Pralatrexate (FOLOTYN®) and Belinostat (BELEODAQ®) for the Treatment of Patients with Relapsed or Refractory Peripheral T-Cell Lymphoma (PTCL)

November 16, 2023

Oncologic Drugs Advisory Committee

Acrotech Biopharma

Introduction

Ashish Anvekar

President

Acrotech Biopharma

Both Pralatrexate and Belinostat Are Approved for Relapsed or Refractory (R/R) Peripheral T-Cell Lymphoma (PTCL)

	Pralatrexate	Belinostat
Mechanism of Action	Dihydrofolate reductase inhibitor	Histone deacetylase inhibitor
Recommended Dose	30 mg/m^2 IV over 3 to 5 min QW for 6 weeks in 7-week cycles	1,000 mg/m^2 IV over 30 min QD on Days 1–5 of a 21-day cycle

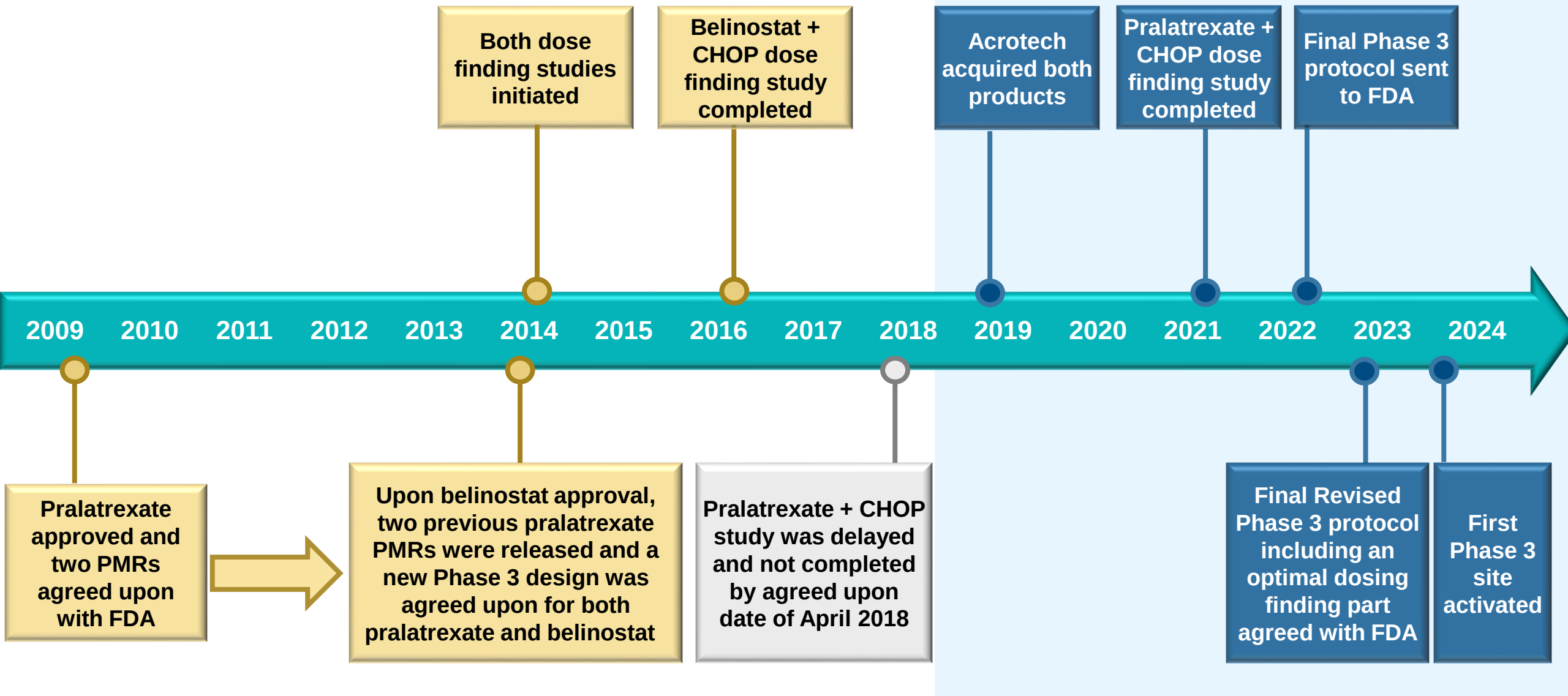
NCCN Guidelines[1]: Pralatrexate and Belinostat are Category 2A Preferred Treatment Regimens in R/R PTCL

- PTCL is a rare, aggressive disease affecting 10,000-15,000 US patients annually[2]
- Most patients with R/R PTCL have limited treatment options
- Most patients relapse and receive multiple lines of therapy

Clear need for both of these effective products with different mechanisms of action

1. NCCN Guidelines Version 1.2023 T-Cell Lymphomas; 2. SEER Cancer Statistics Review (CSR) as of 2011, most recent

Confirmatory PMR Trial Design Change History



Other Post-Marketing Requirements (PMR) Studies Fulfilled or Underway

Pralatrexate Post-Marketing Requirements	Completion
1. SPI-FOL-101: Ph 1 dose-finding for Pralatrexate-CHOP*	✓
2. *In vitro* transporter studies to determine if OAT substrate (N=5)	✓
3. PDX-016: Ph 1 excretion and metabolic profile in patients with advanced cancer	✓
4. PDX-019: Ph 1 PK in patients with renal impairment	✓
5. SPI-FOL-102: Ph 1 in patients with hepatic impairment	~ Dec 2024
Belinostat Post-Marketing Requirements	**Completion**
1. SPI-BEL-12-104: Ph 1 dose-finding for Belinostat-CHOP	✓
2. *In vitro* studies: Biotransformation to metabolites	✓
3. SPI-BEL-12-103: Ph 1 PK/PD excretion	✓
4. NCI-8846: Ph 1 PK in patients with hepatic impairment	✓
5. SPI-BEL-105: Ph 1 PK in patients with renal impairment*	✓
6. SPI-BEL-106: Ph 1 Genotype Study to evaluate safety & PK*	✓
7. SPI-BEL-107: Ph 1 drug-drug interactions*	✓

***Study completed by Acrotech after 2019 acquisition**

Agenda

Disease Background and Treatment Landscape

Owen A. O'Connor, M.D., Ph.D.
American Cancer Society Research Professor
Professor of Medicine, University of Virginia Comprehensive Cancer Center
Director, Translational Orphan Blood Cancer Research Center
Director, Program for T-Cell Lymphoma Research
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PMR Studies: Phase 1 Results and Phase 3 Design

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PMR Study Timeline

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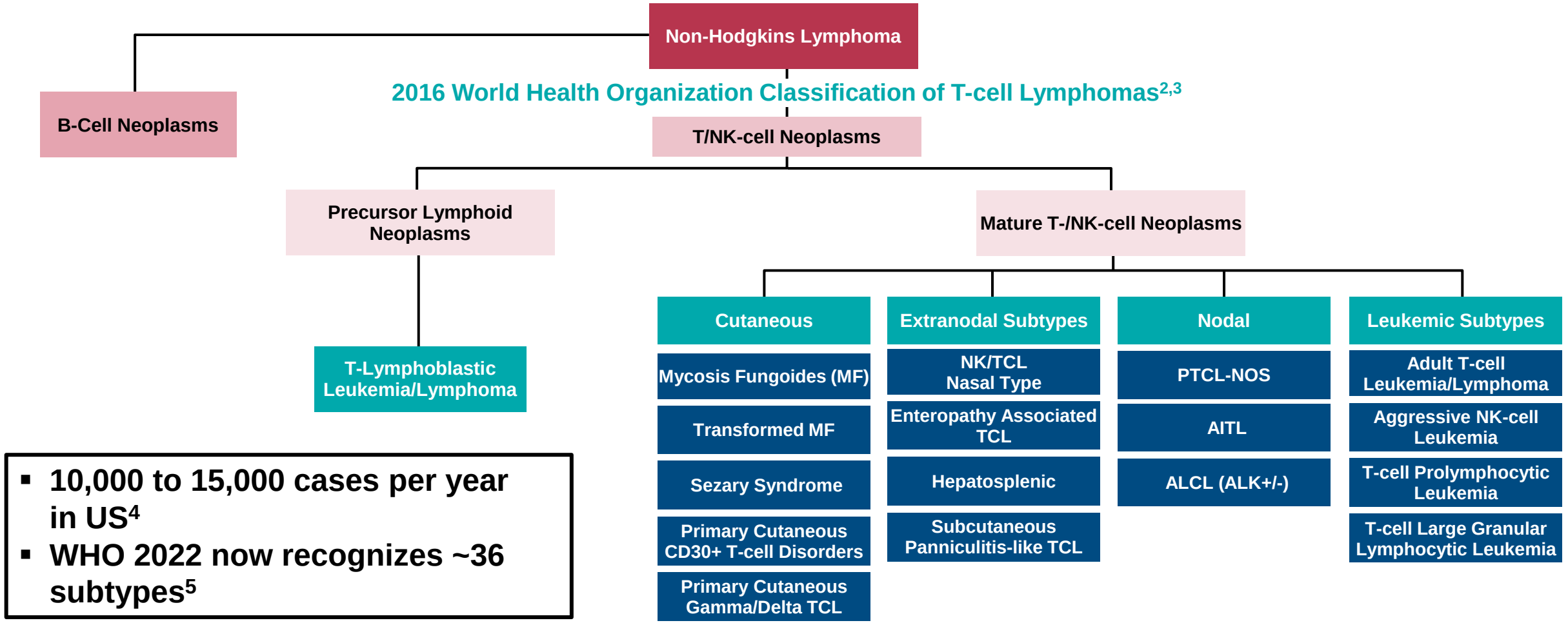
Why Has Progress in PTCL Been Slow? T-Cell Neoplasms are Rare and Heterogenous[1] Diseases



- 10,000 to 15,000 cases per year in US[4]
- WHO 2022 now recognizes ~36 subtypes[5]

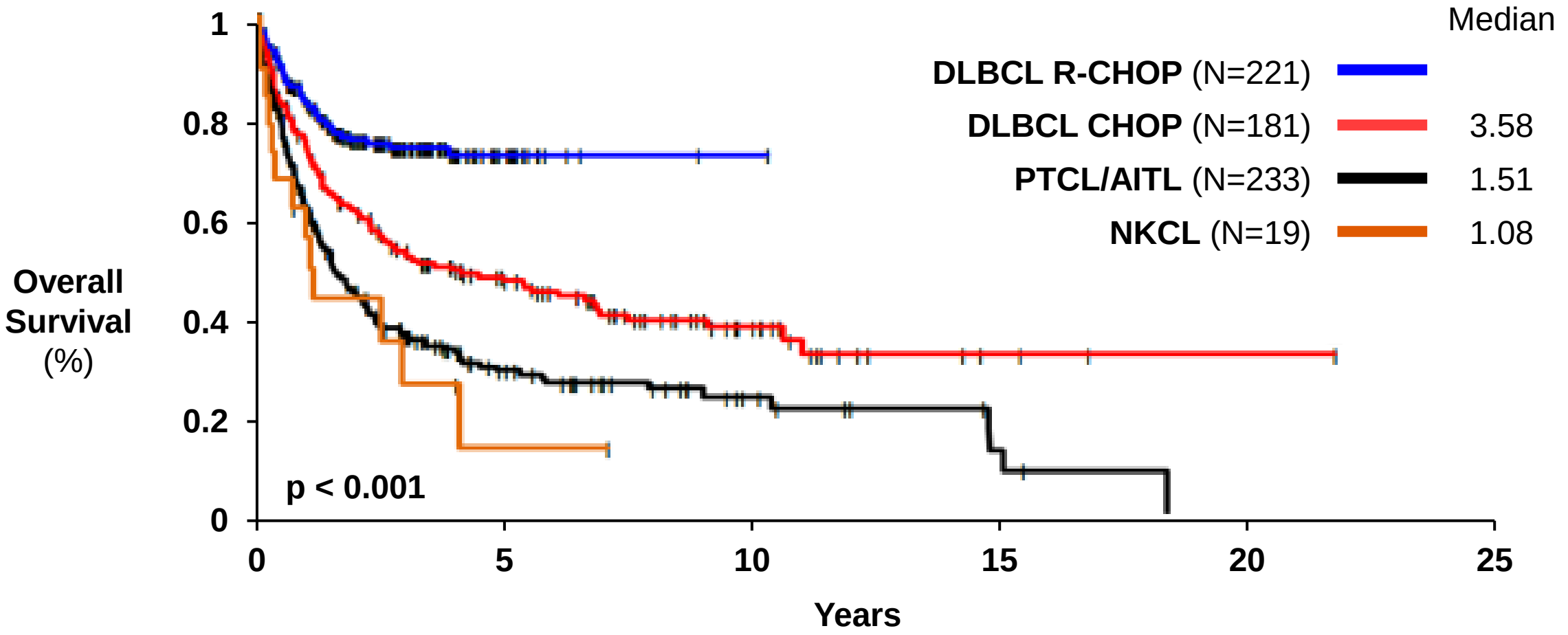
1. Armitage et al, 2004.; 2. Adapted from Rodriguez et al, 2008; 3. Adopted from Swerdlow et al, 2016; 4. SEER Cancer Statistics Review (CSR) as of 2011, most recent; 5. Alaggio et al, 2022

PTCL are Aggressive, Often Do Not Respond to Conventional Therapy, and Lack a Standard of Care (SOC)

- No prospective randomized data establishing a SOC
- Study leading to CHOP as ‘SOC’ did not enroll a single patient with PTCL
- CHOEP, the 2nd most commonly used regimen, based on German retrospective study that failed to show an advantage over comparators
- NCCN recommends a clinical trial as preferred treatment in both front-line and in the relapsed or refractory setting
- All subtypes are often ‘lumped’ into single category

Rarity, heterogeneity and aggressiveness of PTCL make defining SOC daunting

Improved Outcomes in Every Type of B-Cell Malignancy and Hodgkin Lymphoma, but None in PTCL



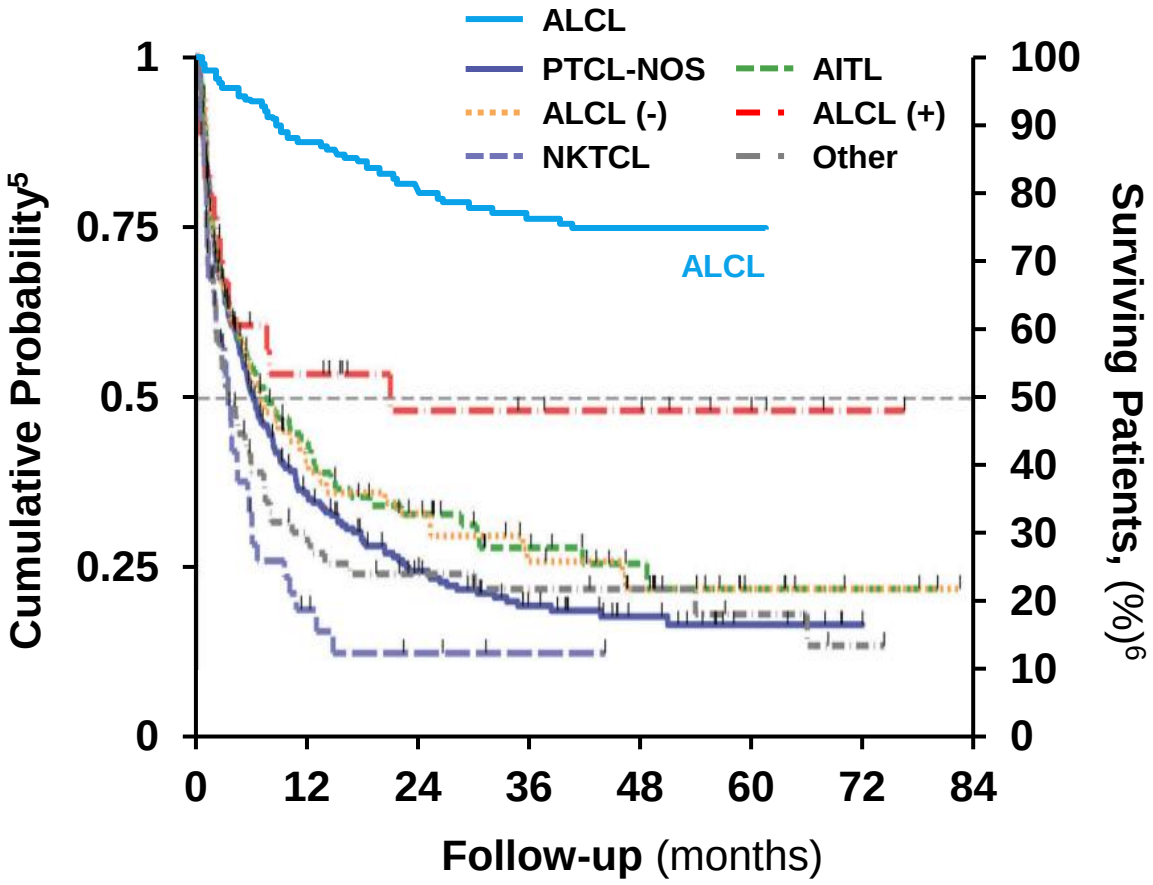
Lone et al, 2018

A Poor Prognosis and Early Relapse with Few Agreed Upon Options

- Unlike B-cell lymphomas, PTCL outcomes remain poor
  - mOS < 2 years
  - 5-year survival of < 30%[1-5]

In < 1 year, 2/3 of patients had R/R disease[5]

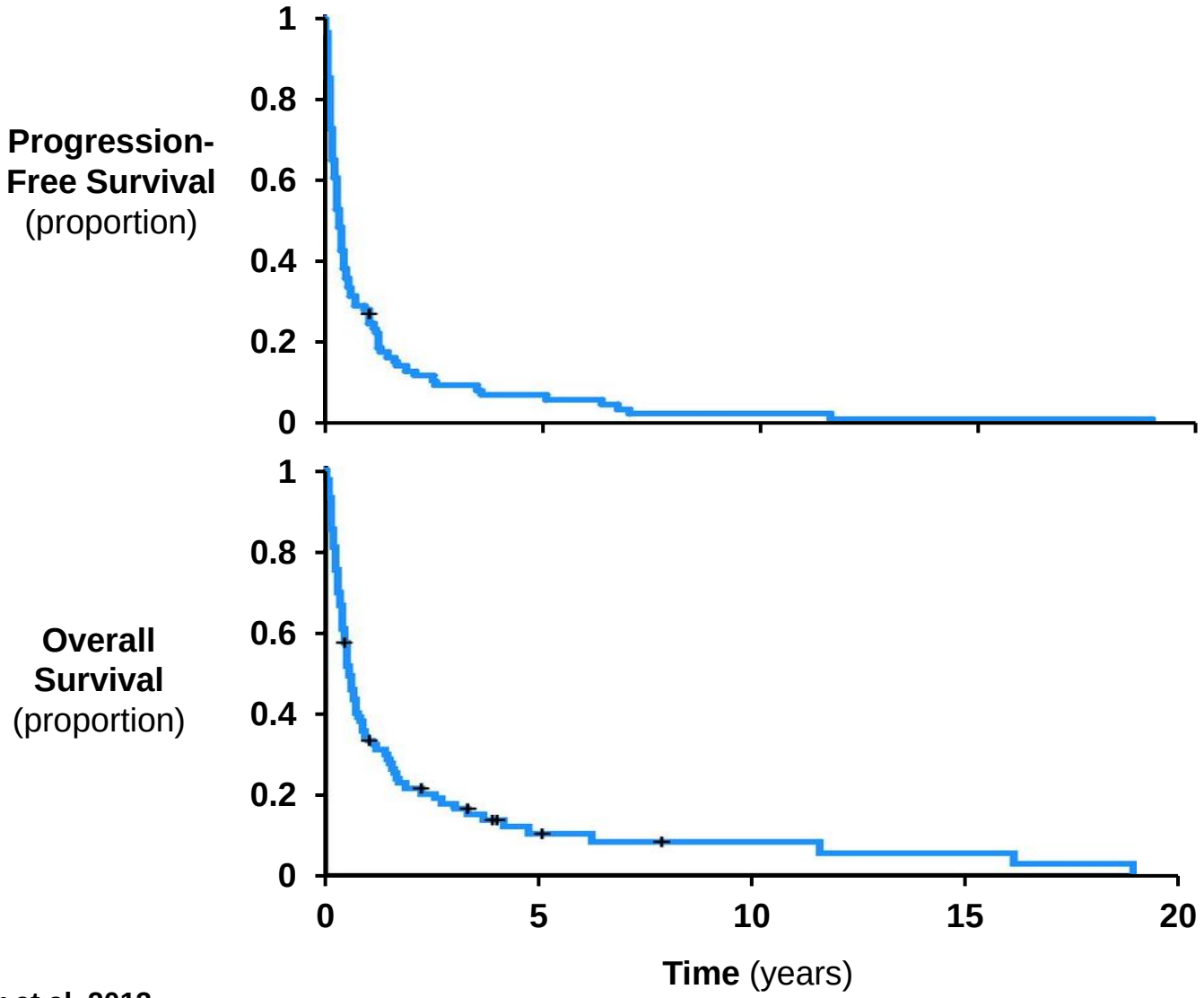
- Even with autologous stem-cell transplant, 5-year outcomes are poor[7,8]
  - PFS 24%
  - OS 33%
  - Unclear if ASCT in 1st remission is beneficial but is often performed



Only ALCL is associated with better OS

1. Vose et al, 2008; 2. Armitage et al, 1998; 3. Lopez-Guillermo et al, 1998; 4. Rudiger et al, 2002; 5. Bellei et al, 2018; 6. Horwitz 2019; 7. Kewalramani et al, 2006; 8. Rodriguez et al, 2019

Chemotherapy in Relapsed or Refractory Setting is Relatively Ineffective



2nd Line Treatment
PFS = 3.7 months

patients treated with chemotherapy (n = 89) with R/R PTCL

2nd Line Treatment
OS = 6.5 months

after first relapse or progression of PTCL

Mak et al, 2013

First-Line Treatment for PTCL has Remained Largely Unchanged for 30 Years

- CHOP/CHOEP remain ‘SOC’ for all other subtypes except ALCL by default
  - CHOP produces an ORR of ~60%[1]
- Unlike R-CHOP in B-cell lymphoma, CHOP based therapy produces sub-optimal outcomes in PTCL[2]
  - Bv-CHP has not demonstrated any OS benefit for non-ALCL patients despite their positivity for CD30 (i.e., PTCL-NOS, AITL)[3]

Except for ALCL subtype, NCCN recommends clinical trial as the preferred treatment

1. Bachy et al, 2022; 2. Gisselbrecht et al, 1998; 3. Horwitz et al, 2022; 4. NCCN Guidelines Version 1.2023 T-Cell Lymphomas

Treatments for Relapsed or Refractory PTCL

	MoA	Indication (PI)
Pralatrexate[1]	Dihydrofolate reductase inhibitor	For the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)
Belinostat[2]	Histone deacetylase (HDAC) inhibitor	For the treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma (PTCL)
Romidepsin[3] ***[Withdrawn]***	Histone deacetylase (HDAC) inhibitor	Withdrawn for the treatment of peripheral T-cell lymphoma (PTCL) in adult patients who have received at least one prior therapy

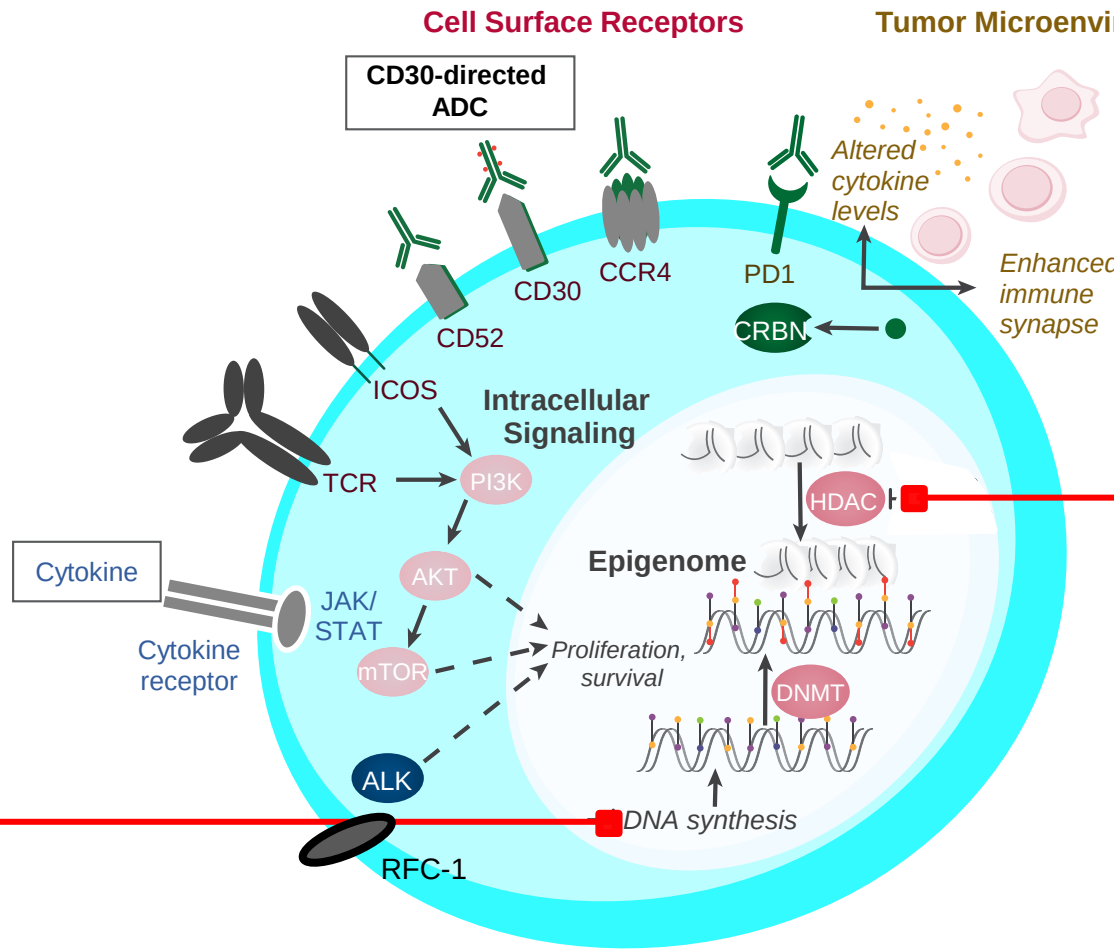
- Romidepsin indication for R/R PTCL withdrawn due to failed Phase 3
- In the relapsed/refractory setting, brentuximab vedotin is only approved for ALCL[4]
- ASCT may be curative, though failure to control disease is major barrier
- CAR-T based therapies for PTCL have not yielded promising results to date

1. O'Connor et al, 2011; 2. O'Connor et al, 2015. 3. Coiffier et al, 2012; 4. Pro et al, 2017

Pralatrexate and Belinostat Offer Different MoA Targeting Critical Pathways

Pralatrexate (folate antagonist)

- High affinity for reduced folate carrier (RFC-1) receptors accelerating uptake
- Impairs DNA synthesis
- Unique properties that distinguish from other anti-folates



Belinostat (HDAC inhibitor)

- Shifts chromatin to "open" conformation which is transcriptionally active
- May increase tumor suppressor genes, silence oncogenes, induce cell cycle death and apoptosis

AKT, protein kinase B; CCR4, chemokine receptor 4; CRBN, cereblon; DNMT, DNA methyltransferase; ICOS, inducible T cell co-stimulator; JAK, Janus kinase; PD1, programmed death receptor 1; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription; TCR, T cell receptor.
Adapted from Mulvey et al, 2020

Studies Supporting Accelerated Approvals of Pralatrexate and Belinostat and Other Supporting Datasets

Pralatrexate and Belinostat: Primary Efficacy Data Supporting Accelerated Approval

	PROPEL Study Pralatrexate[1] N = 109	BELIEF Study Belinostat[2] N = 120
Overall response rate (ORR), n (%)	**32 (29%)**	**31 (26%)**
Best overall response		
Complete response (CR)	**11 (10%)**	**13 (11%)**
Complete response unconfirmed (CRu)*	**1 (1%)**	**-**
Partial response (PR)	**20 (18%)**	**18 (15%)**
Duration of response, median (95% CI)	**10.1 months** (3.4–NE)	**13.6 months** (4.5–29.4)
Progression-free survival (PFS), median (95% CI)	**3.5 months** (1.7–4.8)	**1.6 months** (1.4–2.7)
Overall survival (OS), median (95% CI)	**14.5 months** (10.6–22.5)	**7.9 months** (6.1–13.9)

1. O'Connor et al, 2011; 2. O'Connor et al, 2015

***CRu is a category between CR and PR (ie, does not strictly match either CR or PR); a CRu does not indicate a short-lasting CR**

New Drugs are Making a Difference: Best Prospective Data Comparing to Traditional Chemotherapy

Response (95% CI)	**Alisertib** N = 102	**Gemcitabine** N = 23	**Pralatrexate** N = 51	**Romidepsin** N = 18
ORR (CR + PR)	**33%** (24%, 43%)	**35%** (16%, 57%)	**43%** (29%, 58%)	**61%** (36%, 83%)
CR	**18%** (11%, 26%)	**22%** (7%, 44%)	**27%** (16%, 42%)	**33%** (13%, 59%)
PR	**16%** (9%, 24%)	**13%** (3%, 34%)	**16%** (7%, 29%)	**28%** (10%, 53%)

The LUMIERE Study failed largely because the dealers choice arm outperformed expectations for the drugs most commonly used in that arm

O'Connor et al, 2018 (LUMIERE Study)

Pralatrexate Efficacy Also Validated Across 3 Single-Arm Studies Leading to Registration

Study	Pralatrexate		
	ORR	CR	Median Prior Lines
Japan[1] (N = 20)	**45%**	**10%**	**3** (1-8)
China[2] (N = 37)	**52%**	**11%**	**2** (1-14)
Taiwan[3] (N = 21)	**57%**	**5%**	**NR**

NR, not reported

1. Maruyama et al, 2017 ; 2. Hong et al, 2019 ; 3. FOT14-TW-401 CSR

Safety Profiles for Pivotal Studies Supporting Accelerated Approvals and Post-Marketing Experience

	PROPEL Study Pralatrexate[1] N = 111	BELIEF Study Belinostat[2] N = 129	R/R sALCL Brentuximab vedotin[3] N = 58
Treatment-related AE Grade 3/4	74%	61%	83%
Treatment-related SAE	44%	47%	41%
Treatment discontinuation due to AEs	23%	19%	19%

	Pralatrexate[1]	Belinostat[2]	Brentuximab vedotin[3]
Post-Marketing Experience	• Toxic epidermal necrolysis identified	• None reported	• Febrile neutropenia • Acute pancreatitis and GI complications • PML • Hyperglycemia • Pulmonary toxicities • Toxic epidermal necrolysis

1. Folotyn Prescribing Information; 2. Beleodaq Prescribing Information; 3. Adcetris Prescribing Information

Pralatrexate and Belinostat are Essential for Management of Relapsed or Refractory PTCL

- Pralatrexate and belinostat are the only FDA approved drugs for patients with R/R PTCL
  - Brentuximab activity resigned to ALCL and relatively ineffective in non-ALCL forms of PTCL
- **No** consensus for treatment in front-line and beyond
  - CHOP is defacto SOC yet NCCN recommends clinical trials
- Independent datasets affirmed marked activity of pralatrexate including 3 registration studies across Asia; many lines of other supporting data have affirmed value of these drugs
- Failure to change natural history of PTCL over past 30 years mandates that we explore all reasonable options

Use of pralatrexate and belinostat in the front-line represent a potentially important advancement for PTCL

PMR Studies: Phase 1 Results and Phase 3 Design

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Department of Lymphoma / Myeloma

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SPI-FOL-101 and SPI-BEL-12-104: Open-Label, Multicenter, Two-Part, Dose-Finding, Dose-Escalation Studies

	Pralatrexate + CHOP[1] N = 52	Belinostat + CHOP[2] N = 23
Enrollment Criteria	▪ Newly diagnosed, untreated, histology-proven PTCL ▪ Eligible for CHOP chemotherapy	▪ Newly diagnosed, untreated, histology-proven PTCL ▪ Eligible for CHOP chemotherapy
Demographics	▪ Majority of patients male and white ▪ Median age = 62 years	▪ Majority of patients male and white ▪ Median age = 63 years
PTCL diagnosis	▪ PTCL,NOS, n = 34 (65%) ▪ ALCL, ALK(-), n = 7 (14%) ▪ AITL, n = 9 (17%)	▪ PTCL,NOS, n = 9 (39%) ▪ ALCL, ALK(-), n = 1 (4%) ▪ AITL, n = 10 (43%)

1. SPI-FOL-101 CSR; 2. SPI-BEL-12-104 CSR

SPI-FOL-101: Pralatrexate Phase 1 PMR Study Design

Part 1 – Dose Finding

- Treated with 10, 15, 20, 25, or 30 mg/m^2 on Days 1 and 8 of each cycle, in sequential cohorts with standard CHOP regimen
- No patients experienced dose-limiting toxicities (DLTs)
- MTD not reached, so 30 mg/m^2 was selected

Part 2 – Expansion Cohort

- 33 additional patients
- Patients treated on Days 1 and 8 every 21 days with up to 6 cycles of therapy, or until toxicity or disease progression

SPI-FOL-101: Pralatrexate ORR of 84% and Acceptable Safety at Recommended Dose

	Cohort 1 10 mg/m^2 Pralatrexate + CHOP N = 4	Cohort 2 15 mg/m^2 Pralatrexate + CHOP N = 3	Cohort 3 20 mg/m^2 Pralatrexate + CHOP N = 3	Cohort 4 25 mg/m^2 Pralatrexate + CHOP N = 3	Cohort 5 30 mg/m^2 Pralatrexate + CHOP N = 6	Expansion 30 mg/m^2 Pralatrexate + CHOP N = 33
ORR	100%	67%	100%	100%	83%	84%*
CR	75%	33%	67%	67%	83%	65%*
PR	25%	33%	33%	33%	0	19%*
Any AEs	100%	100%	100%	100%	100%	100%
AEs leading to death	0	0	0	0	0	3%
Any SAEs	50%	67%	33%	0	33%	36%
AEs leading to dose reduction	0	0	0	0	17%	21%
AEs leading to dose interruption	0	100%	67%	0	50%	42%
AEs leading to discontinuation	0	0	0	0	33%	21%

*2 patients not included in efficacy analysis (did not get imaging)

SPI-BEL-12-104: Belinostat Phase 1 PMR Study Design

Part A – Dose Escalation

- Cohort 3 received 1,000 mg/m^2 on Days 1–3 of every cycle with CHOP
- Cohort 5 received 1,000 mg/m^2 on Days 1–5 of every cycle with CHOP
- No patients treated in Cohort 1, 2 and 4
- No DLTs in Cohort 5, so 1,000 mg/m^2 on Days 1-5 was selected

Part B – Expansion Cohort

- Total of 15 patients treated, 12 additional patients in expansion cohort
- Patients treated on Days 1-5 every 21 days with up to 6 cycles of therapy, or until toxicity or disease progression

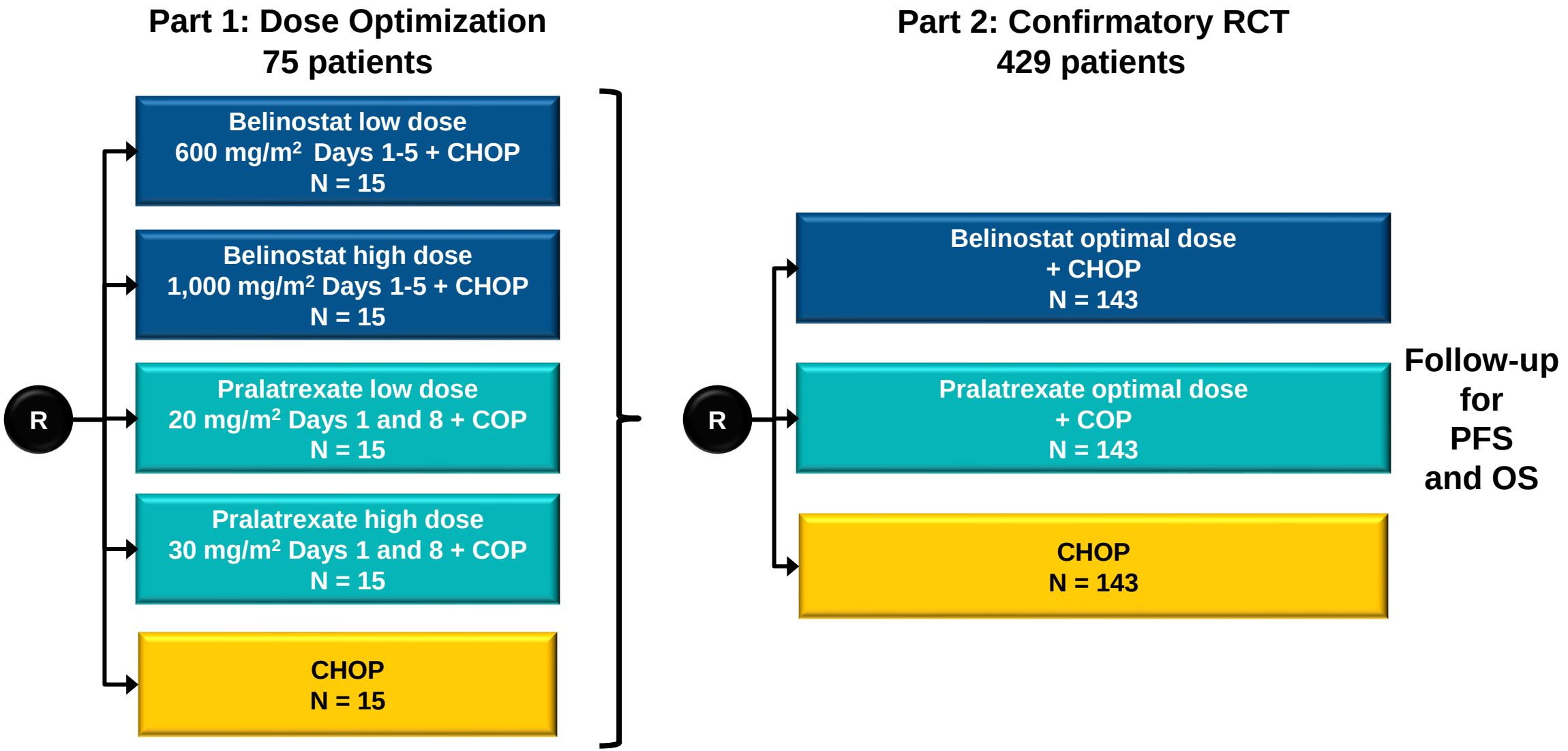
SPI-BEL-12-104: Belinostat ORR of 86% and Acceptable Safety at Recommended Dose

	Cohort 3* 1000 mg/m² Belinostat (Day 1-3) + CHOP N = 8	Cohort 5* + Expansion 1000 mg/m² Belinostat (Day 1-5) + CHOP N = 15
ORR	**86%†**	**86%†**
CR	**57%†**	**71%†**
PR	**29%†**	**14%†**
Any AE	**100%**	**100%**
Any SAE	**38%**	**47%**
AE leading to dose reduction	**13%**	**0**
AE leading to dose interruption	**25%**	**13%**
AE leading to discontinuation	**13%**	**0**

Johnston et al, 2021
***No patients treated in Cohorts 1, 2 or 4; †1 patient not evaluable for efficacy**

Phase 3 PMR
Belinostat + CHOP and Pralatrexate + COP for First-Line PTCL

SPI-BEL-301 Phase 3 PMR Study Design in Patients with Newly Diagnosed, Untreated PTCL



SPI-BEL-301 Phase 3 PMR Endpoints

Part 1: Dose Optimization

Part 2 dose based on

Primary Endpoint

- **Safety**
- **ORR at 3 months**

Other parameters

- **Pharmacokinetics**
- **Exposure-response relationship**

Optimal Dose

Part 2: Confirmatory RCT

Primary Endpoint

- PFS

Secondary Endpoints

- OS
- ORR
- Treatment compliance

Exploratory Endpoints

- Dose intensity
- DoR
- % receiving HSCT

Safety Profiles

SPI-BEL-301 Phase 3 PMR Independent Data Monitoring Committee (IDMC)

- 2 clinicians and 1 biostatistician
- Periodical review of patient-level efficacy and safety data
  - Efficacy: ORR, PFS, OS, dose intensity, treatment compliance
  - Overall safety, including mucositis, neutropenia, hemorrhagic events
- Planned IDMC meetings
  - End of Part 1 data following enrollment of 75 patients with 3 months data
  - Planned meeting at 6 months after first patient in Part 1, and after each additional 100 enrolled patients in Part 2
  - Annual meetings
- Recommend study continuation or discontinuation
  - First futility analysis at end of Part 1
  - Second futility analysis after 120 PFS events in Part 2

SPI-BEL-301 Phase 3 PMR Statistical Considerations

- **Part 1**
  - N = ~75 (15 per arm) expected to last 24 months
- **Part 2**
  - Will not include patients or data from Part 1
  - Sample size of 429 patients
    - CHOP study reference for assumptions[1] for PFS
    - Hazard Ratio 0.7 (mPFS improves from 10 to 14 months)
    - 80% power, 2.5% one-sided type I error rate, 10% drop-off
    - 379 PFS events (126 each treatment, 127 control)
    - OS: same assumptions, mature data requires longer follow-up

1. Bachy et al, 2022

Summary of Confirmatory PMR Study Design

- One of largest randomized studies capturing heterogeneity of PTCL
- Study design based on discussions with FDA
  - Part 1 dose optimization
  - Part 2 confirmatory clinical benefit
- IDMC will review safety and efficacy at regular intervals

PMR Study Timeline

Ashish Anvekar

President

Acrotech Biopharma

Timeline for Completion of SPI-BEL-301

Milestone/Submission	Date
Part 1 initiation	Oct 4, 2023
Part 1 trial completion	Oct 2025
Part 2 initiation	Dec 2025
Part 2 Accrual of 25% of patients	Apr 2026
Part 2 Accrual of 50% of patients	Sep 2026
Part 2 Accrual of 75% of patients	Feb 2027
Part 2 Accrual of 100% of patients	Aug 2027
Trial completion with 2-year follow-up	Feb 2030

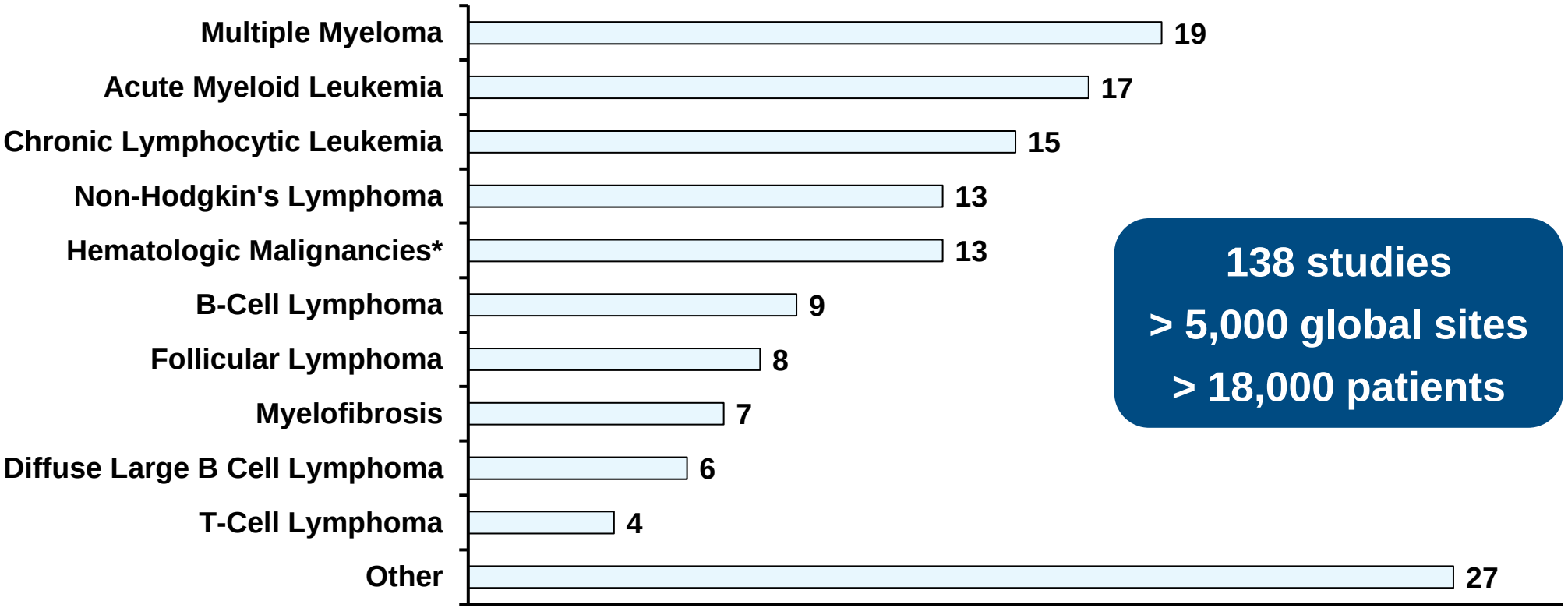
End of Part 1 Data Review ~ Dec 2025

Interim PFS results for first 120 events ~ Feb 2028

Final PFS results ~Mar 2030

Experienced CRO with Global Presence and Proven Ability to Conduct and Complete Clinical Studies

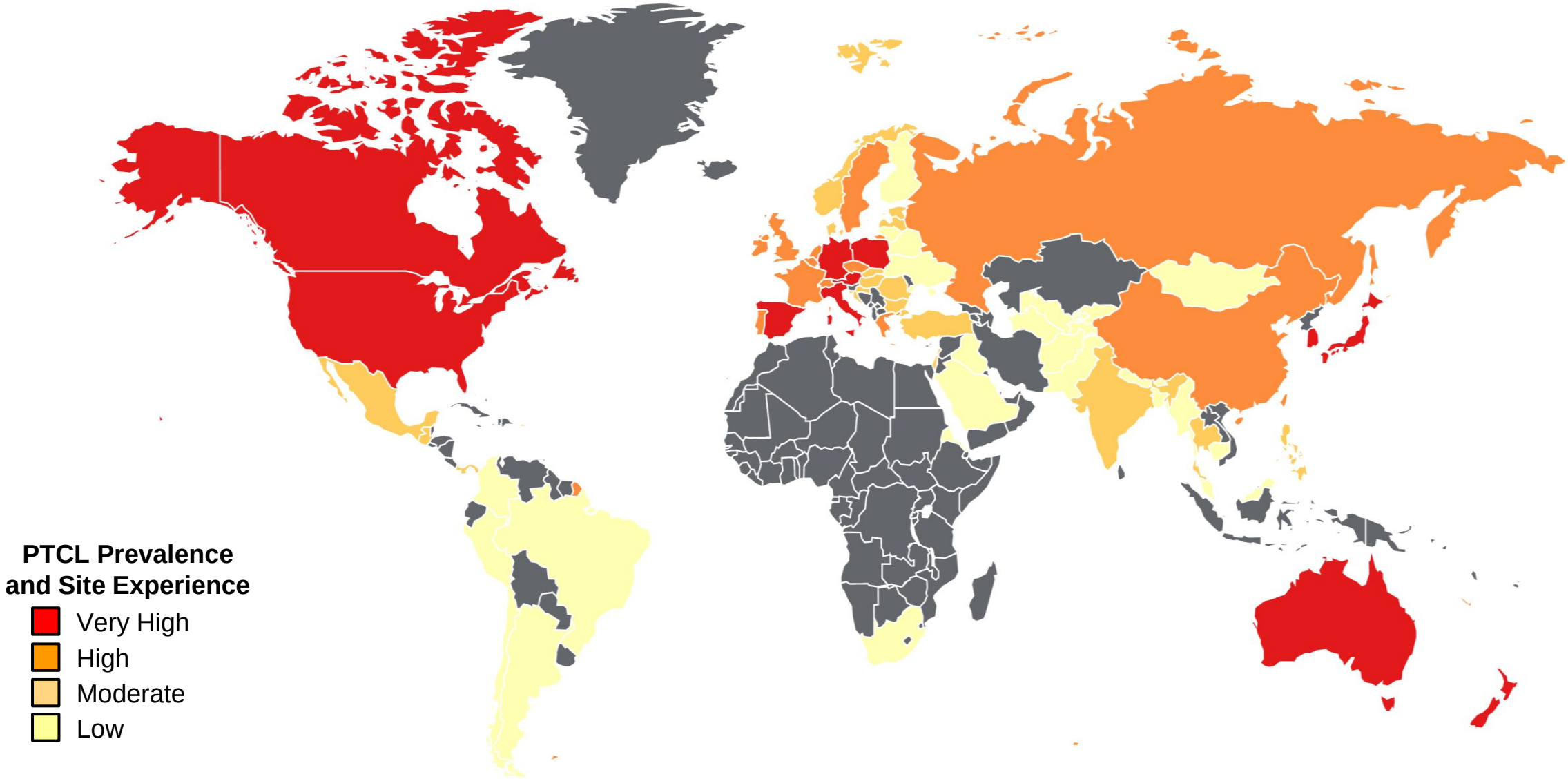
Number of Hematology-Oncology Clinical Trials (All Phases, 2016-2021)



138 studies
> 5,000 global sites
> 18,000 patients

*Indication was broadly defined and not otherwise specified in the protocol.
All experience data: 2016-2021. Data is representative of all Syneos Health company experience. Does not include non-interventional or healthy volunteer studies.

SPI-BEL-301 has Targeted Sites in Countries with Greatest Ability to Enroll Patients with PTCL



SPI-BEL-301 Proceeding as Planned

- Company has taken proactive steps to initiate Phase 3 study
  - CRO has screened sites
  - 77 sites in 10 countries have agreed to participate to date
- Protocol approved by central Institutional Review Board in US in August 2023
- First site in US initiated in October 2023

SPI-BEL-301 Will Recruit from Many Sites, Targeting at Least 50% of Patients from US and Canada

	SPI-BEL-301 - Part 1 N = 75	SPI-BEL-301 - Part 2 N = 429
Total participating sites	**77**	**100**
Planned patients recruited from US and Canada, n **(%)**	23 **(31%)**	275 **(64%)**
Estimated enrollment rate, patients / site / month	**0.14**	**0.21**
Estimated time for enrollment completion, months	**18**	**21**

Acrotech has Investigated Potential Strategies to Shorten Timeline

- Increased # of sites → shorten enrollment time

- Trial in another indication will not reduce timeline because will need to create protocol and identify optimal dose

Acrotech is Committed to Completing PMRs

- Phase 1 pralatrexate PK study in patients with hepatic impairment targeted to be completed by December 2024
- Phase 3 study in patients with newly diagnosed PTCL opened for enrollment in October 2023

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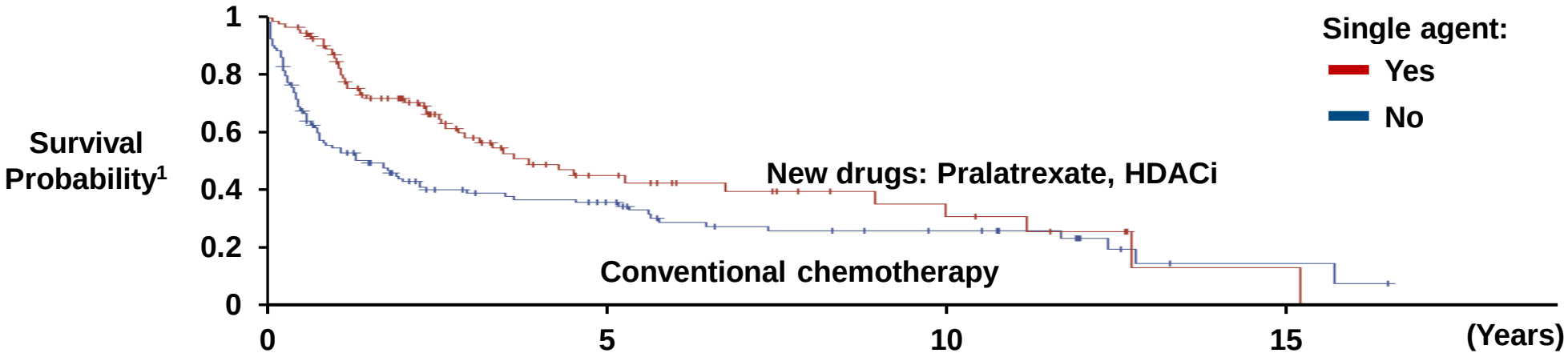
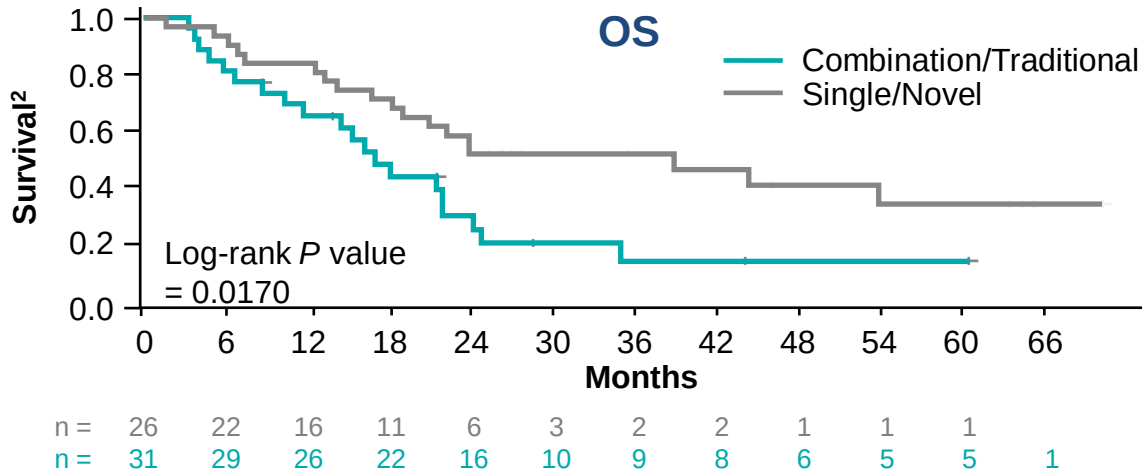
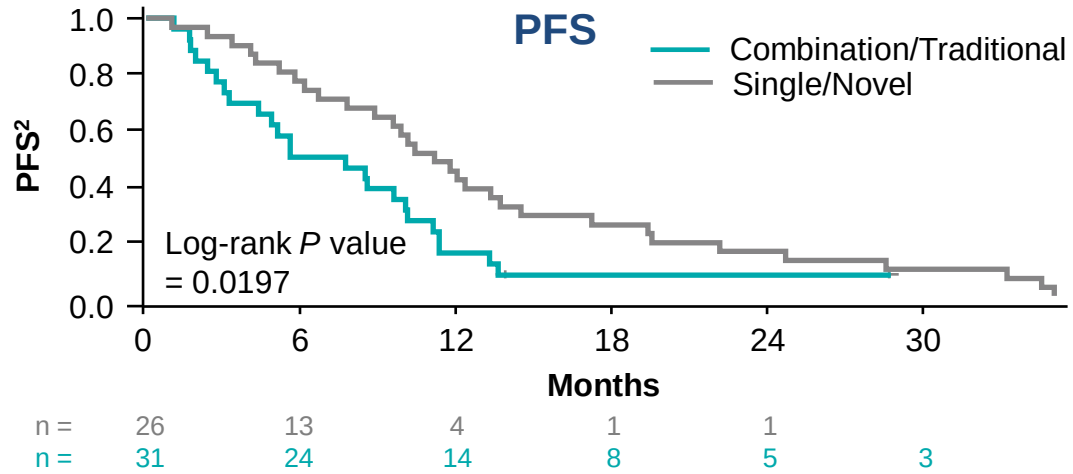
Q&A Slides Shown for the Record

Single Agents Likely Offer A Survival Benefit







Greater OS and PFS with the use of single agents vs combination chemotherapy for PTCL first retreatment observed in the COMPLETE registry

1. Ma et al, 2020; 2. Stuver et al, 2019

Survival Benefit of Single Agents may be Associated with Fewer Grade 3 / 4 AEs

	Combination Chemotherapy N = 26	Single Agent N = 31
Any grade 3/4 AE	81%	65%
Anemia	31%	16%
Fatigue	31%	19%
Febrile neutropenia	23%	16%
Neutropenia	46%	26%
Thrombocytopenia	54%	32%
Supportive measures		
Anti-emetics	58%	58%
Blood/platelet transfusion	42%	29%
Growth factor, EPO	15%	3%
Growth factor, GCSF	62%	26%
Opioid analgesics	27%	26%

The COMPLETE study is a prospective registry of 499 patients, who progress after front-line therapy or have primary refractory disease, who enrolled between 2010 and 2014 at academic and community sites in the United States detailing patient demographics, treatment and outcomes for patients with aggressive T cell lymphomas

Stuver et al, 2019