Development of a „Novel-Novel“ Combintion Therapy Supported By RWE

Disclaimer

The opinions and views expressed in this presentation are solely my own and do not represent the views of my employer or any affiliated organization.

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The project discussed in this presentation was realized with my former employer. Currently, I am working at Sanofi.

Developing Combination Therapies Requires To Isolate The Contribution of Individual Effects To The Overall Effect

Guidance for Industry

Codevelopment of Two or More New Investigational Drugs for Use in Combination

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2013
Clinical Medical

Development of Cancer Drugs for Use in Novel Combination – Determining the Contribution of the Individual Drugs' Effects Guidance for Industry

DRAFT GUIDANCE

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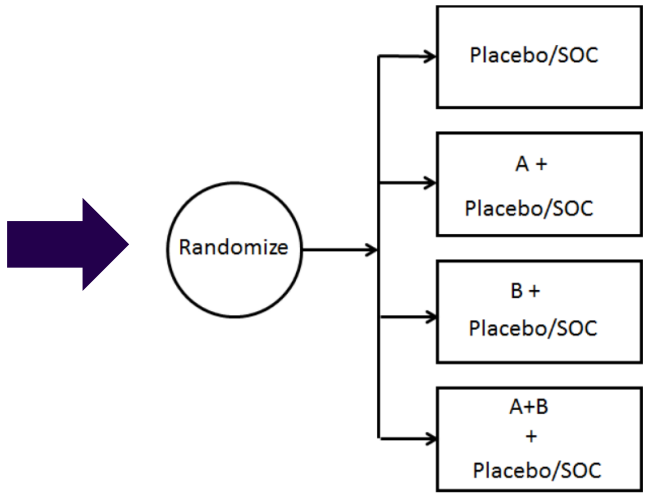
For questions regarding this draft document, contact (OCE) OCE Guidances at OCE-Guidances@fda.hhs.gov or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2025
Clinical/Medical

„By-the-books approach"



Isolate contribution of individual effects to overall effect

➢ **What else can we do to isolate the contribution of individual effects?**

„Real-Life" Development Scenario

- **Company asset:** monoclonal antibody (mAB) → kills leukemia/lymphoma tumor cells

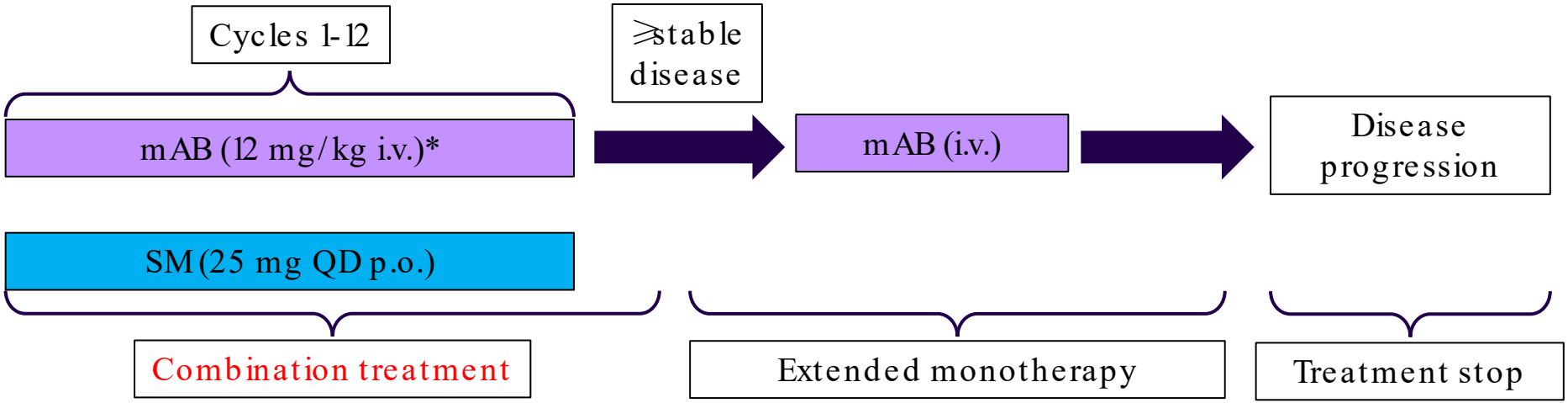
- **Phase 1 dose escalation in CLL completed (leukemic indication)**
  - „Recommended Phase 2 Dose" selected (→ 12 mg/kg)

- **Phase 2 PoC Studies completed:**
  - Different leukemia/lymphoma indications explored (mAB *mono-therapy*):
    - ALL (leukemic indication)
    - Basket trial including various lymphoma indications
      - **Early evidence of clinical activity of the mAB mono-therapy in lymphoma**

- **Phase 2 PoC study in DLBCL initiated (→ aggressive lymphoma subtype)**
  - Indication: relapsed/refractory DLBCL ineligible for transplant
    - *Dire* prognosis
    - Limited treatment options
  - Study explored a novel combination:
    - mAB + small molecule (SM) → SM boosts anti-tumor immunity
    - SM: FDA approved in *other* hemato-oncological indications, but not in DLBCL

- **Treatment landscape in R/R DLBCL ineligible for transplantation (back in 2018)**
  - Standard of care (SoC) per NCCN/ESMO: different chemo-cocktails (→ off-label use)
  - Two CAR T products approved (→ but: accessibility hurdles)

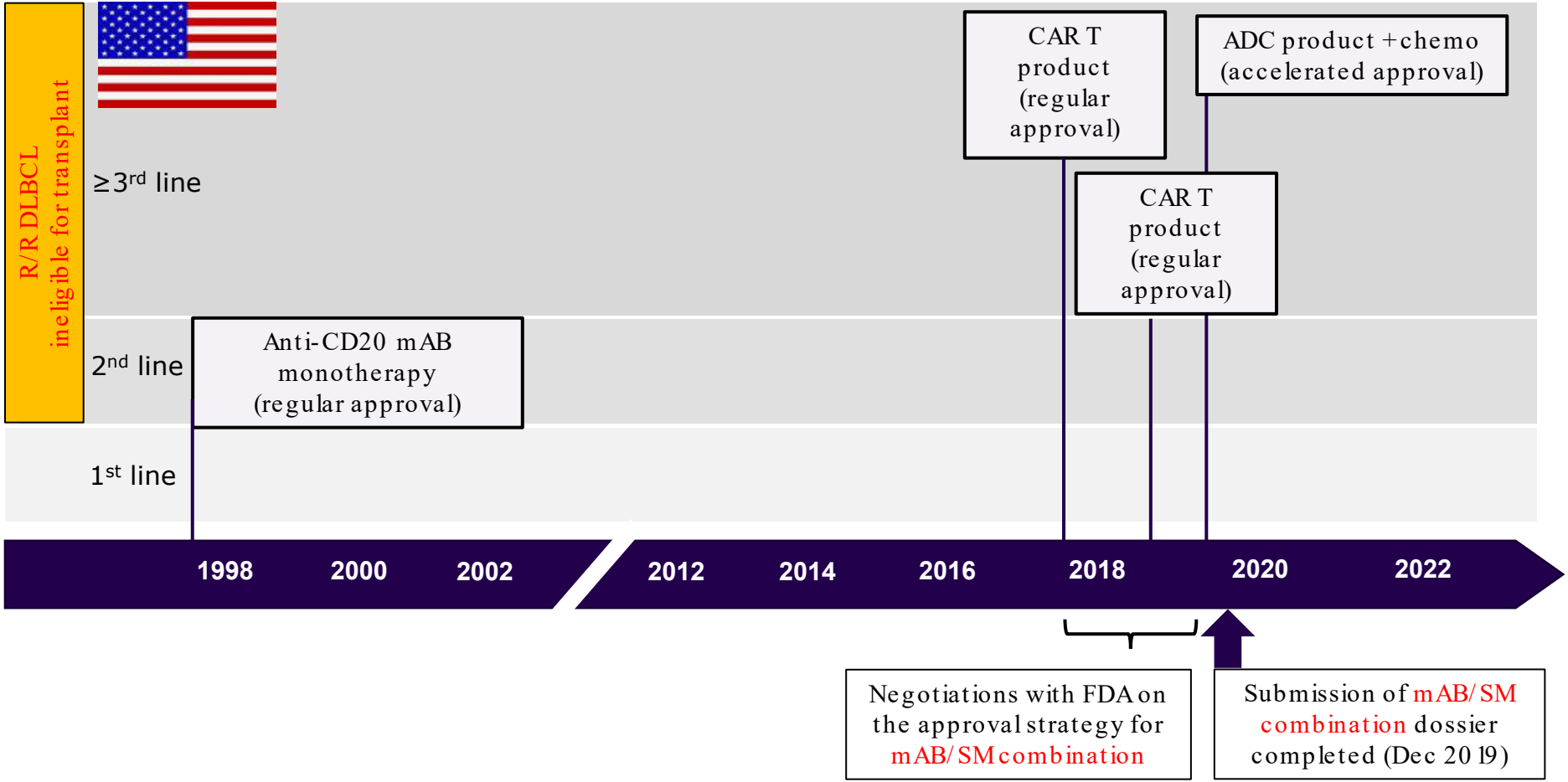
Phase 2 Evaluating mAB+SM Combination (Proof of Concept Study)



- Sample size: ~80 patients (single-arm; R/R DLBCL not eligible for transplant)
- Endpoints:
  - Primary: Response
  - Secondary: PFS, DoR, OS, occurence of TEAEs
- Doses:
  - mAB: RP2D as defined in phase 1 dose-escalation trial (CLL indication)
  - SM: as per label of *other* indications

*Cycles 1-3: every week; from cycle 4 onwards: every 2 weeks

Landscape Of Approved Drugs At The Time When Phase 2 Results Became Available



Treatments For R/R DLBCL (Transplant Ineligible) At The Time When Efficacy Data Of The Combination Treatment Became Available

Endpoint summary statistic	SoC (off-label use of chemo-therapeutics)	CAR T products (regularly approved*) N= ~70-100	ADC + chemo (obtained accellerated approval#) N= ~40	mAB monotherapy (phase 2 basket trial) N= ~40	mAB+SM combination treatment (phase 2 PoC study) N= ~80
ORR	~30-40%	~50-80%	~60%	26%	~60%
CR	~10-25%	~40-60%	~40%	6%	~40%
Median DoR	~4 mo	~11 mo to not reached	~11 mo	~20 mo	~21 mo
Median PFS	~3-6 mo	~6m	~9 mo	~3 mo	~12 mo
Median OS	~6-10 mo	~11-25 mo	~12 mo	Not collected	Not estimable (estimated 30-month rate ~60%)
Incidence of „severe" adverse events	„sometimes "	„frequently"	„sometimes "	„rare"	„sometimes"
Accessibility & treatment eligibility	„Less contrained"	„More constrained"	„Less constrained"	„Less constrained"	„Less constrained"

#*Based on single-arm trials | Based on randomized phase 2 trial (~40 vs. ~40)

Pursued Development Path In Line With „New FDA“ Guidance

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This guidance reflects FDA's current thinking regarding the use of clinical data for demonstration of contribution of effect for the following types of novel combinations in oncology:

- Two (or more) investigational drugs[4] that have not been previously approved by FDA for any indication
- An investigational drug with a drug(s) approved for a different indication
- Two (or more) drugs approved for a different indication(s)

B. External Data to Demonstrate the Contribution of Effect

The rationale for use of external data to provide evidence of the contribution of effect for the individual drugs to the overall combination regimen can be supported by several factors. These include: 1) there is strong biological plausibility for the combination regimen, 2) the natural history of the disease is highly predictable, 3) the drug as a single agent has been demonstrated to not be as effective as compared with its use in combination with other classes of drugs, and/or 4) the magnitude of the treatment effect of the combination is expected to be large. To consider this approach, among other considerations, the external data should be from comparable populations studied across the combination and the components, contain detailed information on clinically relevant confounding variables, and use similar methods of response assessment and variable collection across the data sources. The limitations of comparisons with external data can include determination of appropriate endpoints for comparison. In general, the strengths and limitations associated with various types of external data should be considered, and any plan to use such data to support contribution of effect should be discussed in advance with the review division.

Cardinal Question

- **Is the observed overall treatment effect of the mAB+SM combination mainly attributed to SM?**

- **That is, is it the combination treatment really superior to SM monotherapy?**

Construction Of An External Control Arm For Causal Inference

RWD of ~500 patients treated with SM monotherapy *

Select those who meet inclusion/exclusion criteria of phase 2 combination treatment trial

Select patients treated at right SM dose (same dose like SM dose used in combination treatment)

Patients treated with mAB+SM combination in phase 2 trial (n= ~80)

Selected "Real-world patients" treated with SM mono-therapy cohort (n= ~140)

Baseline covariates for propensity score estimation:
- Age
- Ann Arbor stage
- Refractoriness to last line
- Number prior therapies
- History of primary refractoriness
- Prior ASCT
- Neutropenia
- Anemia
- Elevated LDH

1:1 nearest neighbor matching (using propensity scores derived via logistic regression)

➢ **ATT estimand**

n= ~80 (combi)

n= ~80 (SM treated)

Primary objective:
- Assess difference in ORR (investigator-assessed)

Secondary objectives:
- Difference in PFS
- Difference in OS
- Difference CR rate
- Difference DoR

* Enrolled across 58 centers in the US and Europe; off-label use

External Data Sources

- University hospitals / academic centers
  - Data of patients treated with SM in an off-label fashion in the context of clinical trials
- Data vendor with large network of practitioners in the US
  - Patients treated with SM in off-label fashion

➢ Systematic data collection via EDC

Achieved Balance With 1:1 Nearest Neighbor Matching

Main efficacy analysis set:

- SMD <0.2 for 7/9 covariates
- For two 2/9 covariates: 0.2 < SMD <0.3
- Variance ratio: ~0.5 to ~1.3

Sensitivity analysis set:

- Caliper applied to achieve SMD <0.1
  (at the expense of smaller sample size)

Results Of the Comparative Analysis

	Comparative Analysis: phase 2 vs. ECA* (Post-Matching)		Literature	Phase 2 basket trial
	SM mono-therapy - Matched population N= ~75	mAB+SM combination treatment - Matched Population N= ~75	SM mono-therapy (DLBCL)	mAB monotherapy (DLBCL)
ORR	~34%	~67% (p<0.0001)	~20-30%	26%
CR	~13%	~40%	~10-20%	6%
Median DoR	~7 mo	~21 mo	~5 mo	20 mo
Median PFS (hazard ratio)	~4 mo	~12 mo (~0.5; p<0.0002)	~3 mo	~3 mo
Median OS (hazard ratio)	~9 mo	Not estimable (~0.5; p=0.0026)	Not available	Not available

- **Novel mAB+SM combination treatment superior to SM mono-therapy**
- Treatment effects of SM mono-therapy in matched population consistent with effects as reported in literature

*ECA = External Control Arm

Inference Logic To Isolate Contribution Of Individual Effects

Treatment 1	Superiority direction	Treatment 2	Rationale
Placebo	<	SM mono-therapy	No placebo effect in DLBCL (tumor does not shrink spontaneously w/o intervention)
Placebo	<	mAB monotherapy	No placebo effect in DLBCL (tumor does not shrink spontaneously w/o intervention)
mAB mono-therapy	<	mAB + SM combination	▪ Inferred via cross-trial comparison ▪ Logic: – Effect of combination treatment is so much higher than the effect of the mAB mono-therapy to be explained by differences in baseline / disease characteristics – Mechanistically plausible that combination treatment is superior to mAB mono-therapy
SM	<	mAB + SM combination	Demonstrated via external control arm (using RWD)

➢ Evidence that efficacy is attributable to the combination
(as opposed to an effect primarily coming from one component)

Sensitivity & Supportive Analyses

- **Pre-specified in a SAP**

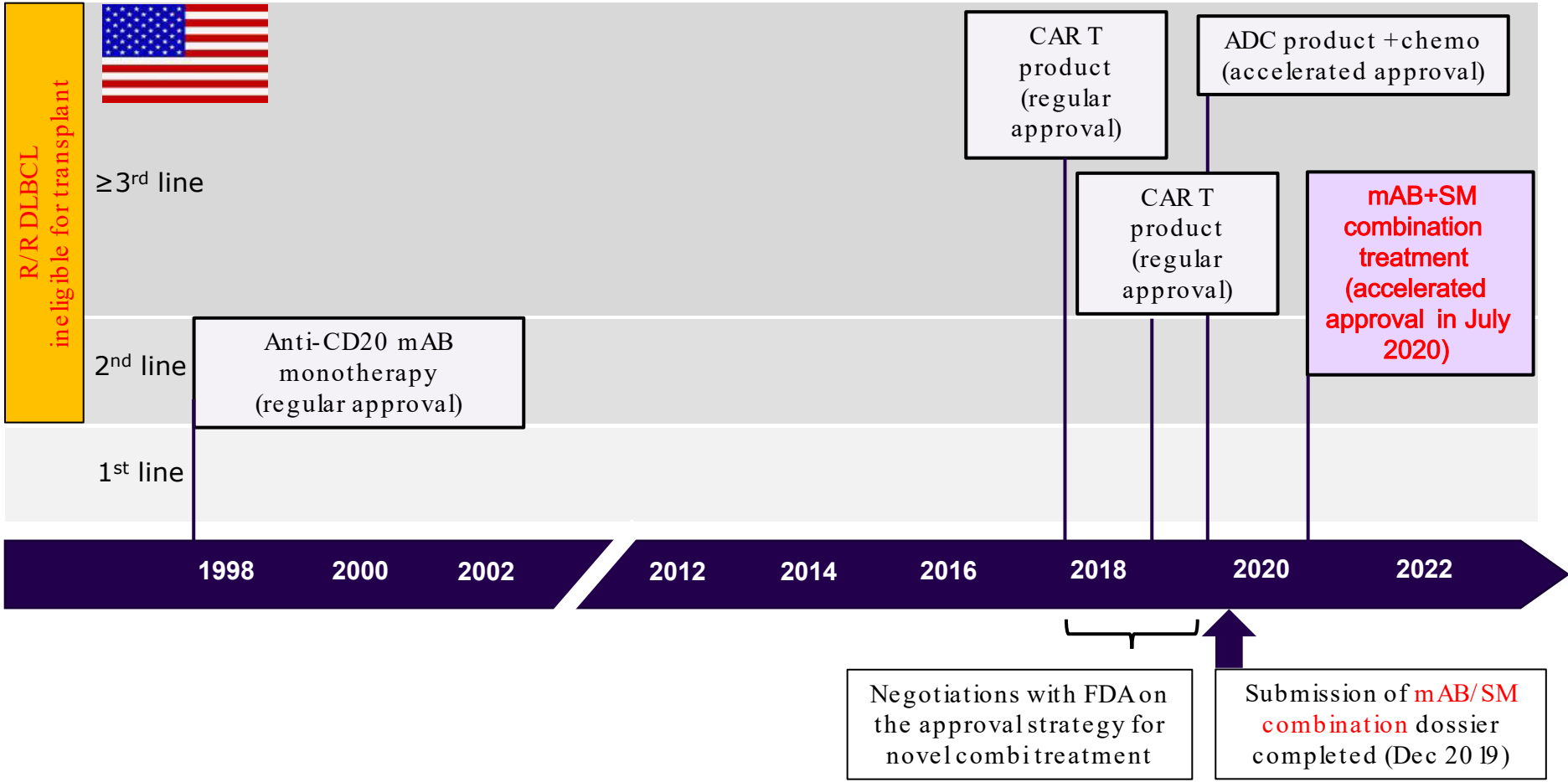
- **Analyes:**
  - Methods for correlated data
    (McNemar, conditional logistic regression, stratified Cox)
  - Caliper (→ smaller SMD at the expense of reduced sample size)
  - Additional baseline covariates for PS model
  - Weighting (→ ATO estimand)
  - Subgroup analyses
  - „Doubly robust" effect estimation
  - Assessment of the impact of potential unmeasured confounding
    (Rosenbaum´s Gamma approach)
  - Multiple imputations of missing covariates

- **Independent validation of response outcomes in RWD cohort**
  - Scans obtained for subset of patients
    → assessed by independent review committee (IRC)
  - Concordance analysis between investigator and IRC assessment

Program-Wide Safety Body of Evidence

- **mAB safety data:**
  - **Safety data from pivotal phase 2 combination treatment trial**
  - **mAB monotherapy safety data**
    - From phase 1 dose escalation (leukemic hem-onc indication)
    - Phase 2 PoC basket trial (DLBCL + other lymphomas)
    - Phase 2 PoC study in ALL (leukemic hem-onc indication)
  - **Safety data of other mAB trials (with other combi partners)**
- **SM monotherapy**
  - USPI (non-DLBCL indications)
  - Published trials (non-DLBCL indications + failed trials in DLBCL)

Treatment Landscape At The Time When Phase 2 Results Became Available



Accelerated Approval

- FDA concluded:

"The response data from this [comparative RWE] study was used to provide context to the results from the single-arm [combination treatment] trial"

- RWD-based external control arm provided *supportive* evidence
- Accelerated approval granted
- Confirmatory trial (post-marketing requirement):
  Randomized phase 3 trial in another patient segment (first line)

Electronic Submission Package

- Full CDISC compliant e-sub package created for RWD:
  - SDTM:
    - RWD mapped to SDTM
      - SDTM domains produced
    - cSDRG
    - Define.xml
    - Populated CRFs / PDRs
  - Integrated ADaM datasets:
    - Contain RWD and the pivotal phase 2 trial data
    - ADRG
    - Define.xml

Reflection: Were The Right Doses Selected?

- Treating physicians frequently reduced the dose of the SM during combination phase due to side effects
- No dose optimization in the spirit of *Project Optimus* has been performed
- Instead:
  - mAB dose established as monotherapy treatment has been used
  - SM dose as per label for *other* indications (as SM mono-therapy)

➢ Titrating at least one of the two components would have been favorable (e.g., exploring 2-3 different SM doses in combination with fixed mAB dose; randomization to these candidate treatment regimens)

That´s It!