Protocol Design: Balancing Scientific Validity

Presented by Andrei Shustov, MD

9:40am-10:40am

UW Husky Union Building

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Protocol Design: Balancing Scientific Validity with Ethical Approaches and Pragmatic Operations

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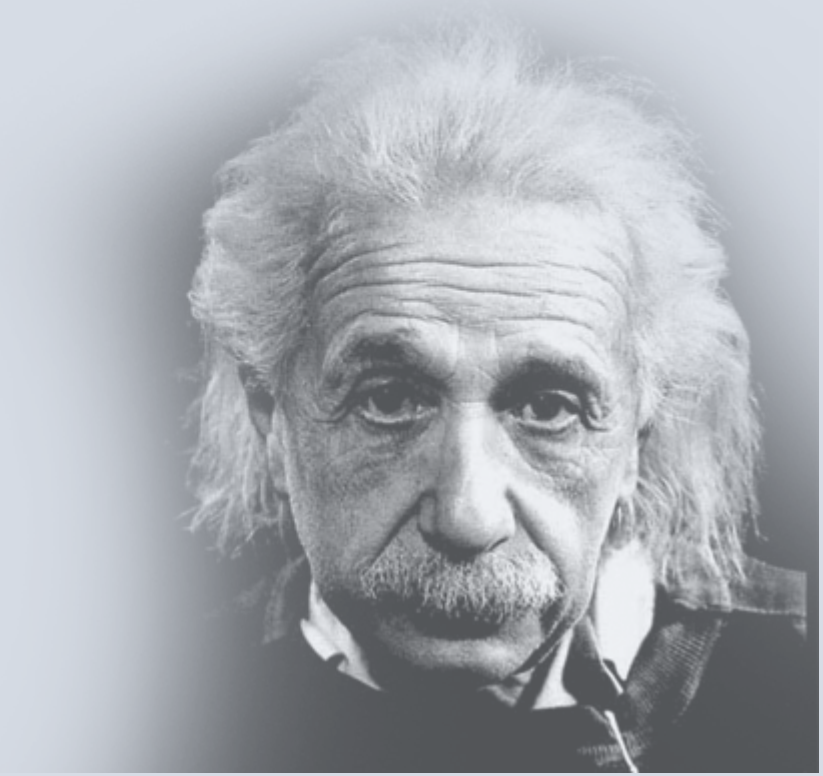
Fred Hutchinson Cancer Research Center

"If we knew what it is we were doing, it wouldn't be called research, would it?"

Albert Einstein



The goals of clinical trials

- Researcher perspective
  - Discover new treatments
  - Evaluate measurable endpoints (i.e. ORR, CR, DOR..)
  - Create new knowledge about Dz
  - Advance career
- Patient perspective
  - Cure, prolong life, improve symptoms
  - Minimize side effects
  - Improve quality of life

Ethical pitfalls of clinical trials

- Phase I
  - Majority of patients are treated at ineffective dose
  - Not powered to assess early efficacy
  - Majority of patients are heavily pretreated and are most susceptible to side effects and lack of efficacy
  - Potential risk over benefit is underemphasized
  - The goal of the study is not sufficiently conveyed to patient population
  - Vulnerable populations are at increased risk
  - End-of-life burden for unlikely benefit

Ethical pitfalls of clinical trials

- Phase II
  - Very exclusive patient population resulting in limited generalization potential
  - Not powered to fully assess toxicity burden
  - Primary objectives are not aligned with patient's goal
  - Very demanding schedules
  - The goal of the study is not sufficiently conveyed to patients
  - Vulnerable populations have limited access
  - Treatment-related QOL burden is under-evaluated

Ethical pitfalls of clinical trials

- Phase III
  - Randomization process
    - Study patients lack access to new therapy
    - Introduced investigator bias
    - Often powered for drug approval and not patient benefit
    - Phase II efficacy looks much better then historical SOC
  - Study powered for efficacy and not toxicity
  - Futility boundary identified “too late”
  - Burdensome enrolment process excludes high risk patients
    - Overestimates efficacy of experimental arm
    - Underestimates efficacy of experimental arm

Ethical pitfalls: special topics

- Informed consent:
  - Should all patients undergoing interventional trials be consented?
  - Does informed consent compromise scientific soundness of the clinical trial?
  - What are special situations?
  - Way around informed consent?

  - Should all of the cancer patients be considered a “vulnerable population”?
  - Should terminal cancer patients considered a “vulnerable population”?

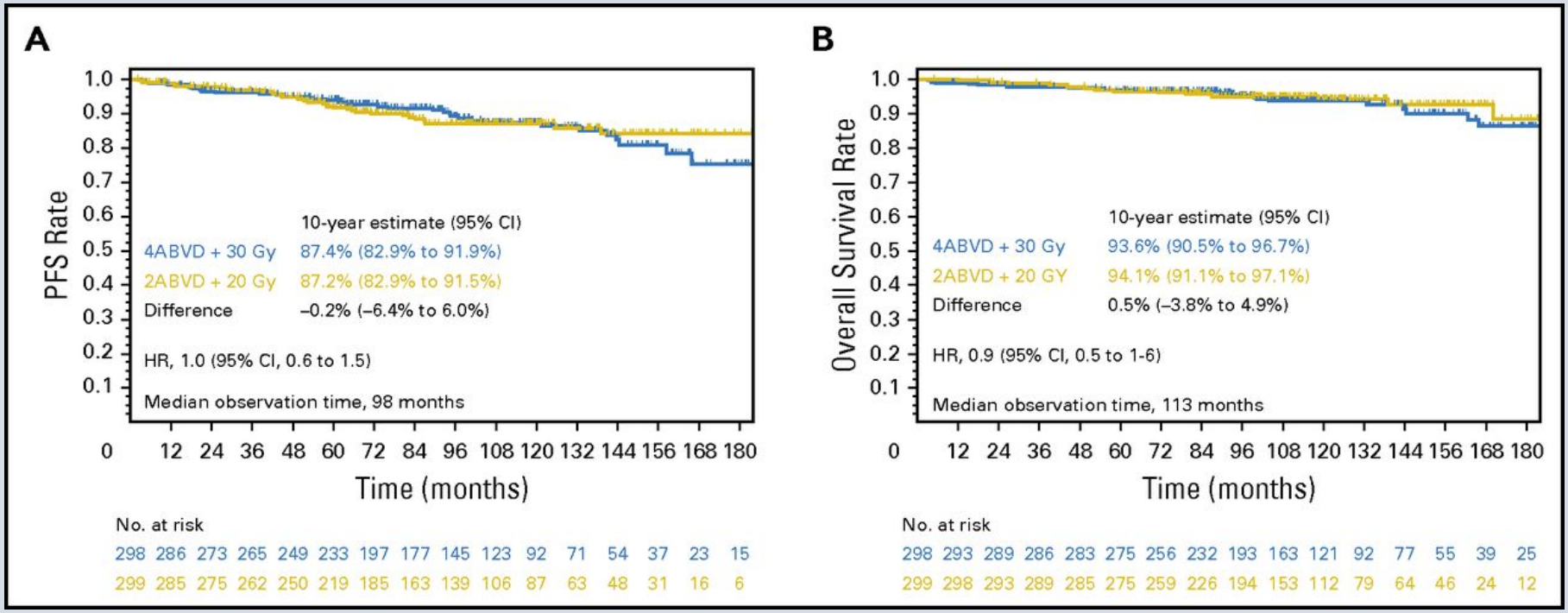
Scientific pitfalls of clinical trials

- All Phases
  - Informed consent compromises scientific soundness
  - Patient non-compliance
  - Rigidness of study designs and protocols
  - Diversity of disease biology and genomics
  - Diversity of pharmacogenomics and immunogenetics of the host (patient)
  - Ethical and regulatory barriers to correlative studies
  - Financial limitations to conduct a comprehensive trial

Operational pitfalls of clinical trials

- All Phases
  - Cost of personnel and materials
  - Facility limitations
  - Patient's preferences
  - Multi-center challenges
  - Central review panel challenges
  - Real time communication challenges across time zones
  - Financial limitations to conduct a comprehensive trial

Early stage Hodgkin Lymphoma

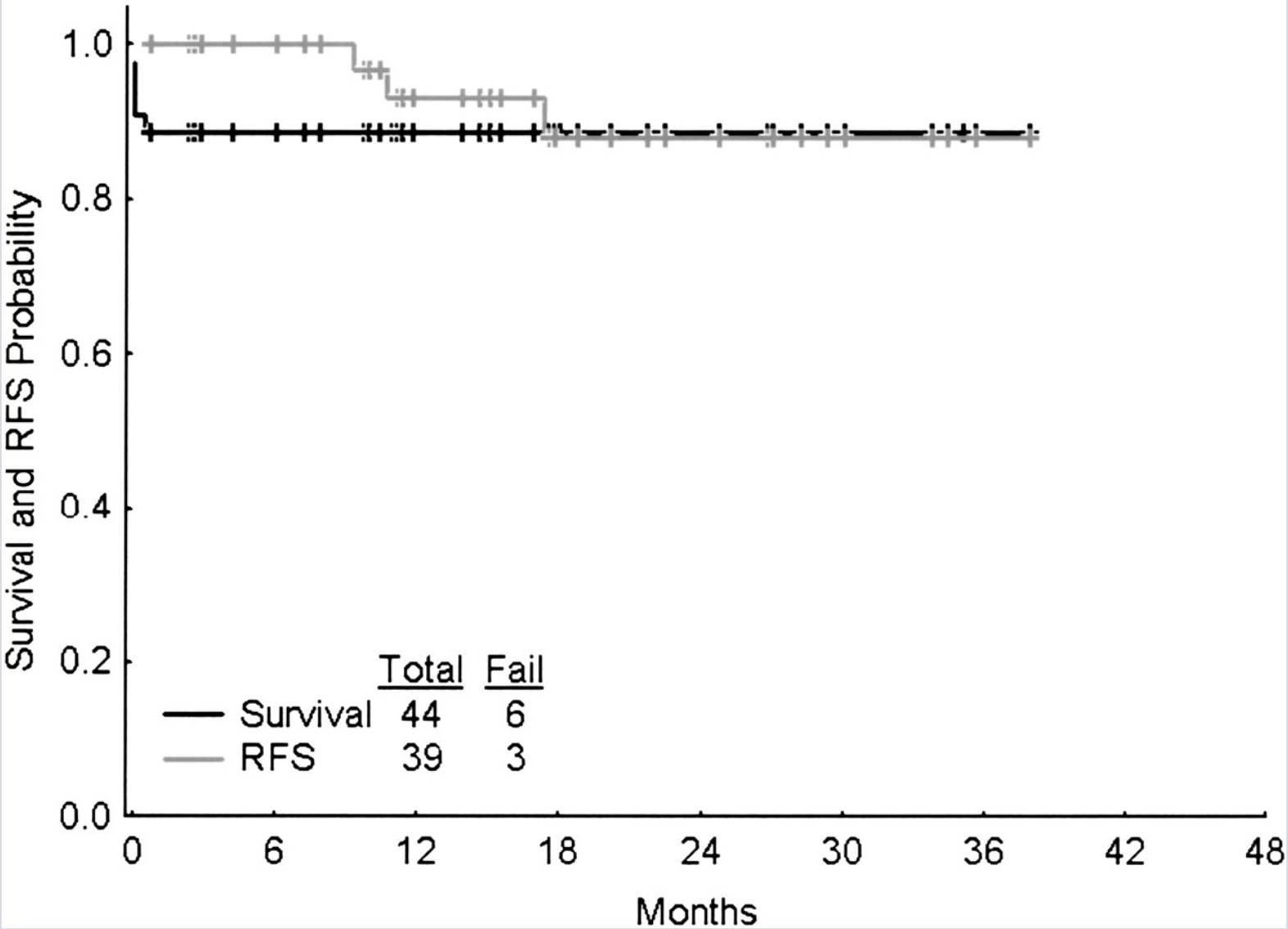


Paul J. Bröckelmann et al. Blood 2018;131:1666-1678

- Should this population be subject to clinical trials?

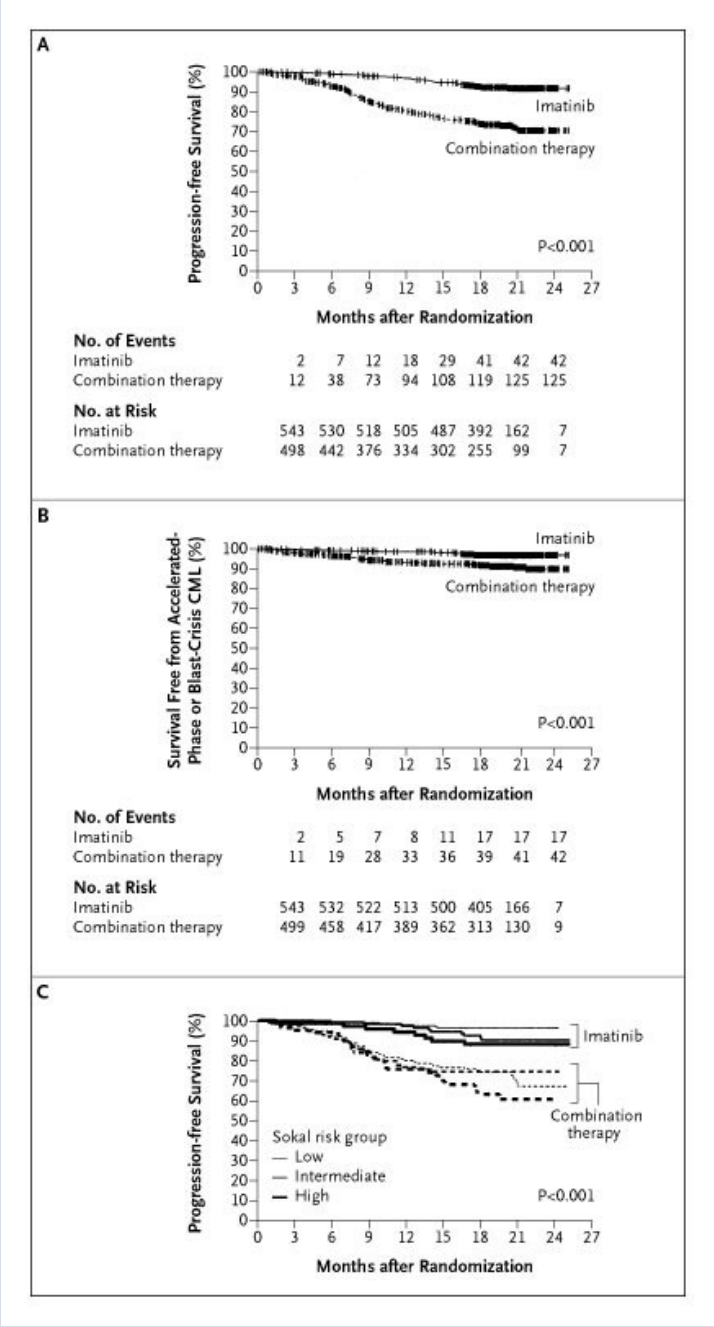
- What are the goals of such studies?

Acute Promyelocytic Leukemia



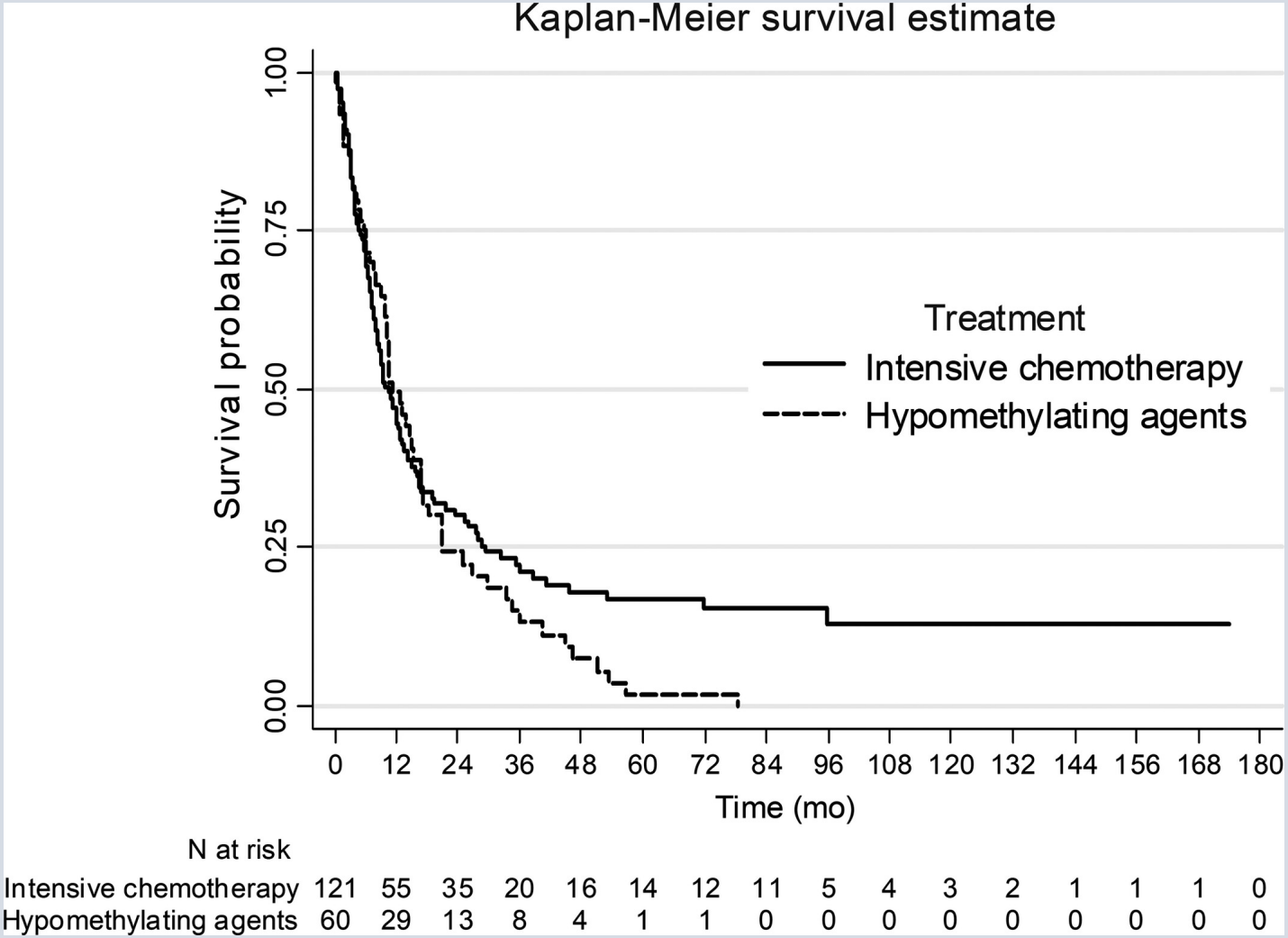
Elihu Estey et al. Blood 2006;107:3469-3473

Chronic Myeloid Leukemia



S. O'Brien et al. N Engl J Med 2003;348:994-1004

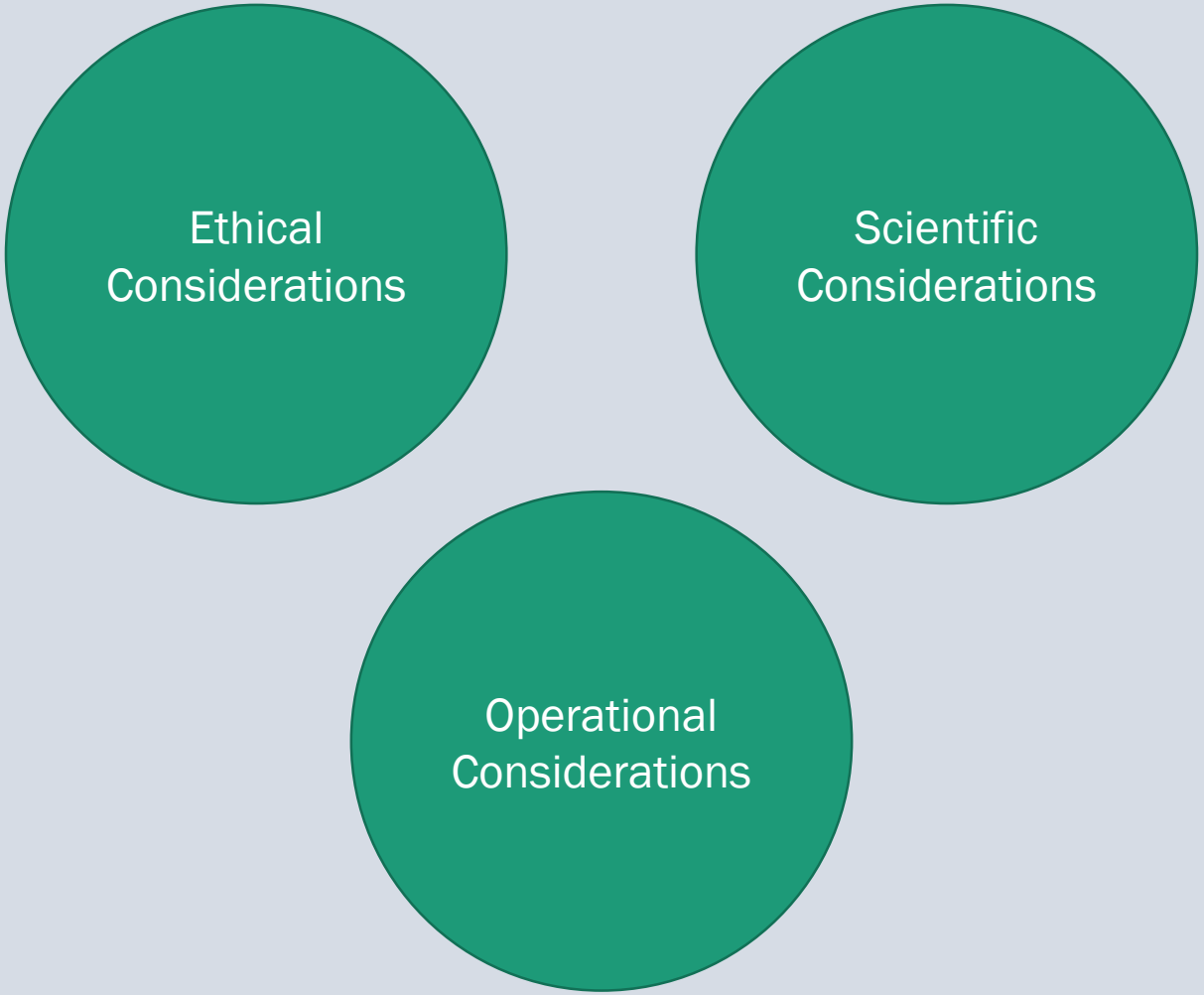
Secondary Acute Myeloid Leukemia in Elderly

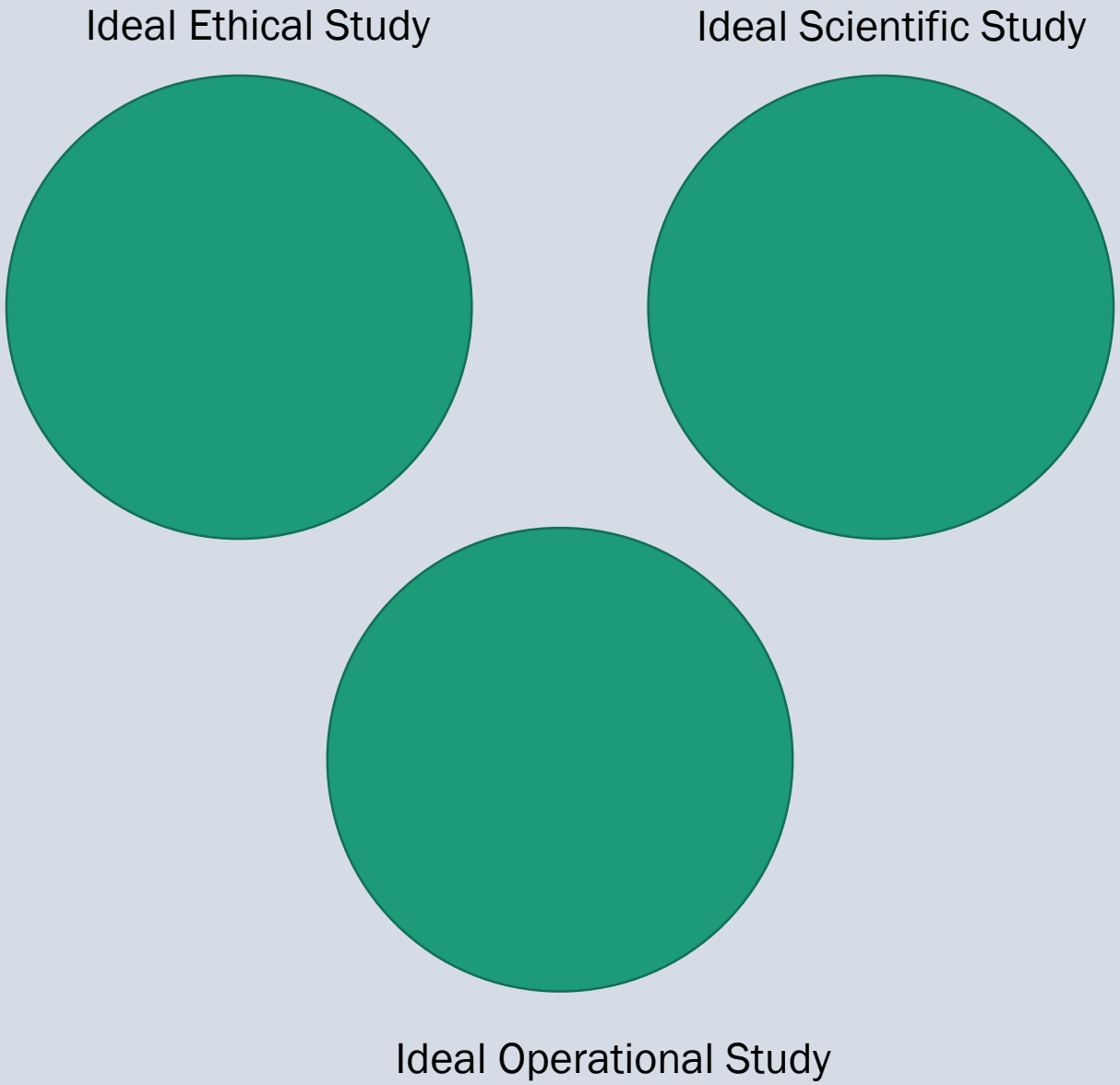


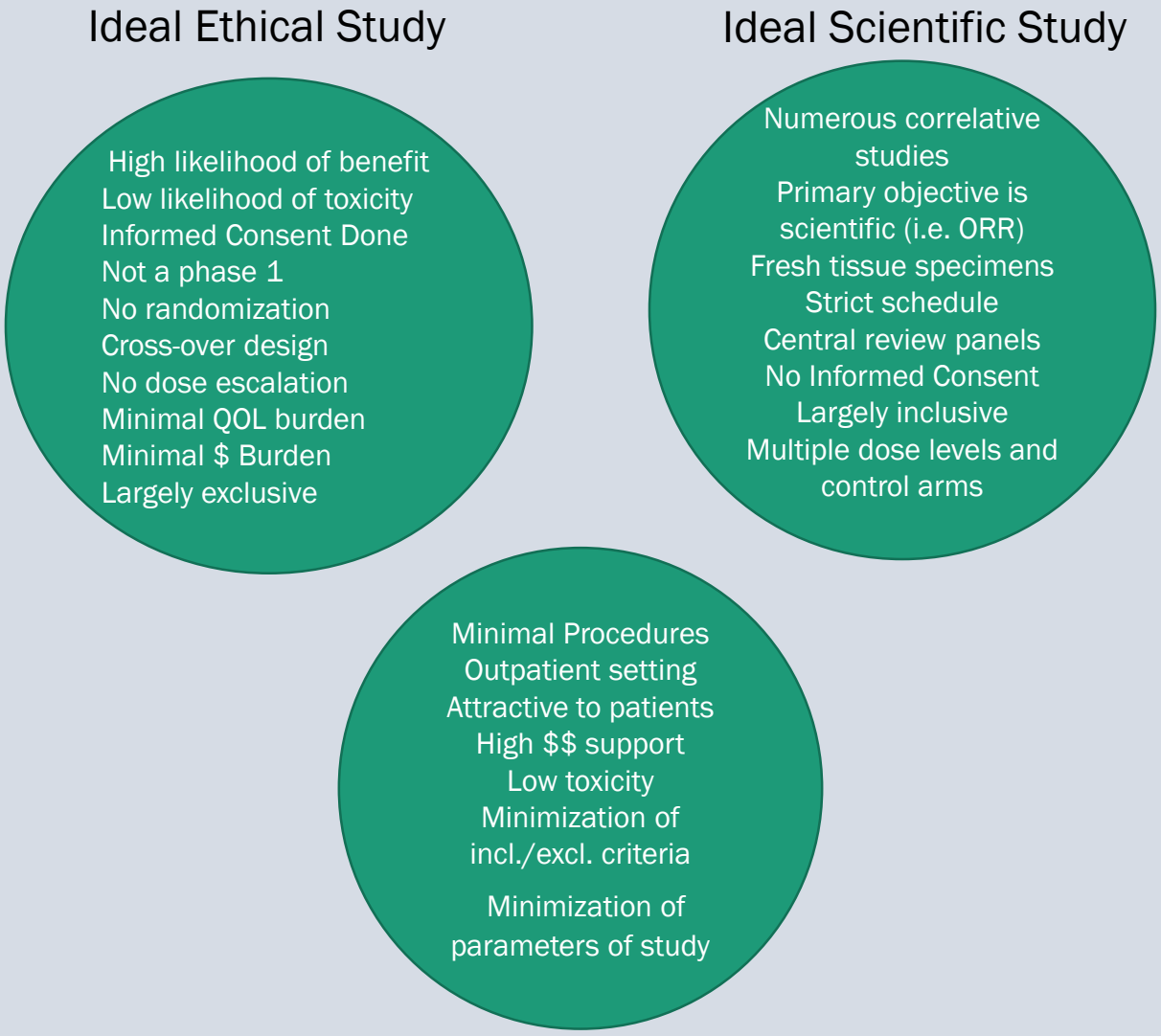
S. Bertoli et al. Cancer Medicine 2019; 8:

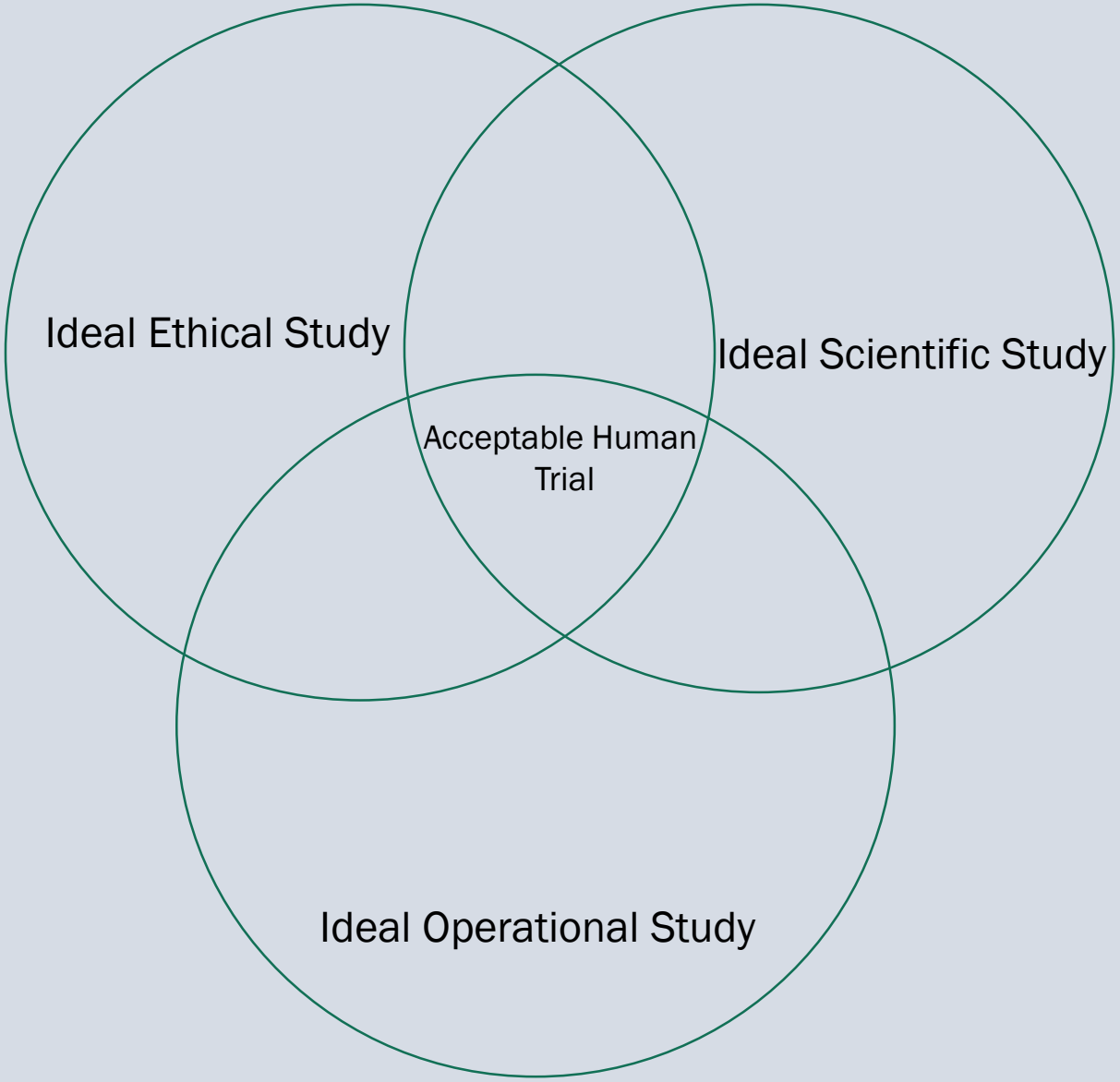
- Should this population be subject to clinical trials?

- What are the goals of such studies?


Ethical Considerations
Scientific Considerations
Operational Considerations


Ideal Ethical Study
Ideal Scientific Study
Ideal Operational Study


Ideal Ethical Study
High likelihood of benefit
Low likelihood of toxicity
Informed Consent Done
Not a phase 1
No randomization
Cross-over design
No dose escalation
Minimal QOL burden
Minimal $ Burden
Largely exclusive
Ideal Scientific Study
Numerous correlative studies
Primary objective is scientific (i.e. ORR)
Fresh tissue specimens
Strict schedule
Central review panels
No Informed Consent
Largely inclusive
Multiple dose levels and control arms
Minimal Procedures
Outpatient setting
Attractive to patients
High $$ support
Low toxicity
Minimization of incl./excl. criteria
Minimization of parameters of study
Ideal Operational Study

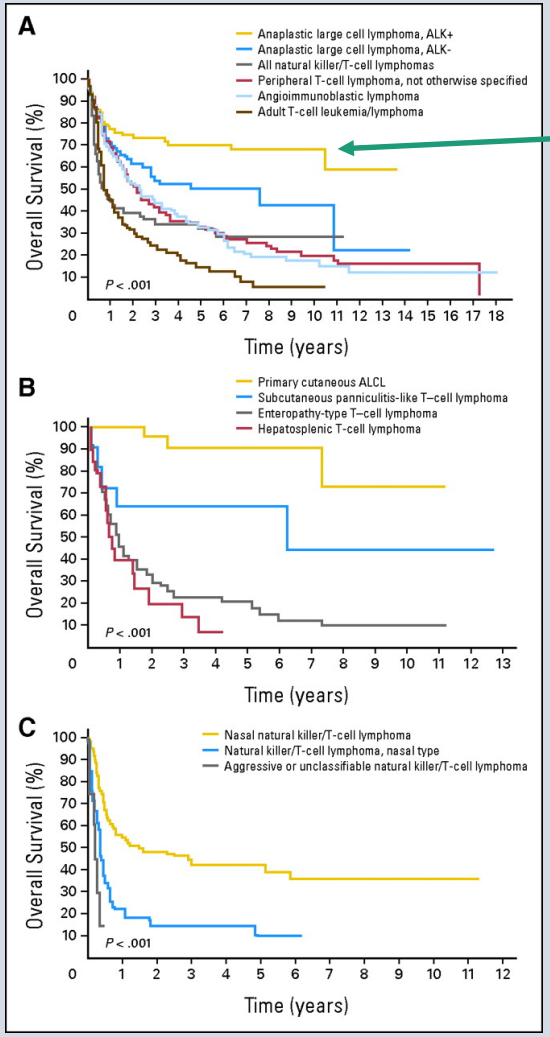

Ideal Ethical Study
Ideal Scientific Study
Acceptable Human Trial
Ideal Operational Study

A Phase IA/IB Open-Label Dose-Finding Study of Ceritinib Combined with Brentuximab Vedotin for Front-Line Treatment of ALK-positive Anaplastic Large Cell Lymphoma

Principal Investigator:

Dr. Andrei Shustov

09/21/2017


A
Anaplastic large cell lymphoma, ALK+
Anaplastic large cell lymphoma, ALK-
All natural killer/T-cell lymphomas
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic lymphoma
Adult T-cell leukemia/lymphoma
Overall Survival (%)
P < .001
Time (years)
B
Primary cutaneous ALCL
Subcutaneous panniculitis-like T–cell lymphoma
Enteropathy-type T–cell lymphoma
Hepatosplenic T-cell lymphoma
Overall Survival (%)
P < .001
Time (years)
C
Nasal natural killer/T-cell lymphoma
Natural killer/T-cell lymphoma, nasal type
Aggressive or unclassifiable natural killer/T-cell lymphoma
Overall Survival (%)
P < .001
Time (years)

ALK+ ALCL

Selected Study Design Basics

- Brentuximab Vedotin: ORR 79%, CR 59%
  - 5-year CR-PFS > 80%
- Ceritinib: Lung Ca ORR 58%; ALCL CR ~ 80%
- bCRM design
- Early stopping rules
- Rigid futility boundary
- Patient #4 risk failure < 2%

CALGB/Alliance 50303: R-CHOP vs DA-EPOCH-R in Newly Diagnosed Diffuse Large B-Cell Lymphoma

Bartlett N et al. *J Clin Onc* 2019; 37

Andrei Shustov, MD
University of Washington
Fred Hutchinson CRC

CALGB/Alliance 50303: Background

- DLBCL: disease with clinically and molecularly different subtypes[1]
  - GCB subtype
  - ABC subtype
- R-CHOP: standard of care for DLBCL[2]
  - Multicenter phase III trial found 5-yr PFS of approximately 65%[3]
- DA-EPOCH-R: dose-intensive treatment alternative
  - Multicenter phase II trial found 5-yr TTP of 81% and 5-yr OS of 84% with DA-EPOCH-R[4]
- Current CALGB/Alliance 50303 compared R-CHOP vs DA-EPOCH-R in pts with untreated stage II-IV DLBCL (subtypes GCB and ABC)[5]

1. Lenz G, et al. N Engl J Med. 2008;359:2313-2323. 2. Sehn LH, et al. Blood. 2015;125:22-32.
3. Cunningham D, et al. Lancet Oncol. 2013;14:1306-1315. 4. Wilson WH, et al. Haematologica. 2012;97:758-765. 5. Wilson WH, et al. ASH 2016. Abstract 469.

Define a Perfect Study

- Does it exist?
- If it does:
  - Prospective
  - Randomized
  - Double-blind
  - Stratified
- Power factors:
  - Multi-center
  - High number of patients
- Hidden pitfalls
  - Selection bias
  - Treatment complexity
  - Excessive burden/delay of Tx
  - Genomic diversity of Dz under study

Define a Perfect Study

- Does it exist?
- If it does:
  - Prospective √
  - Randomized √
  - ~~Double-blind~~
  - Stratified √
- Power factors:
  - Multi-center √
  - High number of patients √
- Hidden pitfalls
  - Selection bias √
  - Treatment complexity √
  - Excessive burden/delay of Tx √
  - Genomic diversity of Dz under study √

CALGB/Alliance 50303: Study Design

- Randomized phase III study

Untreated, newly diagnosed stage II-IV DLBCL (stage I PMBCL), ECOG PS 0-2, LVEF > 45%, tumor biopsies available, no CNS disease
(N = 465)

6 cycles

DA-EPOCH-R*
Rituximab 375 mg/m^2 IV
Cyclophosphamide† 750 mg/m^2 IV
Doxorubicin† 10 mg/m^2 IV on Days 1-4
Etoposide† 50 mg/m^2 IV on Days 1-4
Vincristine 0.4 mg/m^2 IV on Days 1-4
Prednisone 60 mg/m^2 BID on Days 1-5
G-CSF as needed SC on Days 6-12
(n = 262)

R-CHOP*
Rituximab 375 mg/m^2 IV
Cyclophosphamide 750 mg/m^2 IV
Doxorubicin 50 mg/m^2 IV
Vincristine 1.4 mg/m^2 IV (max 2 mg)
Prednisone 40 mg/m^2 PO on Days 1-5
G-CSF as needed SC
(n = 262)

- Primary endpoint: EFS
- Secondary endpoints:
  - RR
  - OS
  - Safety

*Included CNS prophylaxis if BM/testicular involvement or elevated LDH plus ≥ 2 extranodal sites. Prophylaxis: MTX IT x 4 doses on Day 1 of Cycles 3-6.
†Increased 20% if ANC nadir > 0.5. De-escalated if ANC < 0.5 for > 3 days.

Bartlett N et al. *J Clin Onc* 2019; 37

CALGB/Alliance 50303: Baseline Characteristics

Characteristic	R-CHOP	DA-EPOCH-R	*P* Value
Median age, yrs (range)	58 (18-86)	58 (19-84)	.85
ECOG PS, %			.20
▪ 0/1	88	87	
▪ 2	12	13	
Stage, %			.66
▪ 1 (PMBCL)	3	3	
▪ 2	22	20	
▪ 3	29	25	
▪ 4	46	52	
IPI criteria, %			.60
▪ 0/1	27	25	
▪ 2	39	36	
▪ 3	25	26	
▪ 4/5	10	13	

- No significant differences in characteristics between treatment arms

Bartlett N et al. *J Clin Onc* 2019; 37

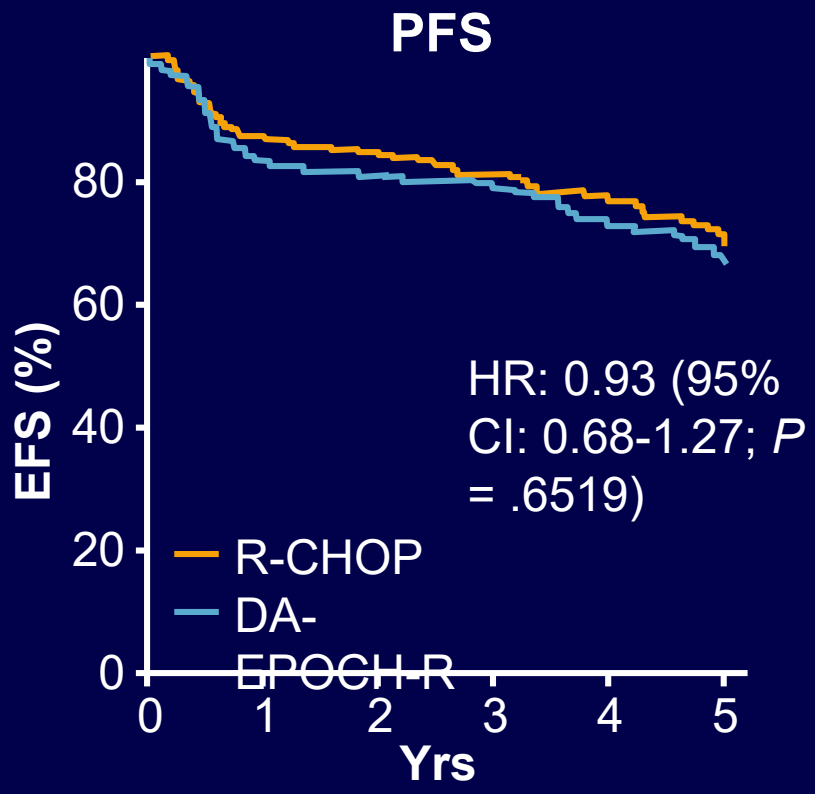
CALGB/Alliance 50303: Response Outcomes

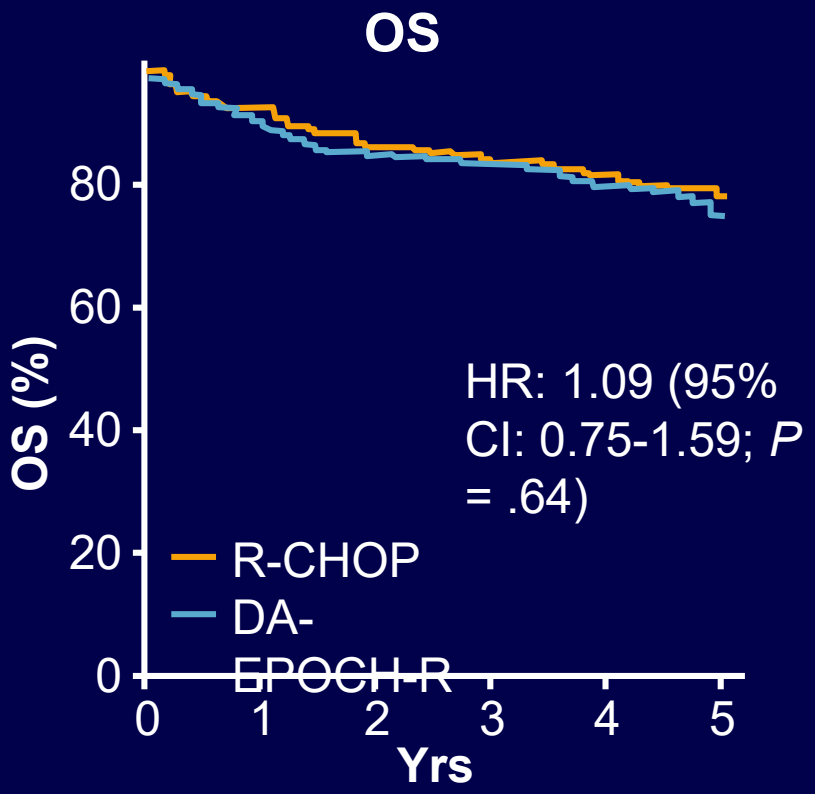
Response, %	R-CHOP	DA-EPOCH-R	*P* Value
ORR	88.0	86.7	.67
▪ CR/CRu	59.6	61.1	
▪ PR	28.4	25.6	
▪ SD	9.2	12	
▪ PD	2.8	1.3	

- No significant difference in response rates between treatment arms

Bartlett N et al. *J Clin Onc* 2019; 37

CALGB/Alliance 50303: Event-Free Survival and OS





Arm	N	Events, n	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	250	83	0.72 (0.67-0.78)	0.66 (0.60-0.72)
DA-EPOCH-R	241	76	0.76 (0.70-0.81)	0.68 (0.62-0.74)

Arm	N	Events, n	3 Yrs (95% CI)	5 Yrs (95% CI)
R-CHOP	250	53	0.85 (0.80-0.89)	0.78 (0.73-0.84)
DA-EPOCH-R	241	56	0.85 (0.79-0.89)	0.77 (0.72-0.83)

Bartlett N et al. *J Clin Onc* 2018;37

CALGB/Alliance 50303: PFS by Age and IPI Score

5-Yr PFS by Subgroup, %	Pts	ALL	R-CHOP	DA-EPOCH-R	*P* Value
Age					
▪ ≤ 60 yrs	59	71	73	70	.073
▪ > 60 yrs	41	63	65	61	
IPI criteria					
▪ 0/1	27	82	90	72	
▪ 2	38	70	72	68	< .001
▪ 3	25	55	50	61	
▪ 4/5	10	53	40	60	

- Posttreatment substudy (n = 171) using PET found no significant difference in 3-yr PFS between PET-positive and PET-negative subsets (80% vs 72%; *P* = .057)

Bartlett N et al. *J Clin Onc* 2019; 37

CALGB/Alliance 50303: AEs

AEs Grade 3-4, %	R-CHOP	DA-EPOCH-R	*P* Value
Treatment-related deaths*	5	5	.975
All grade 3-4 AEs	76.3	96.5	< .001
▪ Hematologic	73.7	97.5	< .001
▪ Nonhematologic	43.2	72.2	< .001
ANC	68	96	< .001
Platelets	11	65	< .001
Febrile neutropenia	18	35	< .001
Infection	11	17	.049
Mucositis	2.1	8.4	.0017
Neuropathy			
▪ Sensory	3.3	18.6	< .001

*5 deaths per arm. R-CHOP: congestive heart failure, 1; CNS bleed, 1; infection, 1; febrile neutropenia, 1; unknown, 1. DA-EPOCH-R: infection, 2; myocardial infarction, 1; unknown, 2.

Bartlett N et al. *J Clin Onc* 2019; 37

CALGB/Alliance 50303: Conclusions

- No differences between R-CHOP vs DA-EPOCH-R for EFS and OS with 5-yr follow-up
- No benefit with DA-EPOCH-R identified among clinical subgroups defined by age and IPI criteria
- Moderately increased rates of grade 3-5 AEs in the DA-EPOCH-R arm vs R-CHOP arm (cytopenias, febrile neutropenia, neuropathy)
- Investigators plan to perform future correlative analyses to potentially identify prognostic subsets, novel treatment targets, and new response or toxicity biomarkers

Bartlett N et al. *J Clin Onc* 2019; 37

Remaining Role For DA-EPOCH-R in DLBCL

- Myc+ DLBCL (?)
- DE DLBCL (?)
- DH DLBCL (?)
- High-Ki67 DLBCL (?)
- High-IPI DLBCL (?)