator)
- Covariates:
  - Age (years)
  - Sex (male, female)
  - Duration between most recent treatment and initial diagnosis
  - Region (USA, Europe)
  - Prior HSCT (yes, no)
  - Number of salvage therapies (1, 2, 3, and 4+)
  - Primary refractory and in/entering first salvage (yes, no)
  - Refractory to last salvage therapy (yes, no)

# Covariate balance before and after propensity score (PS) adjustments

| | Before PS adjustments | | | After PS adjustments | | |
|---|---|---|---|---|---|---|
| | **Historical comparator** | **Blinatumomab** | **p-value** | **Historical comparator** | **Blinatumomab** | **p-value** |
| Age, Mean (SD) | 38 (14) | 41 (17) | 0.0018 | 38 (14) | 36 (16) | 0.35 |
| Female, % | 44% | 37% | 0.09 | 44% | 38% | 0.48 |
| Duration since initial diagnosis in months, mean (SD) | 11 (12) | 24 (23) | <0.0001 | 14 (17) | 17 (17) | 0.34 |
| Region – Europe, % | 83% | 50% | <0.0001 | 77% | 77% | 0.93 |
| Prior alloHSCT, % | 21% | 34% | 0.0003 | 23% | 21% | 0.61 |
| Number of salvage therapies, mean (SD) | 1.5 (0.8) | 2.3 (1.0) | <0.0001 | 1.6 (0.9) | 1.7 (0.9) | 0.96 |
| Primary refractory, % | 6% | 2% | 0.0395 | 5% | 11% | 0.41 |
| Refractory to last salvage, % | 21% | 52% | <0.0001 | 27% | 25% | 0.75 |

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