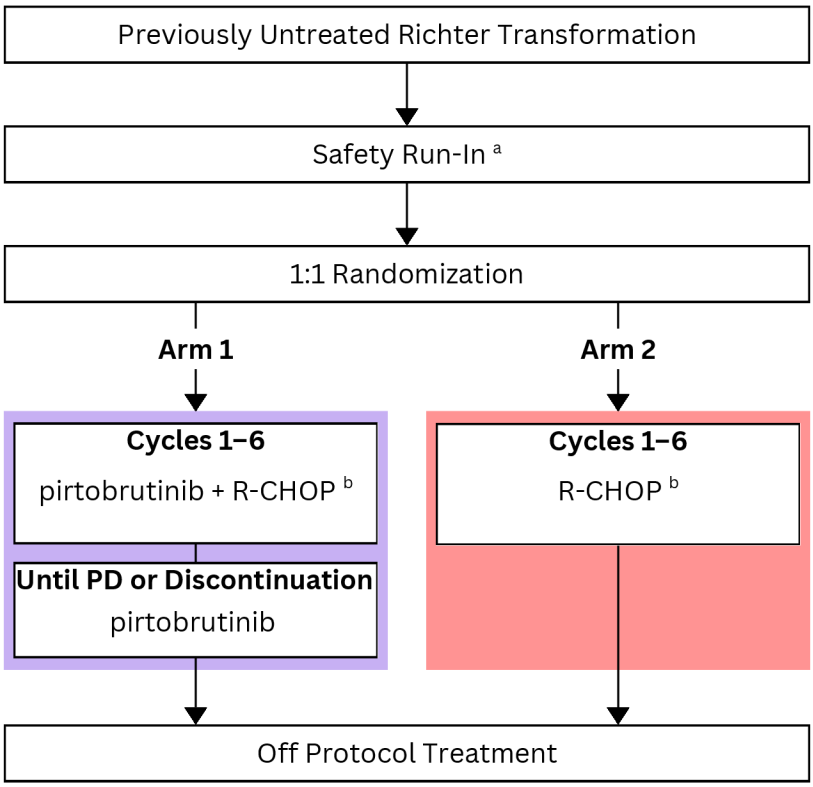
S2504

A Randomized Phase III Study of **Pir**tobrutinib plus R-CHOP vs. R-CHOP for Participants with Previously Untreate**d** R**i**chter Tr**a**nsfor**m**ation (pirAMID)

SCHEMA



[a] 6 participants ≥ 75 years old and 6 participants < 75 years old will be non-randomly assigned to Arm 1 for the Safety Run-In. Participants will be monitored for toxicity through Cycle 2.

[b] R-mini-CHOP for participants ≥ 75 years old.

KEY ELIGIBILITY

- ≥ 18 years old.
- Zubrod Performance Status 0–2.
- Diagnosed Richter Transformation (RT) from CLL/SLL w/ histologic or cytologically confirmed large B-cell lymphoma.
- No prior treatment for RT, except corticosteroids ≤ equivalent dose of prednisone 700 mg total for < 7 days.
- No prior exposure to pirtobrutinib.
- Prior treatments for CLL/SLL or its complications (AIHA, ITP) allowed.
  - After RT diagnosis, CLL/SLL treatment w/ CLL/SLL directed drugs (including BTK inhibitors) allowed for disease control.
- Must have measurable disease by PET/CT or hematopathology assessment w/in 42 days prior to registration.
- No contraindications to anthracycline. Prior anthracycline exposure allowed if cumulative dose is:
  - ≤ 100 mg/m^2, for R-CHOP participants or
  - ≤ 250 mg/m^2, for R-mini-CHOP participants.

TREATMENT OVERVIEW

ARM	AGENT	DOSE		ROUTE	DAY	SCHEDULE [c]
		< AGE 75	≥ AGE 75			
Arm 1	Pirtobrutinib	200 mg	200 mg	PO	Daily	Cycles 1–6
Arms 1 & 2	Rituximab/Rituximab Hyaluronidase [d]	375 mg/m^2	375 mg/m^2	IV or SQ	Day 1	Cycles 1–6
	Cyclophosphamide	750 mg/m^2	400 mg/m^2	IV	Day 1	Cycles 1–6
	Doxorubicin	50 mg/m^2	25 mg/m^2	IV	Day 1	Cycles 1–6
	Vincristine [e]	1.4 mg/m^2	1 mg/m^2	IV	Day 1	Cycles 1–6
	Prednisone	100 mg	40 mg	PO	Days 1–5	Cycles 1–6
	G-CSF: Pegfilgrastim OR Filgrastim	Weight-based dosing		IV or SQ	Varied	Cycles 1–6

[c] One cycle = 21 days.

[d] Rituximab must be given via IV for Cycle 1. Rituximab hyaluronidase SQ injection may be given for Cycle 2 and beyond.

[e] For participants < age 75, the maximum dose for vincristine is 2 mg per cycle.

MAINTENANCE OVERVIEW

ARM	AGENT	DOSE		ROUTE	DAY	SCHEDULE [f]
		< AGE 75	≥ AGE 75			
Arm 1	Pirtobrutinib	200 mg	200 mg	PO	Daily	Cycles 7+

[f] Continue daily pirtobrutinib maintenance until PD or discontinuation of treatment for other reasons per Protocol Section 7.10.

The *pir*AMID trial

S2504: A RANDOMIZED PHASE III STUDY OF **PIR**TOBRUTINIB PLUS R-CHOP VS. R-CHOP FOR PARTICIPANTS WITH PREVIOUSLY UNTREATE**D** R**I**CHTER TR**A**NSFOR**M**ATION (***pir*AMID**)

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Background

- Richter transformation (RT) remains a major unmet need due to its aggressive biology, poor prognosis, and resistance to standard therapies
- R-CHOP is commonly used in RT but is associated with limited efficacy and substantial toxicity
- The BRUIN study demonstrated promising efficacy and favorable safety of pirtobrutinib monotherapy in RT, including in heavily pretreated patients (Wierda W, Lancet Haematology, 2025)
- Combining pirtobrutinib with R-CHOP is a rational strategy to enhance the efficacy of standard immunochemotherapy while maintaining tolerability
- R-mini-CHOP provides a validated, safer alternative for older (aged ≥75 years) patients who may not tolerate full-dose R-CHOP
- A randomized trial comparing pirtobrutinib + R-CHOP versus R-CHOP in previously untreated RT is scientifically and clinically justified

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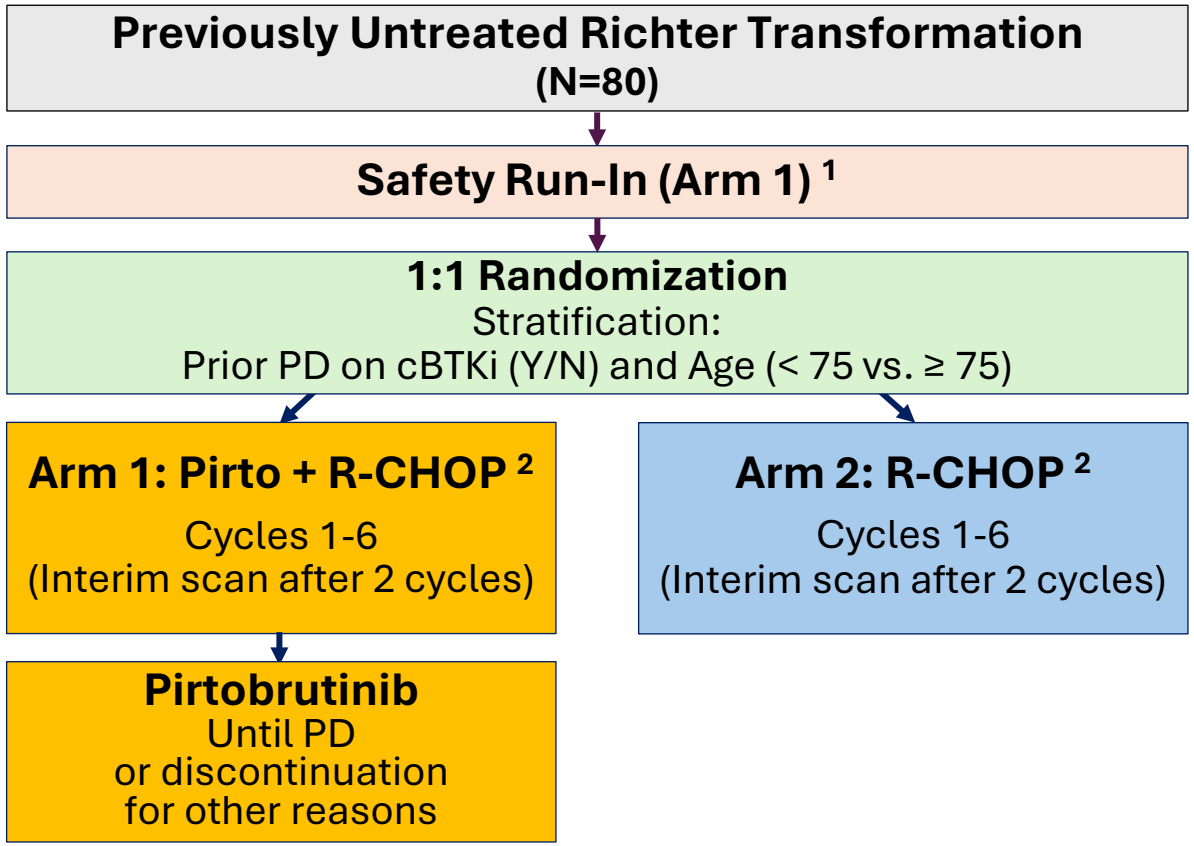


– 6 participants < Age 75 and 6 participants ≥ Age 75 will be non-randomly assigned to Arm 1.
  - **Participants will be monitored for toxicity through Cycle 2.**

Primary Endpoints:
- **PFS**
- **OS**

Secondary Endpoints:
- **CR**
- **Safety**

Translational Medicine Endpoints
- **Primary: Evaluate association between high-risk Richter-associated mutations (*TP53*, *CDK2NA*, or *MYC*) and OS within each arm by NGS and WES analyses**

1. Refer to S2504 Sections 7.4 and 15.6 for Safety Run-In information.
2. **R-mini-CHOP for participants age 75 and older.**

- cBTKi: covalent BTKi
- CR: Complete remission
- PD: Progressive disease
- PFS: Progression-free survival
- OS: Overall survival
- R-CHOP: rituximab/rituximab hyaluronidase, cyclophosphamide, doxorubicin, vincristine, and prednisone

Study Objectives

Safety Run-In (Pre-Randomization)

- **Age < 75:** Safety of pirtobrutinib + R-CHOP
- **Age ≥ 75:** Safety of pirtobrutinib + R-mini-CHOP

Randomized Phase

- **Primary Objectives:**
  - Investigator-assessed **PFS** (pirtobrutinib + R-CHOP vs R-CHOP)
  - If investigator-assessed PFS is improved with pirtobrutinib, then evaluate **OS** (pirtobrutinib + R-CHOP vs R-CHOP)
- **Secondary Objectives**
  - **CR rate** comparison between arms
  - **Safety profile:** frequency & severity of AE

Additional Objectives

- OS: **Transplant vs no transplant**
- OS: **CAR-T vs no CAR-T**
- **BTK resistance mutations** → association with **PFS, OS**
- **Clonal relatedness (CLL–LBCL)** → association with **PFS, OS**

Patient-Reported Outcomes (PROs)

- Compare **symptoms between arms** (PRO-CTCAE, FACIT GP5)

Translational Medicine Objectives

Primary Objective

- Assess impact of **high-risk Richter mutations** (TP53, CDKN2A, MYC pathway) on **OS within treatment arms**

Secondary Objectives

- Association of mutations with **ORR, CR, PFS, OS**
- Interaction: **mutation status X treatment arm** (CR, ORR, PFS, OS)

Mutational landscape (baseline + progression)

- Outcomes by **specific mutations** (≥5 patients)
- **MRD (ctDNA)** correlation with **PFS, OS**
- **Clonal relatedness** association with **PFS, OS**

Eligibility

Disease Eligibility

- Richter Transformation (CLL/SLL → LBCL)
- Confirmed LBCL (histology/cytology)
- Measurable disease (PET/CT or pathology)
- Baseline PET/CT within 42 days

Prior Therapy

- Prior CLL therapy allowed
  Exception: no prior pirtobrutinib
- No prior RT-directed therapy
  Exception: short steroids or bridging CLL therapy
- Washout:
  CLL agents ≥ 3 days
  Chemo/anti-CD20 ≥ 2 weeks
- Anthracycline eligibility required
- Avoid strong CYP3A inducers

General & Labs

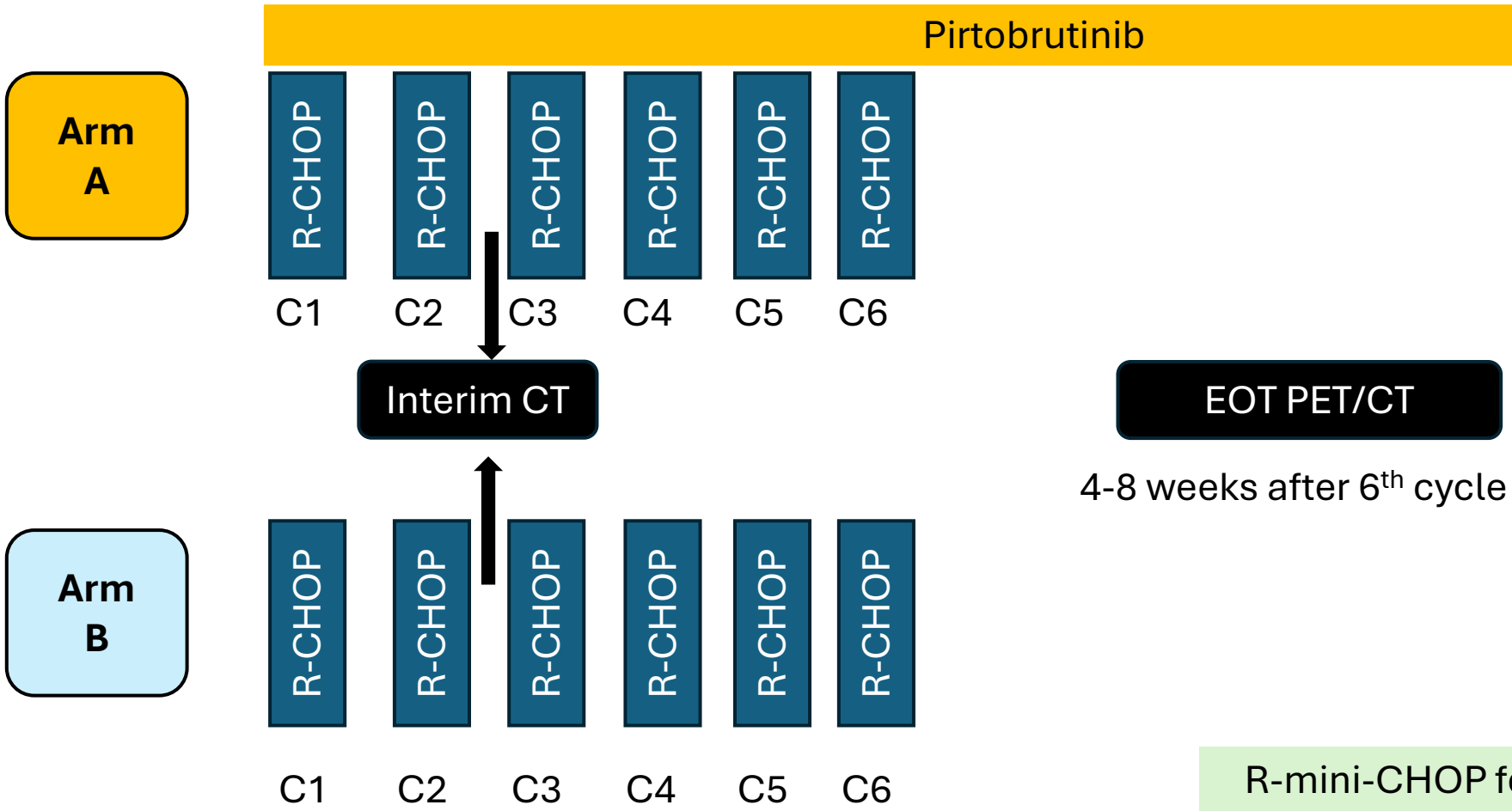
- Age ≥ 18, Zubrod/ECOG 0–2
- Adequate organ function:
  - ANC ≥ 0.75
  - Platelets ≥ 50
  - Hgb ≥ 8
  - Bilirubin ≤ 1.5 x IULN
  - AST/ALT ≤ 3 x IULN
  - CrCl ≥ 30 mL/min

Key Clinical Criteria

- Cardiac: LVEF ≥ 45%, no major arrhythmia
- Infections: HIV/HBV/HCV controlled
- Other:
  - No major surgery (<28 days)
  - No conflicting malignancy
  - Able to take oral meds
  - Not pregnant; contraception required

No eligibility waivers allowed

Overview of Treatments



R-mini-CHOP for participants age 75 and older

Statistical considerations (1)

Sample Size & Accrual

- Up to 102 enrolled → 80 eligible participants
- Safety Run-in: 12 eligible and evaluable participants (6 per run-in cohort)
- Accrual rate: ~2–3 participants/month (after 6-month ramp-up)

Statistical Design

- Randomization: 1:1; hierarchical testing PFS → OS
- Primary endpoints powered to detect HR = 0.50 for both PFS and OS
  - PFS: 10 → 20 months (90% power, one-sided $\alpha \leq 5\%$)
  - OS: 15 → 30 months (89% power marginal; 80% power with hierarchical strategy)
- 2 interim analyses each for PFS and OS
- Final PFS analysis: 75 PFS events; Final OS analysis: 72 deaths (triggered only if PFS positive)

Statistical considerations (2)

Safety Run-In Design (Age-Stratified)

- **Age <75:** n=6, non-randomized → pirtobrutinib + R-CHOP (≤2 cycles)
- **Age ≥75:** n=6, non-randomized → pirtobrutinib + R-mini-CHOP (≤2 cycles)

- **Replacement Criteria**
  - Discontinue before 2 cycles **without ≥10-day delay**, OR
  - <50% of planned pirtobrutinib doses (Cycle 1–2)

- **Open Randomization If**
  - ≤1/6 patients with ≥10-day delay (pirtobrutinib-related) **AND**
  - **No Grade 5 events** related to pirtobrutinib

- **Modify/Stop If**
  - ≥2/6 patients with ≥10-day delay (pirtobrutinib-related) **OR**
  - ≥1 Grade 5 event related to pirtobrutinib

Supportive Care

- **G-CSF:** Required (Day 2–4 post chemo); any formulation OK
- **Antiemetics:** 5-HT3 pre-chemo + take-home meds
- **Infection Prophylaxis:**
  - Antiviral strongly recommended
  - HBV+ → mandatory antiviral
  - Other prophylaxis per clinician
- **CNS Prophylaxis: Not allowed**
- **General Care:** Standard supportive measures permitted (transfusions, antibiotics, etc.)

Specimen Submission

Specimen Type / Amount	Timepoint	Required? / Reason	Specimen Collection, Processing & Handling	Kit Provided?
Lymph Node Biopsy • FFPE block (preferred) OR • 1 high-quality 4-5 micron H&E slide and 15 unstained, 4-5 micron, positively-charged slides	• Baseline (Archival, if collected) (± 30 days from registration) • Progression (only if performed)	Required for Integrated TM	Follow the Specimen Collection and Processing Instructions. Note: The corresponding partially redacted pathology report must be included with the specimen shipment.	No
Buccal Swab	• Baseline (or at any time if missed during screening)	Required with participant consent for Banking	Follow the Specimen Collection and Processing Instructions | SWOG	Yes; See Protocol Section 15.3. Order kits online at https://kits.bpc-apps.nchri.org
Peripheral Blood Two 10 mL Streck cfDNA tubes	• Baseline (prior to treatment on C1/D1) • C3D1 (± 3 days) • Arm 1: C7D1 (± 3 days) • Arm 2: EOT(± 3 days) • Progression (within 14 days after progression)			
Peripheral Blood 20 mL EDTA tubes	• Baseline (prior to treatment on C1/D1) • C3D1 (± 3 days) • Arm 1: C7D1 (± 3 days) • Arm 2: EOT(± 3 days) • Progression (within 14 days after progression)	Required for Integrated TM		No

Patient Reported Outcomes

PRO-CTCAE

- Timepoints:
  - Pre-registration/baseline (within 7 days prior to randomization)
  - At C3D1, C5D1, C7D1 (± 14 days) while participant is on protocol therapy
- There will be no protocol-directed action for PRO-CTCAE responses.

FACIT GP5

- Timepoints:
  - Pre-registration/baseline (within 7 days prior to randomization)
  - At Week 6, Week 12, and Week 18 (± 14 days) while participant is on protocol therapy.

Both Instruments

- Offered in English and Spanish.
  - Accessible via the S2504 protocol abstract page on the CTSU website under Documents >> CIRB Approved Documents tab >> Support Documents filter
- Anyone involved in the collection of patient-reported outcomes data in SWOG trials should review the Patient Reported Outcome Questionnaires training program available via CTSU CLASS (login required).

Participant Registration, Drug Ordering and Timing Considerations

Start of Treatment:

Initiation of treatment must be planned to start no more than **7 calendar days** after registration.

Drug ordering

- Pirtobrutinib is supplied by Lilly and distributed by McKesson.
  - Pirtobrutinib must be ordered after participant registration to S2504; No starter supplies are available.
  - Fax the **S2504 Pirtobrutinib Order Form** to McKesson at the number listed on the order form.
  - **Allow up to 5 business days after submission of the drug order request form for study drug to arrive**.
- R-CHOP components are commercially available; ordered per institutional practice

Collection kit ordering

- Only banking specimens (buccal swabs, Streck cfDNA blood tubes) have kits provided
  - Order kits via kits.bpc-apps.nchri.org.
  - Note: TM specimens (EDTA blood, lymph node FFPE) use institutional supplies, no kit.
- Allow 3–4 business days for receipt (if order was placed by noon ET on a business day).
- Order kits before treatment starts to ensure correct collection timing.

Slot Reservation During Safety Run-In

- **Slot reservation is required <u>during the Safety Run-In</u>.**
  - During the safety run-in: Even if the site plans to enroll right away, participants must have a slot reserved in advance of the registration.
  - **Prior to discussing protocol entry with the participant:** Site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the participant. Refer to Section 13.2 of the protocol for information that will be required during for the Slot Reservation.
    - Detailed slot reservation instructions are accessible from the **Slot Reservation Quick Reference Site User Guide** within the OPEN tab on the CTSU website under 'Training and Demonstration Materials' for detailed instructions
  - AFTER a slot reservation confirmation is obtained, site staff may then proceed to enroll the participant to this study.

Why This Study Matters – Patient/Family Perspective (1)

Presented by: **Gail Sperling, MPH,** SWOG Leukemia Committee Patient Advocate

- ***Richter Transformation is rare, aggressive, difficult to treat***
  - RT remains a major unmet need due to its aggressive biology, poor prognosis and resistance to standard therapies
  - R-CHOP is commonly used RT but is associated with limited efficacy and substantial toxicity
  - New approaches urgently needed
- ***Why this trial?***
  - Studies demonstrate efficacy and safety in monotherapy for RT
  - Attack the cancer from two angles
    - R-CHOP damages and kills the cells
    - Pirtobrutinib blocks their ability to recover and keep growing
  - Improve effectiveness of standard treatment with a manageable toxicity profile
  - Collect critical info (secondary and tertiary objectives)
  - Patients/families may argue that *any* improvement in DFS and OS is significant
  - Get patients to transplant?

Why This Study Matters – Patient/Family Perspective (2)

Presented by: **Gail Sperling, MPH,** SWOG Leukemia Committee Patient Advocate

- ***Patient Benefits***
  - Safety run-in for both arms (ages 18 – 75+)
  - Pirtobrutinib is more targeted, better tolerated, fewer side effects
  - Flexibility in eligibility criteria and plans to manage serious AEs
  - Patient-Reported Outcomes (**PROs**) to compare symptoms between arms available in English and Spanish – 14-day flexibility in administration
- ***Accrual rate assumptions***
  - Feasible based on polling of major centers (2 -3 per month)
  - Study open across NCTN
- ***Patient Advocate Summary***
  - From a Patient Advocate perspective, strong support: “a randomized trial comparing pirtobrutinib + R-CHOP versus R-CHOP in previously untreated RT is scientifically and clinically justified”
  - This trial across NCTN sends positive message to patients and their families that the research community is committed to finding new approaches that have the potential to be superior to the current SOC, improve QOL, impact practice guidelines and help establish future treatment strategies (across different age groups) for this high-risk population.

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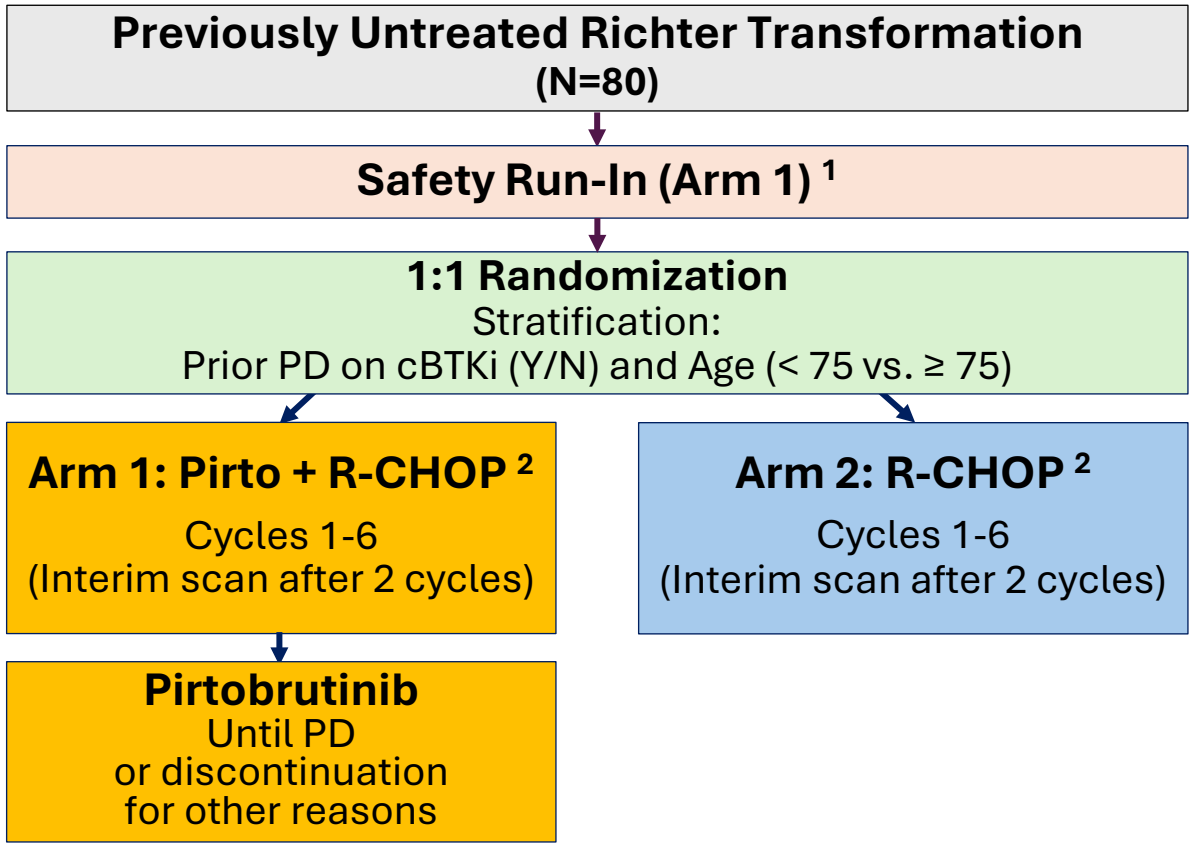

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Acknowledgements

- NCI/CTEP
- Eli Lilly
- SWOG study team
- SWOG Leukemia and Lymphoma committees
- Alliance and ECOG
- Patient advocates

Questions? / Discussion

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Thank you

https://www.swog.org/S2504HealthcareProviderHandout

Scan the QR code (or follow the hyperlink) to download the S2504 Healthcare Provider Handout