Timely Completion of Confirmatory Trials after Oncology Accelerated Approvals

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ODAC Agenda

1. Discuss the timely completion of confirmatory trials after accelerated approval
   - Risks of delayed confirmatory trials
   - Causes of delays
   - Strategies to minimize risk

2. Review delayed confirmatory trials for pralatrexate and belinostat (Acrotech Biopharma and FDA)

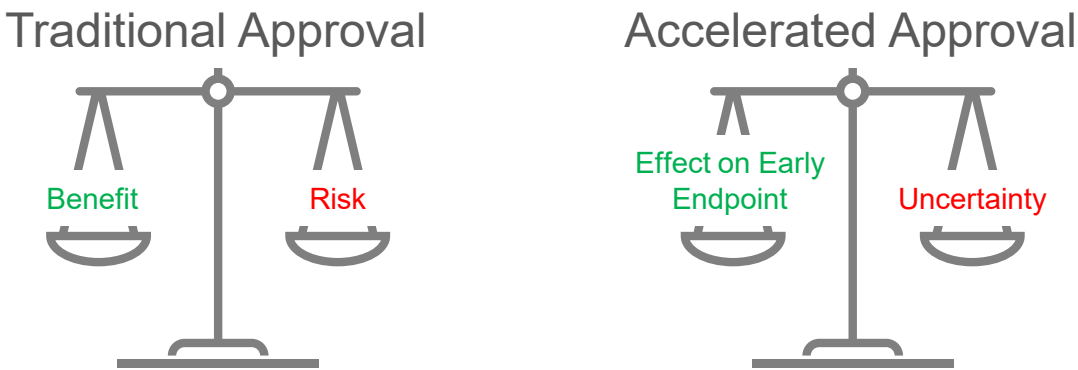
Key Points

1. Accelerated approval provides earlier access to life-saving drugs for patients with cancer, but is associated with an inherent period of vulnerability after approval and before clinical benefit is verified

2. Reducing this period of vulnerability is best done prospectively through a comprehensive development strategy with rational timelines

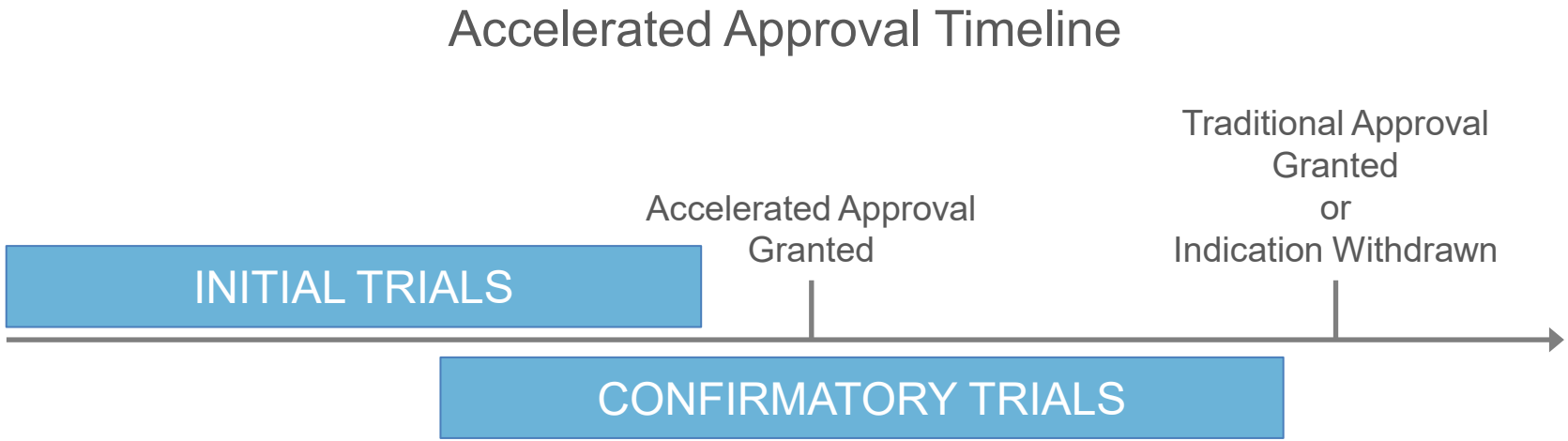
Accelerated Approval

- Provides early access to drugs based on early clinical endpoints that are reasonably likely to predict clinical benefit
- Balanced against some uncertainty that the drug may not provide clinical benefit



Confirmatory Trials

Post-marketing confirmatory trials are required to verify clinical benefit



Withdrawal of Accelerated Approval

FDA may withdraw approval, among other reasons, if:

- "a study required to verify and describe the predicted effect on irreversible morbidity or mortality, or other clinical benefit of the product fails to verify and describe such effect or benefit;"

OR

- "other evidence demonstrates that the product is not shown to be safe or effective under the conditions of use;"

– Section 506(c) of the FD&C Act

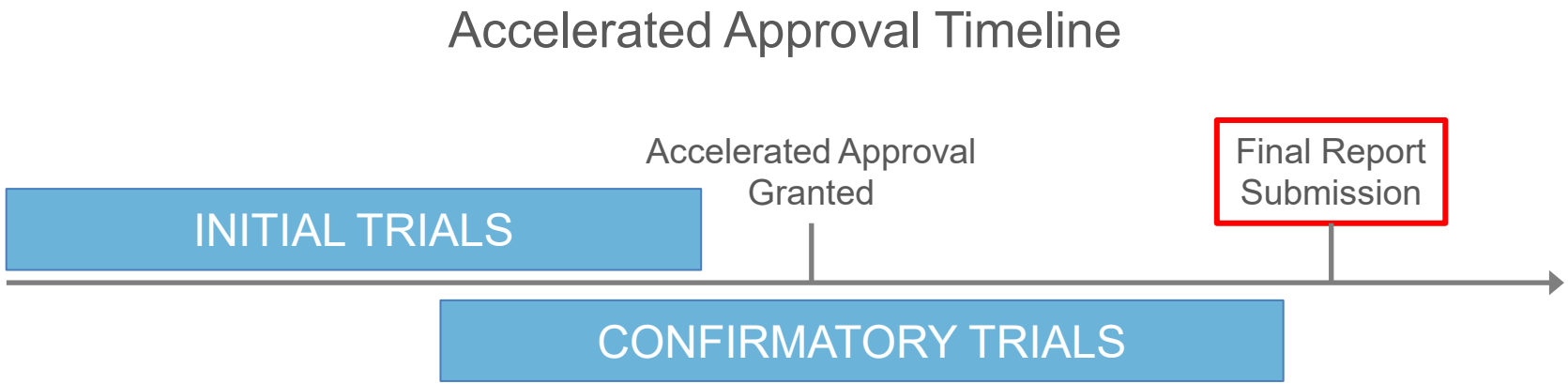
Withdrawal of Accelerated Approval

- Decision to withdraw an accelerated approval is not automatic

- FDA considers:
  - Available confirmatory trial results
  - Current benefit-risk assessment and available therapies
  - Potential safety advantage

Confirmatory Trial Timelines

Timelines for confirmatory trial completion and final report submission are agreed upon at time of accelerated approval



Confirmatory Trial Conduct

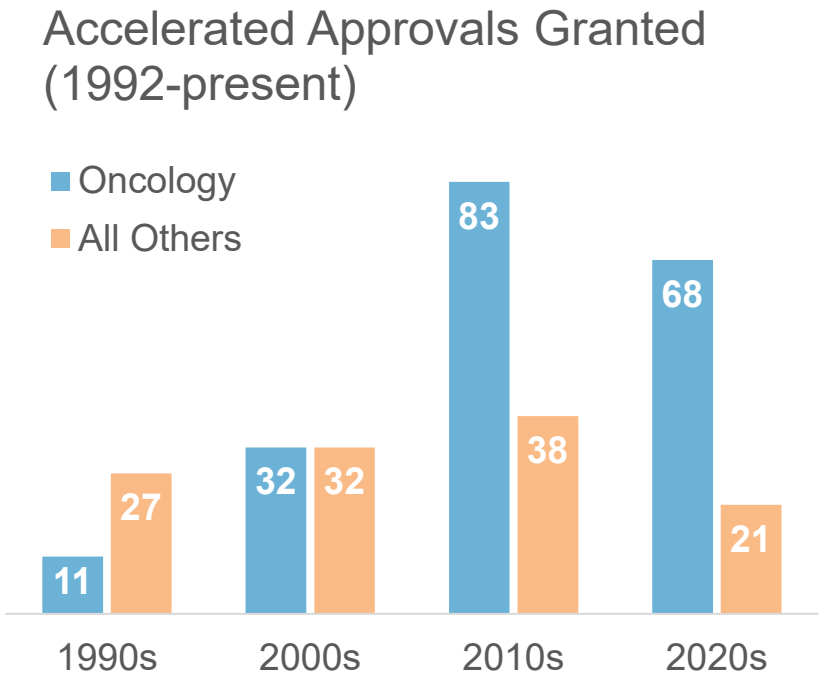
FDA *"may withdraw approval of a product approved under accelerated approval…if the sponsor fails to conduct any required postapproval study of the drug with due diligence"*

– Section 506(c) of the FD&C Act

- Confirmatory trial(s) should be completed in the shortest time period that is reasonable within the context of the disease and unmet need

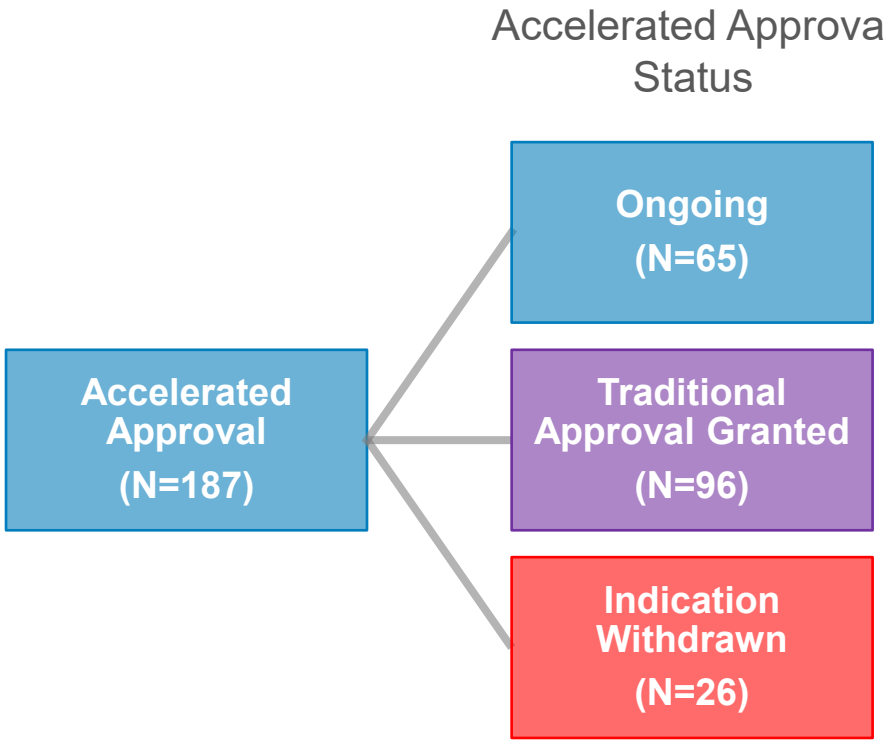
Accelerated Approval in Oncology

Majority (60%) of accelerated approvals have been granted in Oncology



Source: FDA analysis

Oncology Accelerated Approval Outcomes



Median 3.1 years after accelerated approval

Median 4.1 years after accelerated approval

Source: FDA analysis

Outline

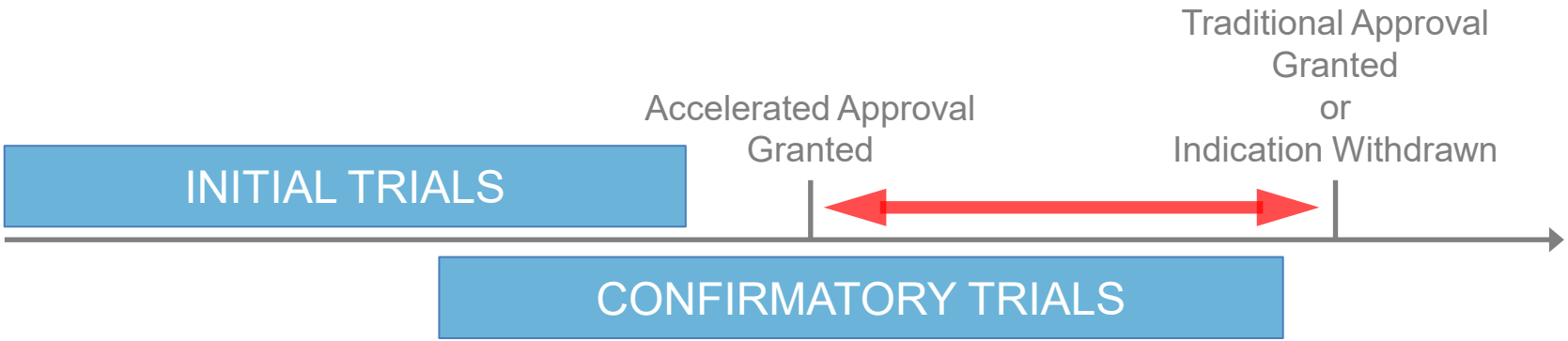
1. Risks of delayed confirmatory trials

2. Causes of delayed confirmatory trials

3. Strategies to minimize time to verification of benefit

Period of Vulnerability after Approval

- The time from accelerated approval to completing the confirmatory trial(s) is a period of vulnerability
- Time that patients may be exposed to a therapy that eventually does not demonstrate clinical benefit



Risk of Accelerated Approval

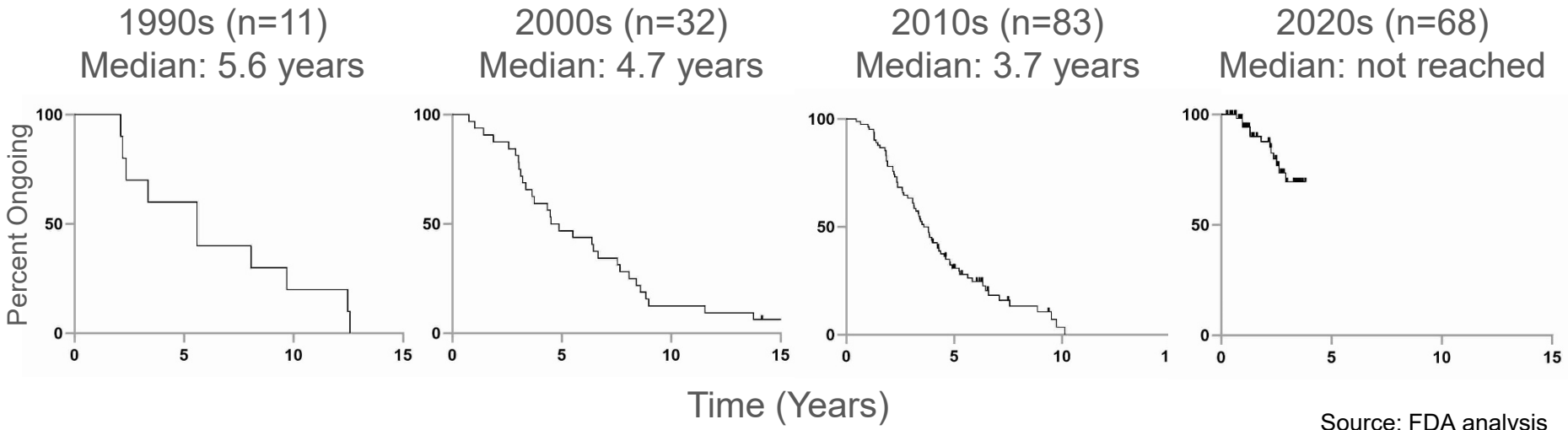
Risk of Accelerated Approval $\neq$ *Risk that Clinical Benefit Is Not Verified*

Risk of Accelerated Approval

$$\textit{Risk of Accelerated Approval} = \textit{Risk that Clinical Benefit Is Not Verified} \times \textit{Time On Market}$$

Time to Verification of Benefit

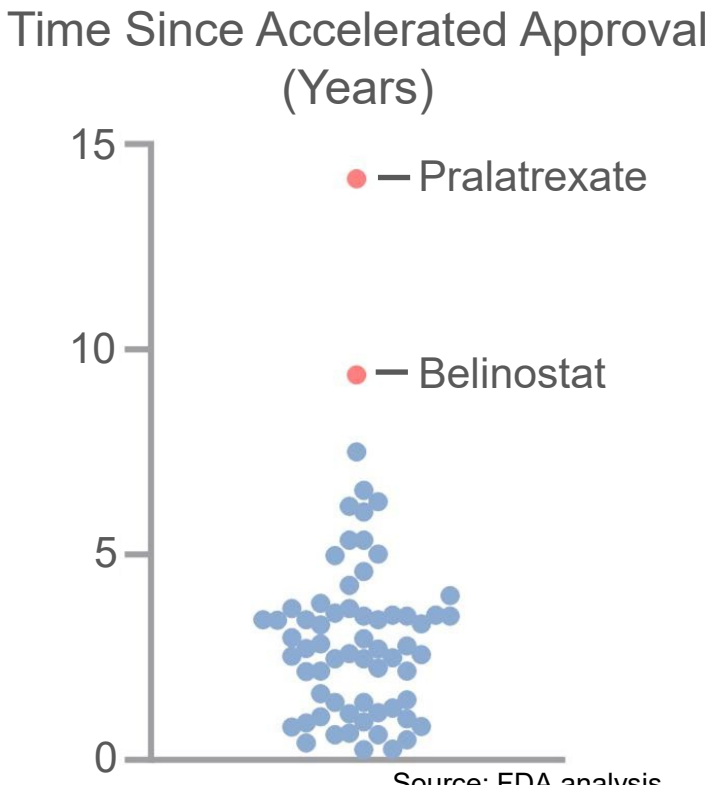
Time to traditional approval or withdrawal after accelerated approval has improved



Source: FDA analysis

Ongoing Oncology Accelerated Approvals

The majority (85%) of ongoing oncology accelerated approvals are less than 5 years old



Source: FDA analysis

Outline

1. Risks of delayed confirmatory trials

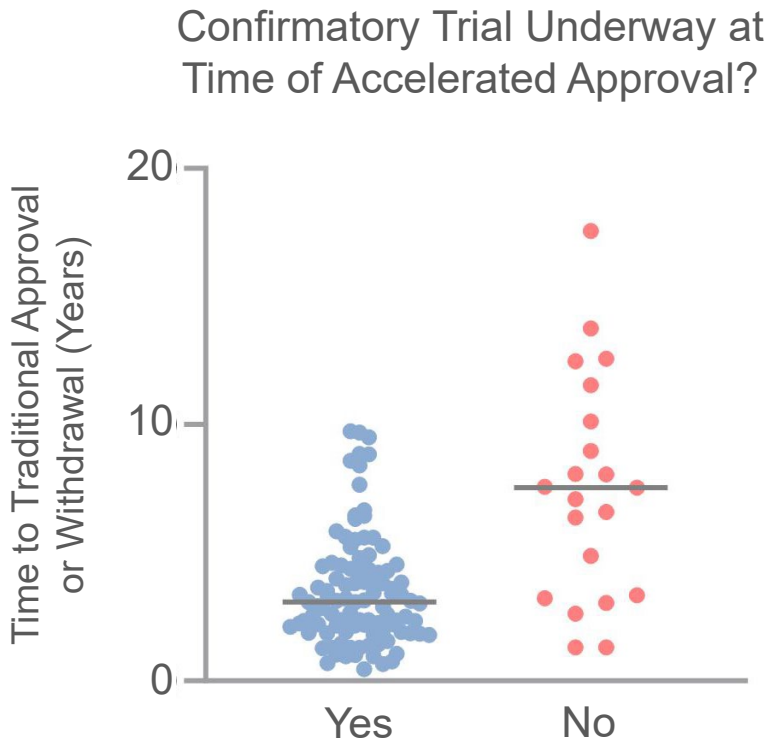
2. Causes of delayed confirmatory trials

3. Strategies to minimize time to verification of benefit

Confirmatory Trial Underway at Approval

Time to subsequent action (traditional approval or withdrawal) is reduced if the confirmatory trial is underway at the time of accelerated approval

- Underway: Median 3.1 years
- Not Underway: Median 7.3 years



Source: FDA analysis

Changes in Trial Feasibility

1. Effect of accelerated approval itself

2. Effect of new available therapies

3. Change in the incidence of the disease

Pralatrexate and Belinostat for PTCL

1. Confirmatory trial not underway at time of accelerated approval

2. Combination dose not established

3. Administrative delays (e.g., change in drug Sponsor)

Abbreviations: PTCL, peripheral T-cell lymphoma

Outline

1. Risks of delayed confirmatory trials

2. Causes of delayed confirmatory trials

3. Strategies to minimize time to verification of benefit

Comprehensive Development Plan

1. Pre-specified pathway(s) to verification of clinical benefit

2. Timing of the confirmatory trial(s)

3. Rational timelines for completion of the confirmatory trial(s)

Confirmatory Trial Well Underway

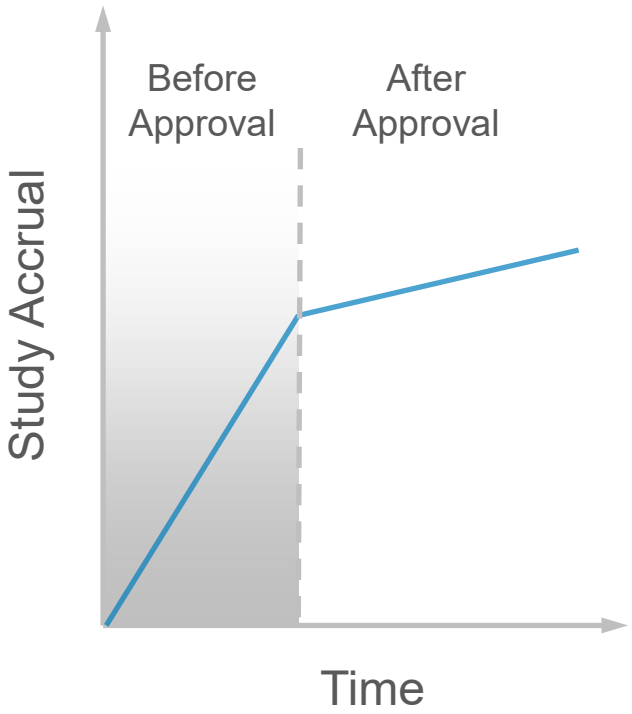
Having the confirmatory trial fully enrolled or near full enrollment at the time of accelerated approval helps to minimize risks of delays:

- Effect of the approval on trial enrollment
- Subsequent changes in available therapies
- Administrative delays in trial initiation or opening sites

Rational Timelines for the Confirmatory Trial

- Confirmatory trials need realistic and data-driven timelines

- Projected accrual should be based on:
  - Disease incidence and natural history
  - The potential effect of accelerated approval on accrual



International Approaches to Mitigate Risk

1. Expedited approval must be renewed
   - European Union
   - United Kingdom
   - Australia
   - Switzerland

2. Maximum time limit on expedited approval
   - Switzerland – 2 years (may be extended in exceptional cases)
   - Australia – 6 years

Regulatory Authority to Minimize Delays

In December 2022, Congress passed the Food and Drug Omnibus Reform Act, which provides additional accelerated approval provisions:

1. FDA can require that confirmatory studies be underway prior to approval

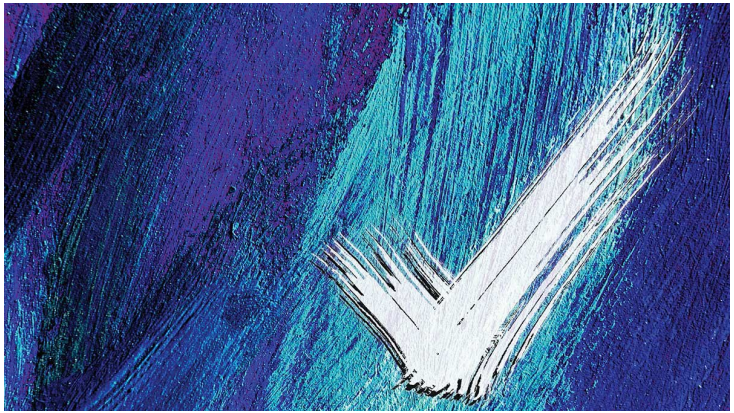
2. Sponsors must submit biannual progress reports on the status of confirmatory studies

3. A streamlined withdrawal process for drugs that do not verify clinical benefit from the market

Project Confirm

Oncology Center of Excellence initiative to increase transparency and accountability for cancer accelerated approvals

- Public, searchable database
- Public education
- Program analysis



https://www.fda.gov/about-fda/oncology-center-excellence/project-confirm

Conclusions

- Accelerated approval allows patients with cancer early access to potentially life-saving drugs

- The measure of success of this program may be minimizing delays in confirmatory trials and verification of benefit
  - Several underlying causes
  - Time to verification of benefit is improving

Conclusions

- Considerations for minimizing delays in confirmatory trial completion
  - Comprehensive development plan
  - Confirmatory trial well underway at time of accelerated approval
  - Rational timelines for completion
  - New regulatory authority to minimize delays
  - Increasing transparency and accountability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Pralatrexate
NDA 022468

Belinostat
NDA 206256

Oncologic Drugs Advisory Committee Meeting

November 16, 2023

Nicholas Richardson, DO, MPH
Deputy Division Director
Division of Hematologic Malignancies II
Office of Oncologic Diseases

Approval in PTCL

Accelerated Approval

- Pralatrexate – September 24, 2009
  - Treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma

- Belinostat – July 3, 2014
  - Treatment of adult patients with relapsed or refractory peripheral T-cell lymphoma

Abbreviations: PTCL, peripheral T-cell lymphoma

ODAC Discussion Topics

- **Discussion:** Discuss the delays in post-approval confirmatory trials for pralatrexate and belinostat, and whether the current plan to verify the clinical benefit of these products in patients with peripheral T-cell lymphoma is reasonable considering the Sponsor's proposed timelines.

- **Discussion:** Discuss strategies to promote timely completion of the confirmatory trial for pralatrexate and belinostat, and insights from this experience that may facilitate completion of confirmatory trials for future accelerated approvals.

Regulatory Approval Pathways

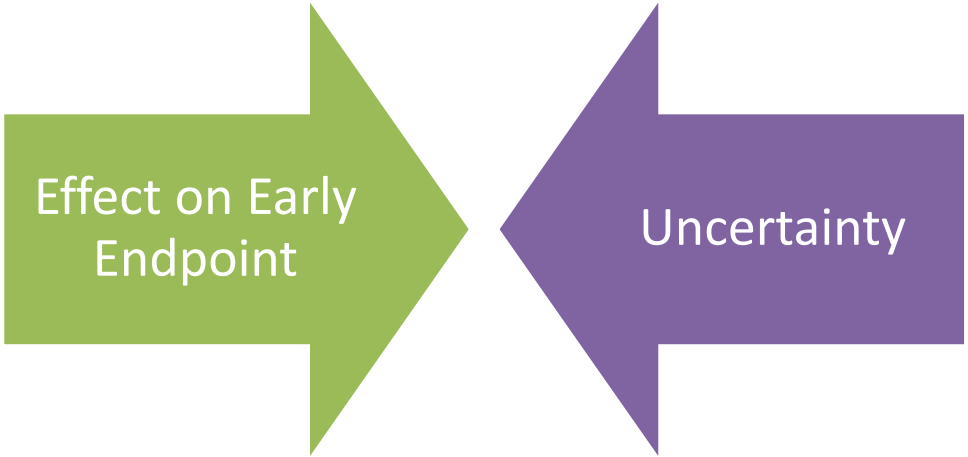
- Traditional (Regular) Approval
  - Approval is based on demonstration of clinical benefit or an effect on an established surrogate

- Accelerated Approval
  - Treatment of serious or life-threatening illness
  - Taking into account the condition and availability of alternative treatments
  - Approval is based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint other than survival or irreversible morbidity
  - May require post-approval trials to verify and describe its clinical benefit

21 CFR 314.510
FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics

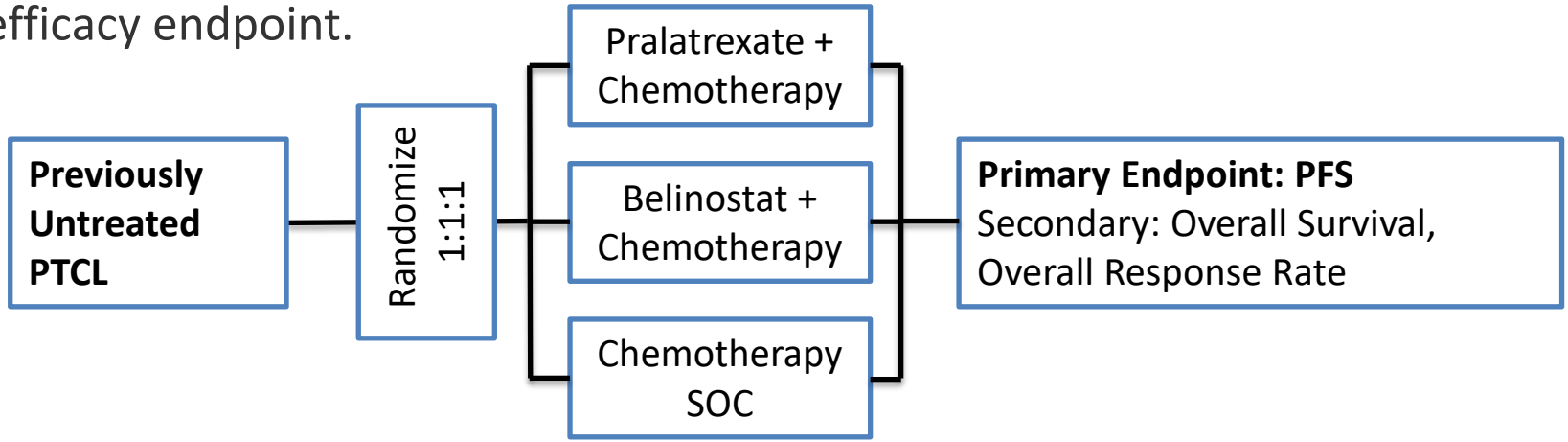
Accelerated Approval

- Relies on early clinical endpoints that are considered reasonably likely to predict clinical benefit



Confirmatory Postmarketing Requirement

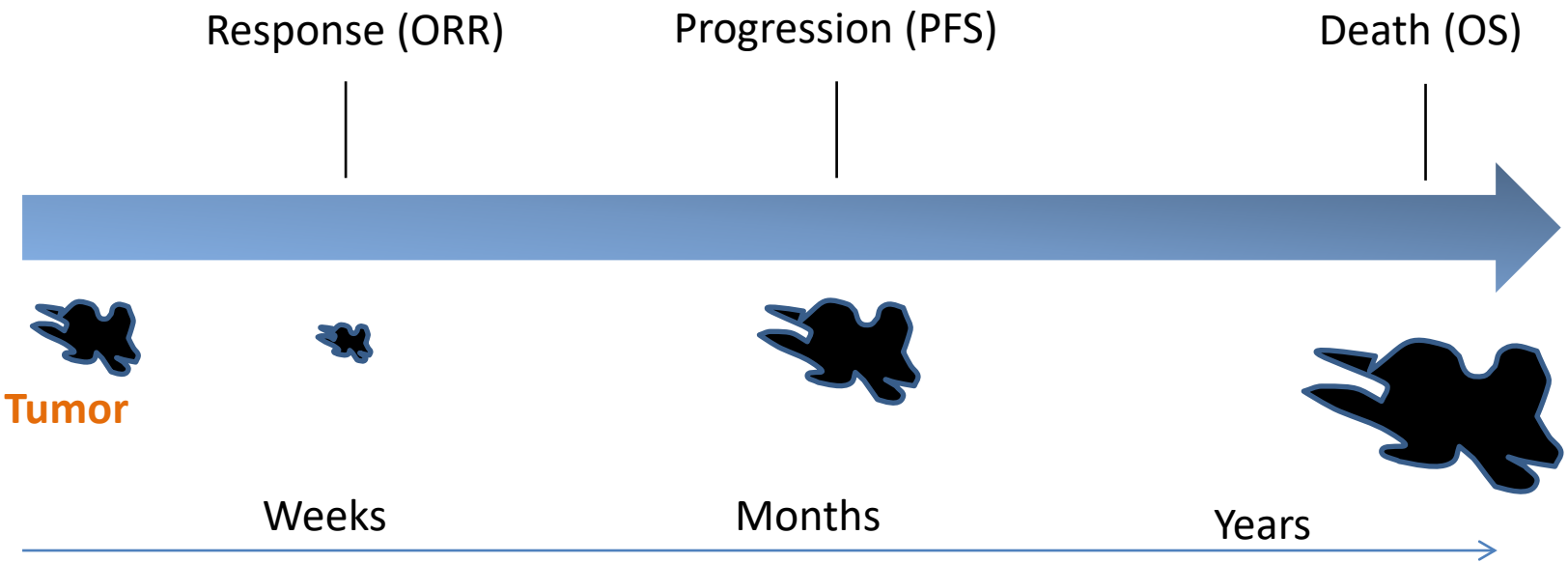
- Current PMRs: Characterize the comparative efficacy and safety of pralatrexate or belinostat when used in combination with a treatment regimen such as CHOP for the initial therapy of patients with PTCL. Perform a confirmatory, prospective randomized (1:1:1) trial of previously untreated patients with PTCL, with progression free survival (PFS) as the primary efficacy endpoint.



Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; PMR, postmarketing requirement; PTCL, peripheral T-cell lymphoma; SOC, standard of care

Conduct of Clinical Trials to Verify Benefit

- Early endpoints may not correlate with longer-term outcomes



Abbreviations: ORR, objective response rate; PFS, progression-free survival; OS, overall survival

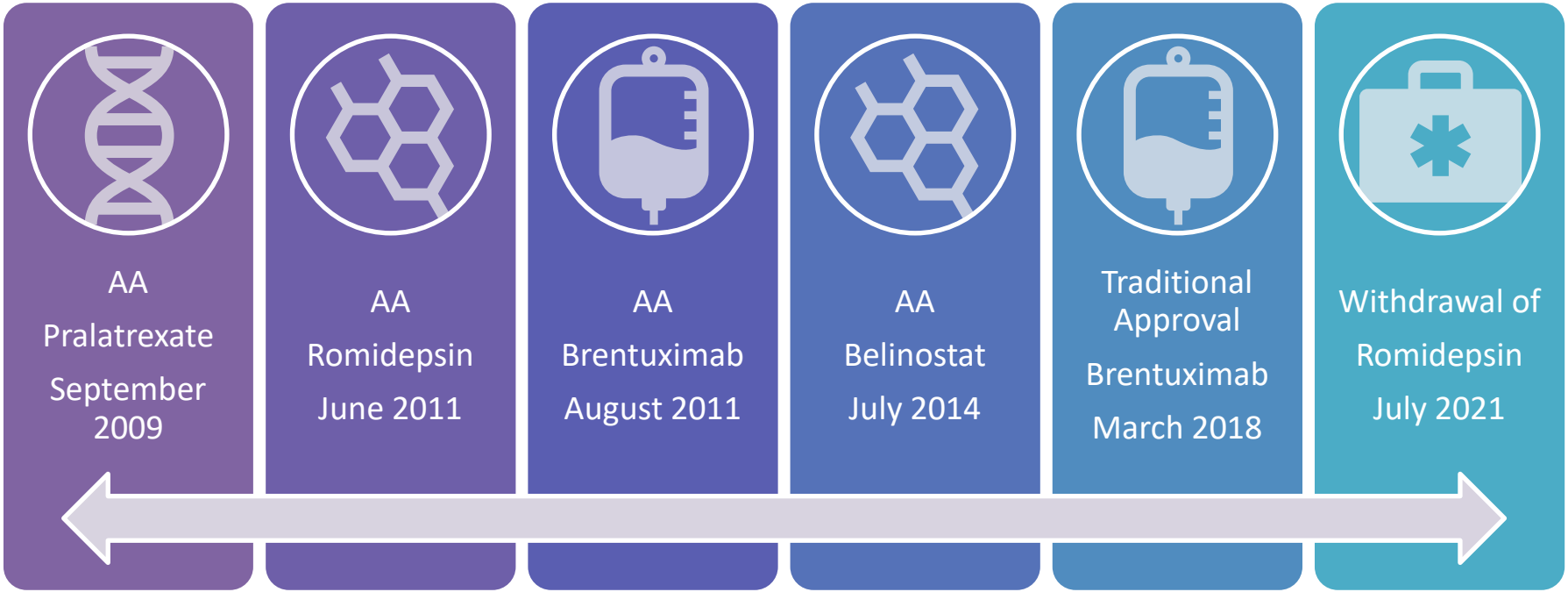
Recent Oncology Trials Exhibit Lack of Correlation

Disease & Setting	Trial	Study Arm ORR % (95% CI)	Control Arm ORR % (95% CI)	PFS HR (95% CI)	OS HR (95% CI)
CLL, R/R	DUO Duvelisib vs Ofatumumab	73 (66, 80)	43 (38, 53)	**0.52** (0.39, 0.69)	**1.09** (0.79, 1.51)
CLL, frontline and R/R	UNITY-CLL U2 vs GC	83 (78, 89)	69 (62, 75)	**0.55** (0.41, 0.72)	**1.23** (-, -)*
Indolent NHL, R/R	313-0125 Idelalisib + BR vs placebo +BR	*	*	**0.74** (0.5, 1.1)	**1.51** (0.71, 3.23)
Multiple Myeloma, R/R	BELLINI Venetoclax + Bd vs Bd	82 (76, 87)	68 (58, 77)	**0.63** (0.44, 0.90)	**2.03** (1.04, 3.95)
NSCLC, advanced, previously treated	CHECKMATE-057 Nivolumab vs docetaxel	19 (15, 24)	12 (9, 17)	**0.92** (0.77, 1.11)	**0.73** (0.60, 0.89)

* Not publicly available

Abbreviations: Bd, bortezomib + dexamethasone; BR, bendamustine + rituximab; CI, confidence interval; CLL, chronic lymphocytic leukemia; GC, obinutuzumab + chlorambucil; HR, hazard ratio; NHL, non-Hodgkin lymphoma, NSCLC, non-small cell lung cancer; PFS, progression-free survival; R/R, relapsed or refractory; ORR, objective response rate; OS, overall survival; U2, ublituximab + umbralisib

Approvals in PTCL



Abbreviations: AA, accelerated approval; PTCL, peripheral T-cell lymphoma

Considerations for Delayed Status to Verify Benefit

- Transfer of ownership
- Dosing
- Toxicity and tolerability
- Delayed initiation of confirmatory trial: October 2023
- Results estimated in 2030

ODAC Discussion Topics

- **Discussion:** Discuss the delays in post-approval confirmatory trials for pralatrexate and belinostat, and whether the current plan to verify the clinical benefit of these products in patients with PTCL is reasonable considering the Sponsor's proposed timelines.

- **Discussion:** Discuss strategies to promote timely completion of the confirmatory trial for pralatrexate and belinostat, and insights from this experience that may facilitate completion of confirmatory trials for future accelerated approvals.

Abbreviations: PTCL, peripheral T-cell lymphoma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Pralatrexate (NDA 022468) and Belinostat (NDA 206256)

FDA Presentation

Oncologic Drugs Advisory Committee Meeting
November 16, 2023

Yvette Kasamon, MD
Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases

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Wentao Fu, PhD
Francis Green, PharmD
Hui Wei, PhD
Jiang Liu, PhD

Topics

1. Regulatory considerations
2. Delays in milestones
3. Dosing and toxicity concerns
4. Promoting timely verification of clinical benefit

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1. Regulatory considerations
2. Delays in milestones
3. Dosing and toxicity concerns
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Accelerated Approval in R/R PTCL

- Pralatrexate: accelerated approval March 2009
  - Based on durable response rate in one single-arm trial
    ORR 27% (95% CI: 19, 36), estimated median DOR 9.4 mo

- Belinostat: accelerated approval July 2014
  - Based on durable response rate in one single-arm trial:
    ORR 26% (95% CI: 18, 35), estimated median DOR 8.4 mo

- Confirmatory trial(s) must be performed with due diligence
  - Projected submission of final report: 2030
    Pralatrexate: 21 years after approval
    Belinostat: 16 years

R/R, relapsed or refractory; PTCL, peripheral T-cell lymphoma; ORR, objective response rate; CI, confidence interval; DOR, duration of response; mo, months

Level of Evidence in PTCL

- Response rate and DOR:
  - Uncertainty in predicting clinical benefit
  - Potential lack of correlation with survival
  - Discordance more likely for drugs with modest efficacy and significant toxicity
  - Pralatrexate and belinostat have modest efficacy and notable toxicities

Level of Evidence in PTCL

- Cited supportive studies for pralatrexate do not inform clinical benefit
  - Multiple single-arm trials cited
  - Single-arm trials do not reliably inform PFS or OS
  - Claims regarding confirmation of efficacy are inappropriate to apply to regulatory decisions
    - LUMIERE trial
    - Case-control study
- Well-controlled randomized trial(s) needed

PFS, progression-free survival; OS, overall survival

FDA Approved Treatments for R/R PTCL

	Pralatrexate	Belinostat	Brentuximab vedotin	Romidepsin - PTCL indication withdrawn 7/2021
Approval year	2009	2014	2011 (AA), 2018	2011
Target	Antifolate	HDAC inhibitor	CD30-directed ADC	HDAC inhibitor
Indication	R/R PTCL Accelerated approval	R/R PTCL Accelerated approval	R/R systemic ALCL[a] Accelerated then traditional approval	R/R PTCL[b] Accelerated approval
Trial	Phase 2 (N=109)	Phase 2 (N=120)	Phase 2 (N=58)	Phase 2 (N=130)
ORR (95% CI)	**27% (19, 36)**	**26% (18, 35)**	**86% (77, 95)**	**26% (19, 35)**
CR rate	8%	11%	57%	15%
Median DOR	9.4 mo	8.4 mo	12.6 mo	17 mo

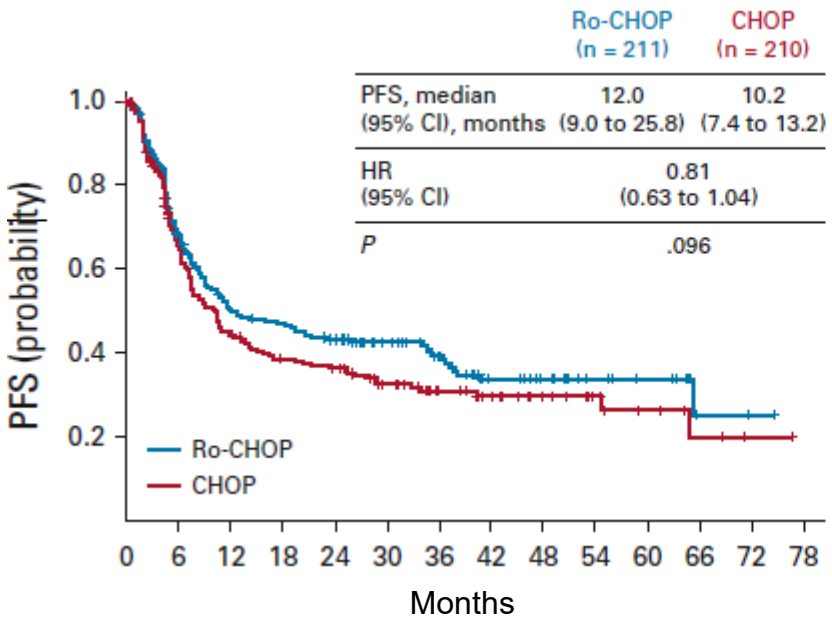
[a] Also approved for select R/R CTCLs, and for previously untreated ALCL and CD30+ PTCL in combination with CHP
[b] Traditional approval for R/R CTCL

Source: FDA analysis

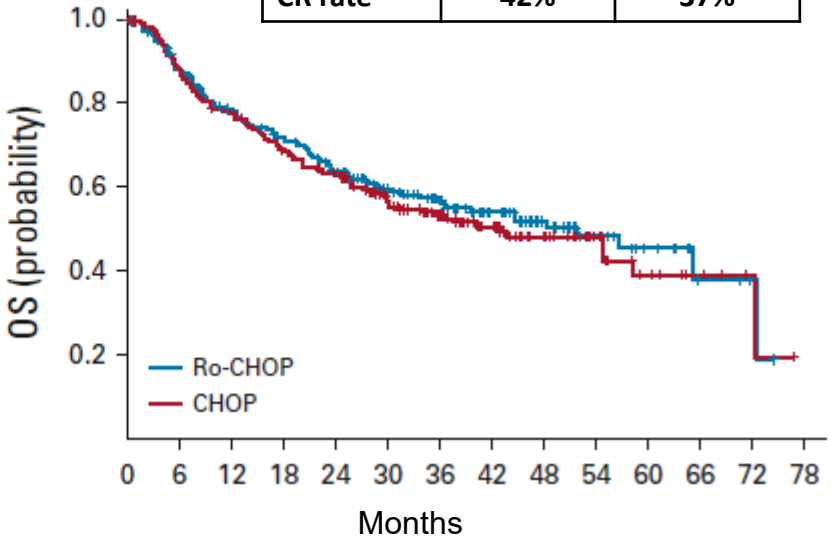
AA, accelerated approval; HDAC, histone deacetylase; ADC, antibody-drug conjugate; ALCL, anaplastic large cell lymphoma; CR, complete response; CTCL, cutaneous T-cell lymphoma; CHP, cyclophosphamide, doxorubicin, prednisone

Ro-CHOP vs. CHOP in Untreated PTCL

- PFS primary endpoint was not met
- Similar OS and response rates



	Ro-CHOP	CHOP
ORR	63%	60.5%
CR rate	42%	37%



Bachy et al, JCO 2021; 40: 242-251

Ro-CHOP, romidepsin + CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); HR, hazard ratio

Ro-CHOP vs. CHOP in Untreated PTCL

- PFS primary endpoint was not met
- Similar OS and response rates
- Greater toxicity with Ro-CHOP

Outcome		Ro-CHOP (N=210)	CHOP (N=208)
Treatment-emergent AEs	Grade 3 or higher	94%	70%
	Grade 4	74%	42%
	Serious	42%	29%
Delivery of CHOP	6 cycles without dose reduction or interruption	53%	60%
	Average RDI < 90%	15%	9%

Potentially compromised delivery of CHOP backbone

Bachy et al, JCO 2021; 40: 242-251

AE, adverse event; RDI, relative dose intensity

Pralatrexate Regulatory History: 2009 ODAC Meeting

Voting question: The Applicant has provided a single arm trial with an ORR of 27%. The majority of these responses were partial responses (18%) and only 8% were CR or CRu. The DOR was < 14 weeks in 55% of responders. **Are the response rate and duration of response results "reasonably likely" to predict for clinical benefit?** Clinical benefit in lymphomas would be defined as an improvement in overall survival or a robust effect on progression-free survival.

Outcome: 10 Yes, 4 No

CRu, complete response unconfirmed

Regulatory History

- Initial confirmatory trial PMRs for pralatrexate were released and reissued due to poor enrollment
  - Randomized trial of maintenance treatment with pralatrexate in previously untreated PTCL
  - Randomized trial of pralatrexate + systemic bexarotene vs. bexarotene alone in refractory CTCL
- New accelerated approval PMRs issued in 2014
  - Confirmatory trial proposed for both drugs:

    Belinostat + CHOP vs. pralatrexate + COP[a] vs. CHOP in previously untreated PTCL
  - Dose-finding PMRs for combination therapy with CHOP

[a] Originally planned pralatrexate + CHOP

PMR, postmarketing requirement; CTCL, cutaneous T-cell lymphoma; COP, cyclophosphamide, vincristine, prednisone

Accelerated Approval PMRs Issued 2014

- Dose-finding PMRs
  - **Establish optimal and safe dose of belinostat in combination with CHOP**

Original Milestone Dates
Trial Completion: 06/2015
Final Report Submission: 04/2017

  - **Establish optimal and safe dose of pralatrexate in combination with CHOP**

Original Milestone Dates
Trial Completion: 12/2015
Final Report Submission: 04/2016

- PMRs to verify clinical benefit
  - **Characterize the comparative efficacy and safety of belinostat when used in combination with a regimen such as CHOP, vs. pralatrexate plus CHOP, vs. CHOP alone for initial therapy of PTCL**

Original Milestone Dates
Final Protocol: 12/2015
Trial Completion: 01/2020
Final Report Submission: 01/2021

Confirmatory Trial: Agreed Jan 2023

SPI-BEL-301: A Phase 2/3 Randomized, Open-Label Study Comparing Efficacy and Safety of the Combination of Bel-CHOP or Fol-COP to CHOP Alone in Newly Diagnosed Patients with PTCL

Part 1: Randomized dose finding

5 arms, N=20 per arm

- **Belinostat 600 mg/m^2 (D1-5) + CHOP**
- **Belinostat 1000 mg/m^2 (D1-5) + CHOP**
- **Pralatrexate 20 mg/m^2 (D1, D8) + COP**
- **Pralatrexate 30 mg/m^2 (D1, D8) + COP**
- **CHOP**

Primary endpoints:

Part 1: Identify optimal dose of belinostat + CHOP and pralatrexate + COP

Part 2: Confirmatory Phase 3 portion

Randomized 1:1:1, N=143 per arm

- **Belinostat (chosen dose) + CHOP**
- **Pralatrexate (chosen dose) + COP**
- **CHOP**

Part 2: PFS per investigator

Key secondary: OS, ORR

Bel, belinostat; Fol, pralatrexate; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; COP, cyclophosphamide, vincristine, prednisone

Transfer of Product Ownership

Date	Regulatory events related to NDA transfer
9/24/2009	Accelerated approval of pralatrexate NDA 22468 issued to Allos Therapeutics Inc.
9/05/2012	Allos acquired by Spectrum Pharmaceuticals as wholly owned subsidiary
7/03/2014	Accelerated approval of belinostat NDA 206256 issued to Spectrum Pharmaceuticals
3/01/2019	Acrotech Biopharma LLC became NDA holder for both pralatrexate and belinostat

New NDA owner assumes responsibility and accountability for all outstanding requirements.

Source: FDA summary. NDA, new drug application

Topics

1. Regulatory considerations
2. Delays in milestones
3. Dosing and toxicity concerns
4. Promoting timely verification of clinical benefit

Accelerated Approval PMRs Issued 2014

- Dose-finding PMRs
  - **Establish optimal and safe dose of belinostat in combination with CHOP**

Original Milestone Dates
Trial Completion: 06/2015
Final Report Submission: 04/2017

Status: Fulfilled on time

  - **Establish optimal and safe dose of pralatrexate in combination with CHOP**

Original Milestone Dates
Trial Completion: 12/2015
Final Report Submission: 04/2016

Status: Fulfilled after ~5.5 year delay (Final Report, 10/2021)

- PMRs to verify clinical benefit
  - **Characterize the comparative efficacy and safety of belinostat when used in combination with a regimen such as CHOP, vs. pralatrexate plus CHOP, vs. CHOP alone for initial therapy of PTCL**

Original Milestone Dates
Final Protocol: 12/2015
Trial Completion: 01/2020
Final Report Submission: 01/2021

Status: Delayed; final protocol ~7 years late

PMR Timelines for Study SPI-BEL-301:

Characterize the comparative efficacy and safety of belinostat in combination with a regimen such as CHOP vs. pralatrexate plus CHOP vs. CHOP alone for initial therapy of patients with PTCL

PMRs 2179-2 and 2178-2	Original Milestones	Latest Proposed Milestones *
Final protocol submission	Dec 2015	Jan 2023
Part 2 initiation	N/A	Dec 2025
25% accrual	April 2017	April 2026
50% accrual	April 2018	Sept 2026
75% accrual	April 2019	Feb 2027
Accrual completion	N/A	Aug 2027
Trial completion	Jan 2020	Feb 2030
Final report submission	Jan 2021	Nov 2030

Missed milestone letters

↓

Protocol first submitted March 2022

↓

Final protocol submitted January 2023

*Milestone dates as proposed by Sponsor 10/16/2023

Other Delays: Safety PMRs

Safety PMRs with > 1 year delay

Product	Safety PMR	Delayed Milestone and Original Date	Most Recent Revised Milestone Date	Date Received (Delay)	Date PMR Fulfilled
Pralatrexate	1547-3 **Renal Impairment**	Trial Complete: 6/2012 Final Report: 1/2013	N/A	Trial Complete: 1/2013 Final Report: 7/2015 (~2.5 year delay)	5/2016
	3086-1 **Hepatic Impairment**	Final Protocol: 12/2015 Trial Complete: 12/2020 Final Report: 6/2021	Trial Complete: 12/2024 Final Report: 5/2025	Final Protocol: 6/2018 (ongoing ~2 year delay in final report)	N/A
	1547-4 **Mass Balance Trial**	Trial Complete: 6/2010 Final Report: 12/2010	Trial Complete: 2/2013 Final Report: 7/2013	Final Report: 5/2015 (~4 year delay)	6/2016
Belinostat	2178-5 **Safety with UGT1A1 Inhibitors**	Trial Complete: 12/2015 Final Report: 3/2016	Trial Complete: 12/2022 Final Report: 6/2022	Final Report: 6/2023 (~7 year delay)	Pending

Source: FDA summary

Topics

1. Regulatory considerations
2. Delays in milestones
3. Dosing and toxicity concerns
4. Promoting timely verification of clinical benefit

Dose Selection for Pralatrexate and Belinostat as Monotherapy

- Original dose selection based on finding the MTD
- Limited exploration of lower doses that may have improved safety

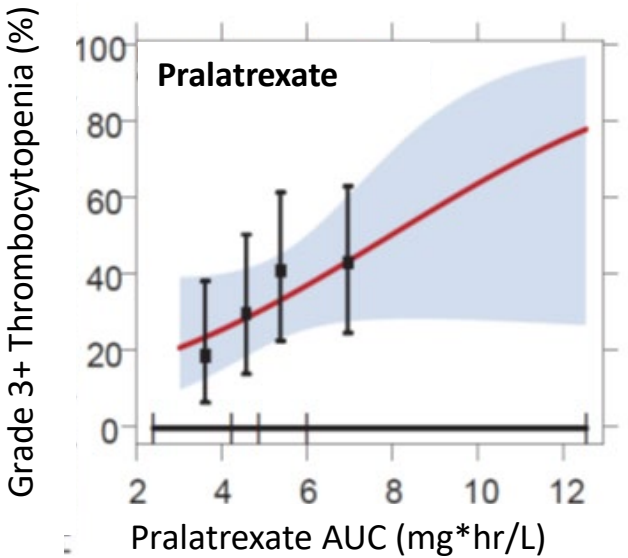
Dose Selection in Patients with Hematologic Malignancies

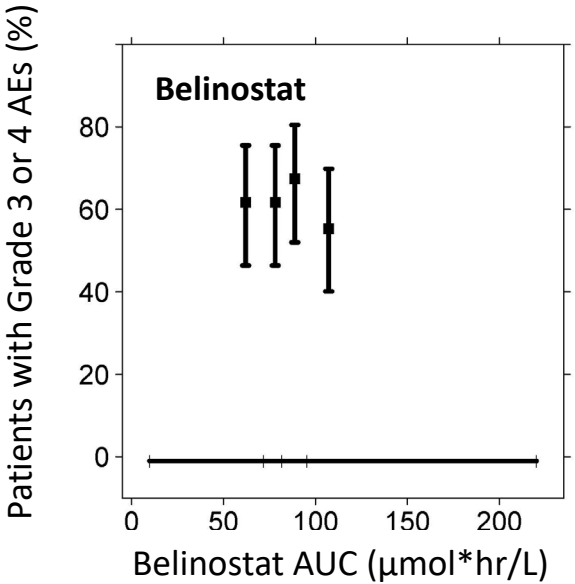
Pralatrexate		Belinostat (21-day cycles)	
30 mg/m^2 weekly 3/4	N=3	600 mg/m^2 QD x 5 days	N=3
30 mg/m^2 weekly 6/7	N=26	900 mg/m^2 QD x 5 days	N=3
45 mg/m^2 weekly 6/7	N=11	1000 mg/m^2 QD x 5 days	N=10

Source: FDA summary
MTD, maximum tolerated dose; QD, once daily

Exposure-Response for Pralatrexate and Belinostat

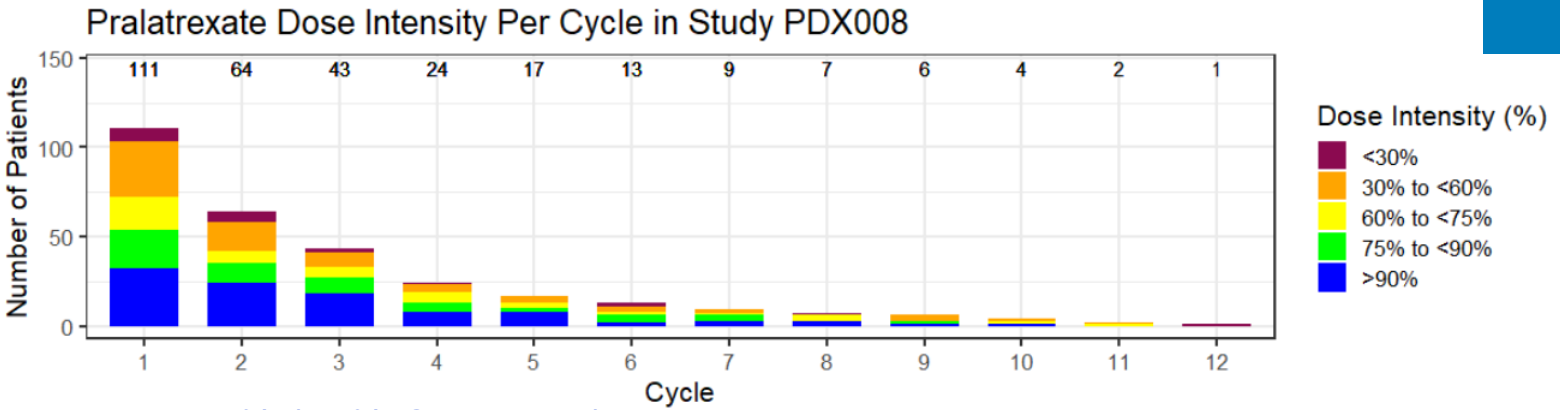
- No association seen between higher exposures and better responses (data limited)
- Higher pralatrexate exposures associated with safety events (thrombocytopenia)
- Both drugs demonstrated significant rates of Grade 3-4 AEs





Source: FDA analysis. AE, adverse event; AUC, area under the curve

Pralatrexate Dosage: Tolerability Concerns



Mucositis: 70% (21% Grade 3-4)

Parameter	Study PDX-008 (N=111)
Grade 3 AE	43%
Grade 4 AE	31%
Serious AE	44%
Discontinuation due to AE	23%
Dose modification	31%

- Majority of patients had dose modification
- Significant rates of AEs, leading to discontinued treatment
- Limited data to assess whether the doses were optimal

Source: FDA analysis. AE, adverse event

Belinostat Dosage: Tolerability

Parameter	BELIEF trial (CLN-19) (N=129)
Total weeks of treatment, median (range)	7 (3 – 135)
Median number of cycles (range)	2 (1 – 33)
Median number of doses (range)	10 (1 – 165)
Any grade 3 or 4 TEAE	61%
Serious TEAE	47%
Discontinuation due to TEAE	19%
Dose delay ≥ 7 days	29%
Infusion interruption	17%
Dose reduction	12%

- Short duration of treatment
- Significant rates of Grade 3 or 4 AEs

Source: FDA analysis. TEAE, treatment-emergent adverse event

Dose Exploration for Pralatrexate and Belinostat in Combination with CHOP

- PMRs issued to assess dosing with CHOP
- Limited dose exploration in combination, prioritizing MTD approach

Pralatrexate		Belinostat	
10 mg/m^2	N=4	1000 mg/m^2 Days 1-3	N=8
15 mg/m^2	N=3	1000 mg/m^2 Days 1-5	N=3
20 mg/m^2	N=3	1000 mg/m^2 Days 1-5 expansion	N=12
25 mg/m^2	N=3		
30 mg/m^2	N=6		
30 mg/m^2 expansion	N=33		

Need for further dose optimization for both drugs, when combined with chemotherapy, before pursuing confirmatory trial

Source: FDA analysis. MTD, maximum tolerated dose

Need for Timely Randomized Data

- The toxicity profile of pralatrexate and belinostat, coupled with modest efficacy in single-arm trials, underscores uncertainty in clinical benefit
- Feasible to conduct RCTs in PTCL in reasonable timeframes
  - Romidepsin + CHOP vs. CHOP in frontline PTCL (N=421)
  - Brentuximab vedotin + CHP vs. CHOP in frontline CD30+ PTCL (N=452)

RCT, randomized control trial

Topics

1. Regulatory considerations
2. Delays in milestones
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Delays and Potential Strategies

- Administrative (transfer of ownership)
  - PMR milestones are agreed upon by both the Sponsor and FDA
  - If sponsor anticipates potential delays, more interactions with FDA should be sought
- Adequate evaluation of dose
  - Delay both in conduct of dose-finding trial (pralatrexate + CHOP), and in FDA feedback on need for additional dose optimization
  - More recent focus on dose optimization (Project Optimus)

Project Optimus

- Initiative to reform the dose optimization and dose selection paradigm in oncology drug development
- Goals
  - Communicating expectations for dose-finding and optimization
  - Provide opportunities for developers to meet with FDA to discuss dose optimization
  - Develop strategies for efficient dose finding

https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence

Delays and Potential Strategies

- Focus on multiregional trials
  - OCE focus on multiregional trials and enrollment may expedite drug development for rare diseases
- Updates to accelerated approval legislation (FDORA)
  - FDA may require ongoing confirmatory trials prior to approval
  - Mandatory progress reports on confirmatory trials enable earlier identification of delays

OCE, Oncology Center of Excellence; FDORA, Food and Drug Omnibus Reform Act

ODAC Discussion Topics

- Discuss the delays in post-approval confirmatory trials for pralatrexate and belinostat, and whether the current plan to verify the clinical benefit of these products in patients with peripheral T-cell lymphoma is reasonable considering the Sponsor's proposed timelines.

- Discuss strategies to promote timely completion of the confirmatory trial for pralatrexate and belinostat, and insights from this experience that may facilitate completion of confirmatory trials for future accelerated approvals.

Backup Slides Shown

Oncology Accelerated Approval Endpoints

- *"may approve…a product for a serious or life-threatening disease…upon determination that the product has an effect on…*

    1. *A **surrogate endpoint** that is reasonably likely to **predict clinical benefit**,*

    2. *Or on a **clinical endpoint** that can be **measured earlier than irreversible morbidity or mortality**, that is reasonably likely to **predict an effect on irreversible morbidity or mortality or other clinical benefit***

– Section 506(c) of the FD&C Act

Oncology Surrogate Endpoints

- Prentice Criteria
  i. The treatment has an effect on survival time
  ii. The treatment has an effect on the surrogate
  iii. The surrogate is associated with survival time
  iv. The treatment effect on survival is captured by the surrogate

– Prentice RL, Statistics in Medicine, 1989

Delayed Confirmatory Trials

Includes products for which FDA is currently reviewing the results of confirmatory trials

Drug Name	Accelerated Approval (AA) Indication	AA Date	Original Projected Completion
Folotyn (pralatrexate)	PTCL	9/24/2009	6/30/2017
Keytruda (pembrolizumab)	Hepatocellular Carcinoma	11/9/2018	10/31/2019
Beleodaq (belinostat)	PTCL	7/3/2014	1/31/2021
Zepzelca (lurbinectedin)	Small cell lung cancer	6/15/2020	2/28/2021
Opdivo (nivolumab)	MSI-H and dMMR) metastatic colorectal cancer	7/31/2017	9/30/2021
Pepaxto (melphalan flufenamide)	Multiple myeloma	2/26/2021	2/28/2022
Lumakras (sotorasib)	KRAS G12C-mutated non-small cell lung cancer	5/28/2021	7/30/2022
Aliqopa (copanlisib)	Follicular lymphoma	9/14/2017	9/30/2022
Jemperli (dostarlimab-gxly)	dMMR recurrent or advanced solid tumors	8/17/2021	10/31/2022
Balversa (erdafitinib)	Urothelial carcinoma (mUC), that has FGFR3 or FGFR2 genetic alterations	4/12/2019	10/31/2022
Rybrevant (amivantamab-vmjw)	Non small cell lung cancer with EGFR exon 20 insertion mutations	5/21/2021	2/28/2023
Tepmetko (tepotinib)	Non-small cell lung cancer harboring MET exon 14 skipping alterations	2/3/2021	4/30/2023


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