ARRANON® (nelarabine) Injection
NDA 21-877

Presentation to
Oncologic Drugs
Advisory Committee

September 14, 2005

Presentation Overview

Introduction	Peter Ho, M.D., Ph.D. VP, Discovery Medicine Oncology, GSK
Disease Overview	Stephen Sallan, M.D. Professor of Pediatrics, Harvard Chief of Staff, Dana-Farber
Efficacy Summary	Richard Larson, M.D. Professor of Medicine, Univ. of Chicago Chair, Leukemia Committee, CALGB
Safety Summary	Mark Russo, M.D., Ph.D. Group Director, Clinical Oncology, GSK
Role in Treatment	William Carroll, M.D. Director, Pediatric Oncology, NYU Chair, ALL Committee, COG
Conclusion	Peter Ho, M.D., Ph.D.

Additional Participants

Susan Blaney, M.D.	Texas Children's Cancer Center
Dan DeAngelo, M.D., Ph.D.	Dana-Farber Cancer Institute
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Varsha Gandhi, Ph.D.	M.D. Anderson Cancer Center
Arthur Forman, M.D.	M.D. Anderson Cancer Center

Additional GSK Participants

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Proposed Indication

- **ARRANON®** (nelarabine) Injection is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens

ARRANON® (nelarabine)

- Purine nucleoside phosphorylase (PNP) deficiency
  - T-cell lymphopenia
  - Abnormal guanine nucleoside metabolism
- Ara-G mimics PNP deficiency state
  - T-cells targeted for selective destruction
- **ARRANON** is a soluble pro-drug of Ara-G
- First clinical trial in 1993
- NCI collaborative development
  - CALGB & COG pivotal studies
  - Cooperative group data for submission

ARRANON® (nelarabine)

- **ARRANON** demonstrates
  - Pharmacological selectivity for T-cells
  - Clinical efficacy
    - in children and adults
    - in relapsed and refractory disease
  - Well characterized safety profile
  - Favorable benefit-risk profile in heavily pre-treated patients
- Meets a significant unmet medical need
- No proven effective alternative therapy available for T-ALL and T-LBL

Disease Overview

Stephen Sallan, M.D.
Professor of Pediatrics, Harvard
Chief of Staff, Dana-Farber

Overview of Patients with T-ALL / T-LBL

- Rare diseases (N~1600/yr)
- T-cell ALL & LBL differ only by % lymphoblasts in bone marrow
- Most in older children & young adults
- Much biology age-independent

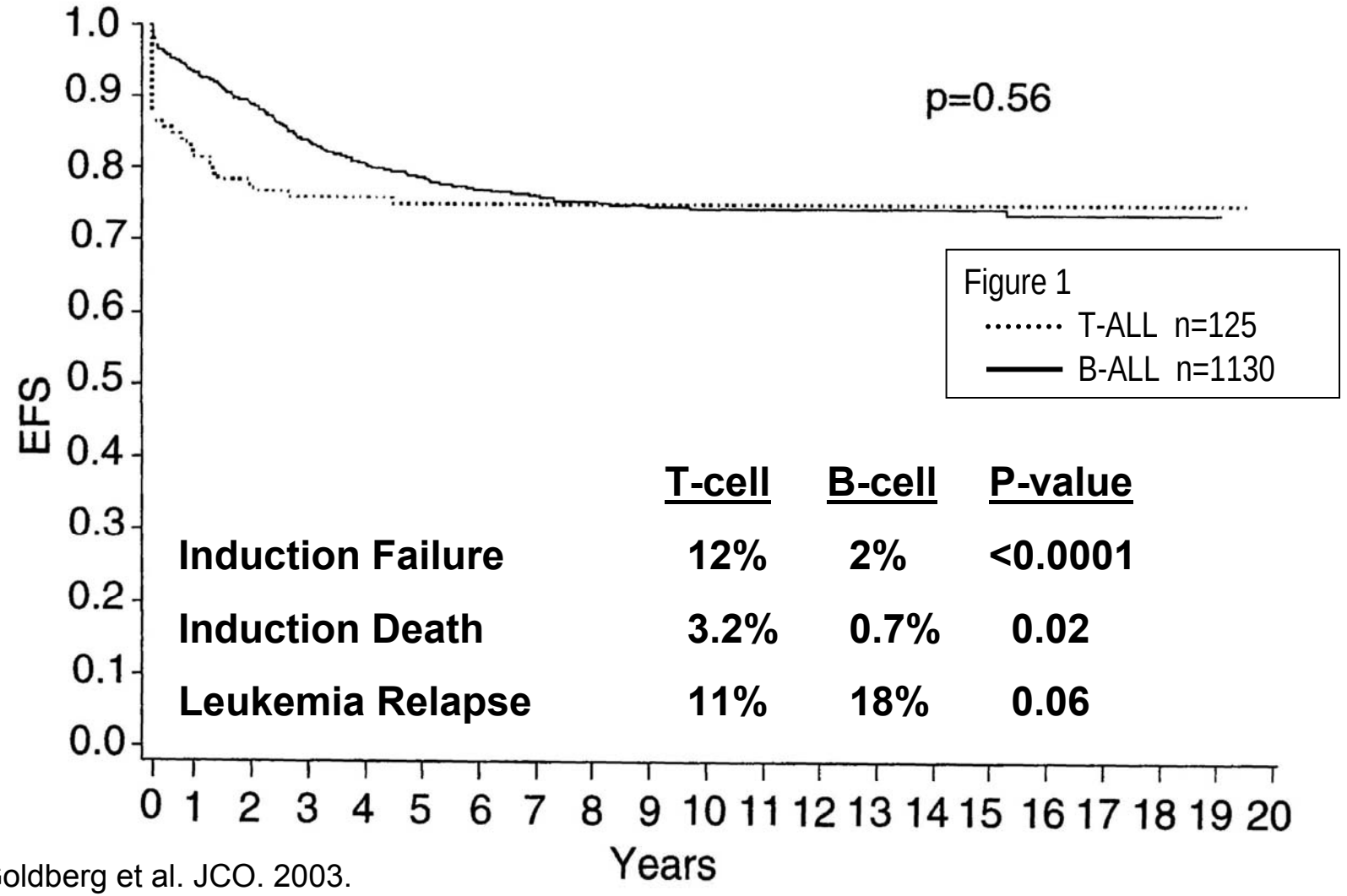
  - e.g., Notch 1 mutations in ~ 50%

  - e.g., Gene expression signatures

Current Treatment

- Multi-agent chemotherapy at time of diagnosis and at 1st relapse
- Treatment with curative intent
  - At diagnosis – chemotherapy
  - 1st relapse – chemotherapy to induce a 2nd complete remission; then curative stem cell transplant

Pediatric Patients with ALL at Diagnosis by Immunophenotype



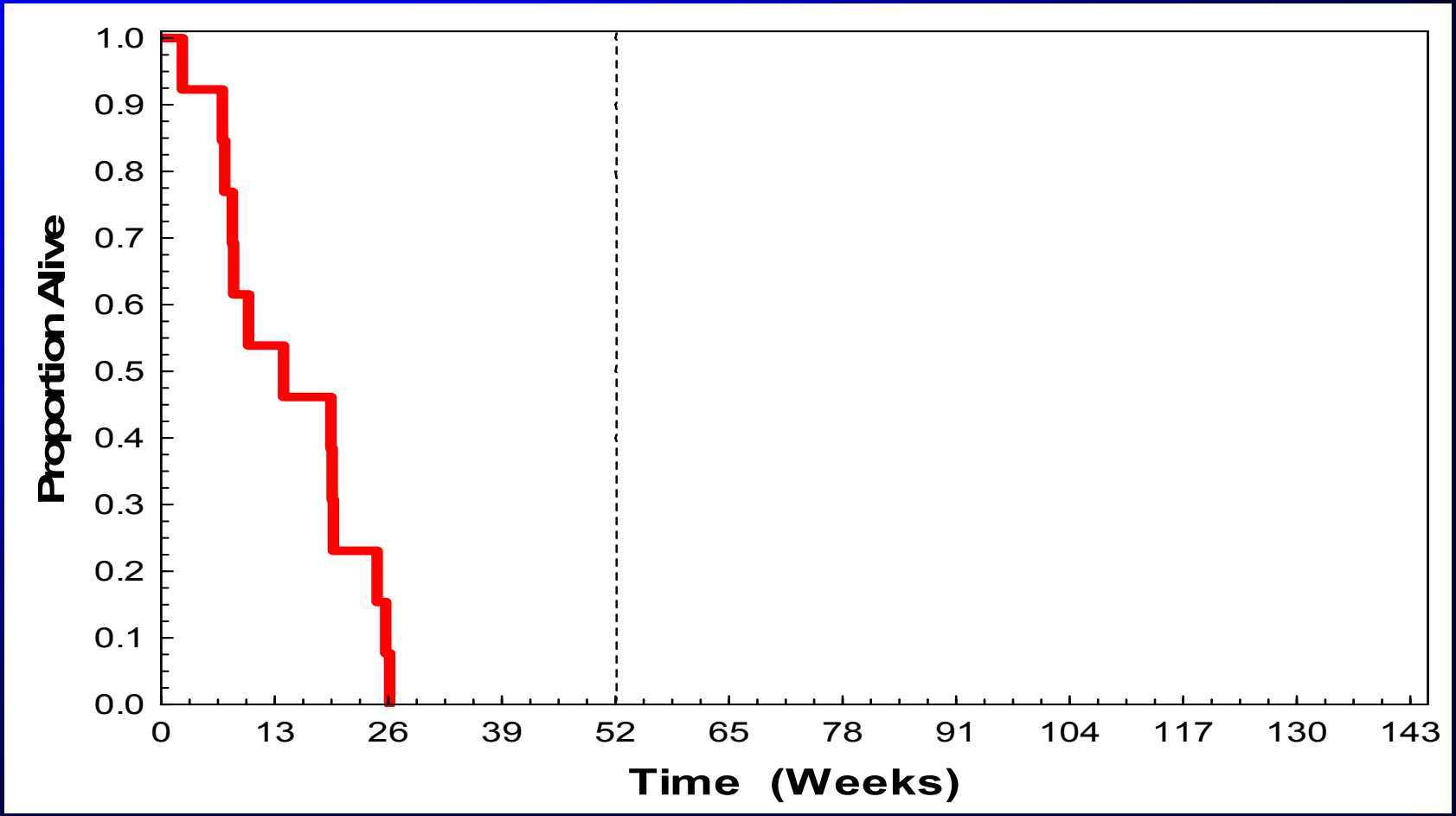
	T-cell	B-cell	P-value
Induction Failure	12%	2%	<0.0001
Induction Death	3.2%	0.7%	0.02
Leukemia Relapse	11%	18%	0.06

Goldberg et al. JCO. 2003.

Patients with T-ALL / T-LBL at 1st Relapse

- ~500 patients per year
- Treatment is with curative intent: multi-agent chemotherapy followed by a SCT
- Outcome for T-cell ALL patients transplanted in 2nd remission is approximately 40% at two years for children and adults.
- Treatment related mortality can be 5-10%.

Outcome After Second Relapse (Patients with T-ALL, N=13)



Sather, et al. COG (unpublished)

Current Drugs in Multi-Agent Regimens

Vincristine	6-MP
Prednisone	6-TG
Dexamethasone	Methotrexate
Asparaginase	Cyclophosphamide
Daunorubicin	Etoposide
Doxorubicin	Cytarabine

New drugs are needed for patients with relapsed and refractory disease.

Efficacy Overview

Richard Larson, M.D.
Professor of Medicine, Univ. of Chicago
Chair, Leukemia Committee, CALGB

Pivotal Studies

- **Adult: CALGB19801**
  - **A Phase II Study of Nelarabine (506U78) in Subjects with Refractory or Relapsed T-Lineage Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL)**

    DeAngelo et al. Blood. 2002; 100(11):198a (Abstract 743).

- **Pediatric: COG P9673**
  - **A Phase II Study of 506U78 in Patients with Refractory T-Cell Malignancies**

    Berg et al. JCO. 2005; 23(15):3376-82.

Efficacy Endpoint Definitions

Parameter	CR	CR*
Bone marrow - Blasts	<5%	<5%
Hemogram - Blasts - Platelets - Neutrophils	0% >100,000 >1500	0%
Physical - Liver - Spleen - Other	NED NED NED	NED NED NED
Extramedullary	NED	NED

NED = no evidence of disease.

Rationale for CR* Endpoint

- Similar to CRi and CRp for patients with AML
- Heavily pretreated patients
  - may never have full hematologic recovery
  - benefit from the absence of disease
- Retreatment & Stem Cell Transplant
  - may occur prior to full hematologic recovery

CR* was agreed with FDA June 1997

Patients with T-ALL/T-LBL

- Prior Therapy
  - One prior induction/regimen
    - Primary refractory disease
    - Relapsed disease
  - Two or more prior inductions/regimens
    - Refractory disease
    - Relapsed disease
- Refractory
  - Primary refractory disease
  - Less than CR following most recent induction attempt

Adult: CALGB 19801

- Open-label, multicenter Phase II study
- Median age: 34 years (range: 16-66 years)
- Refractory or relapsed T-ALL or T-LBL
- Dose*: 1500 mg/m^2 days 1, 3, 5, every 21 days
- Two cycles for induction plus two for consolidation
- 39 patients treated:
  - 11 patients with 1 prior multi-agent induction/regimen
  - 28 patients with ≥ 2 prior multi-agent inductions/regimens
- Enrolled over 37 months

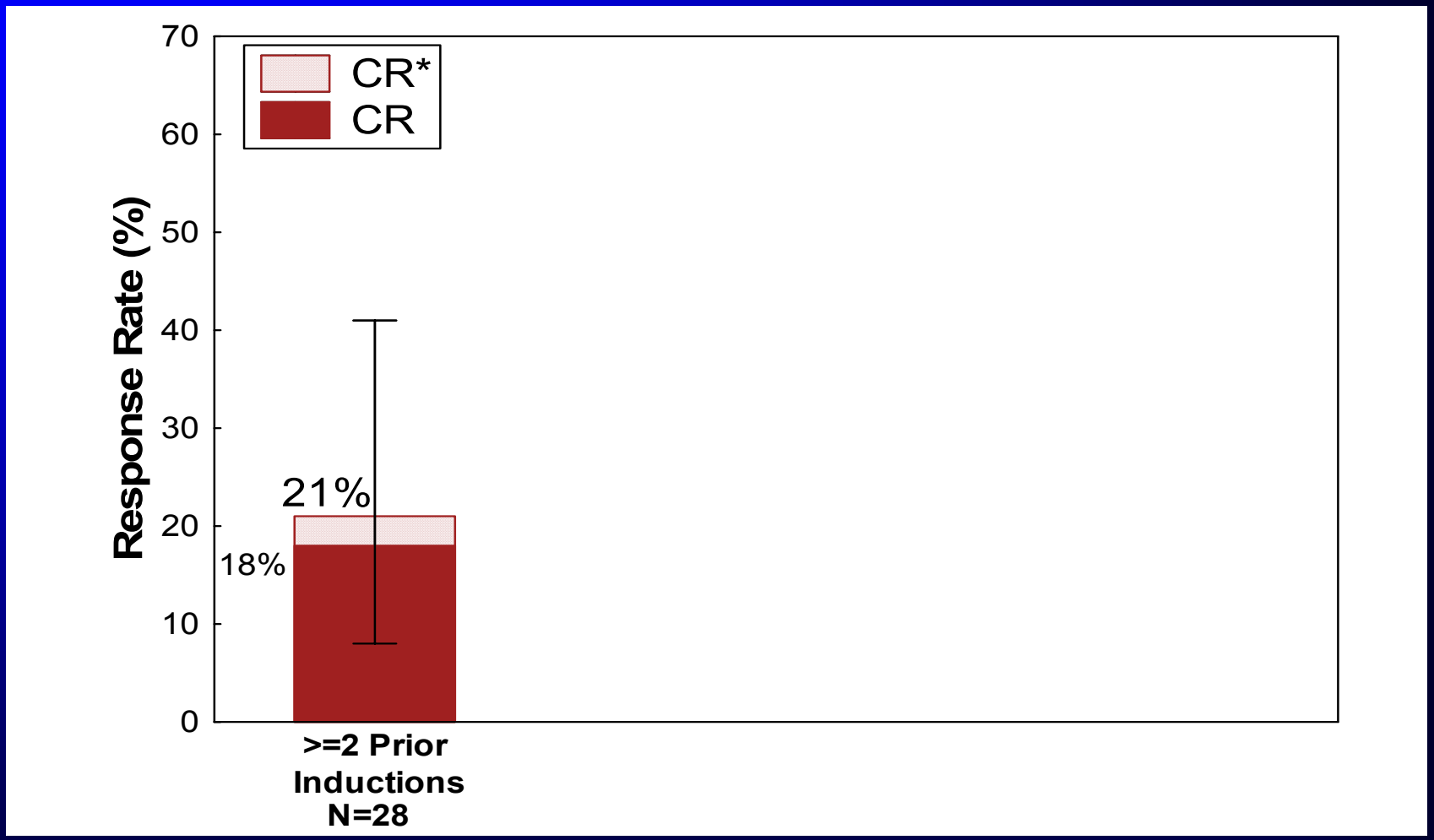
* Recommended Dose

Adult: CALGB 19801 Response Rate & Duration ≥ 2 Prior Inductions (N=28)

Response	CR	CR plus CR*
Response Rate	18%	21%
Median Duration of Response (weeks)	29	24
Duration of Response (weeks)	15 to 195+	4 to 195+

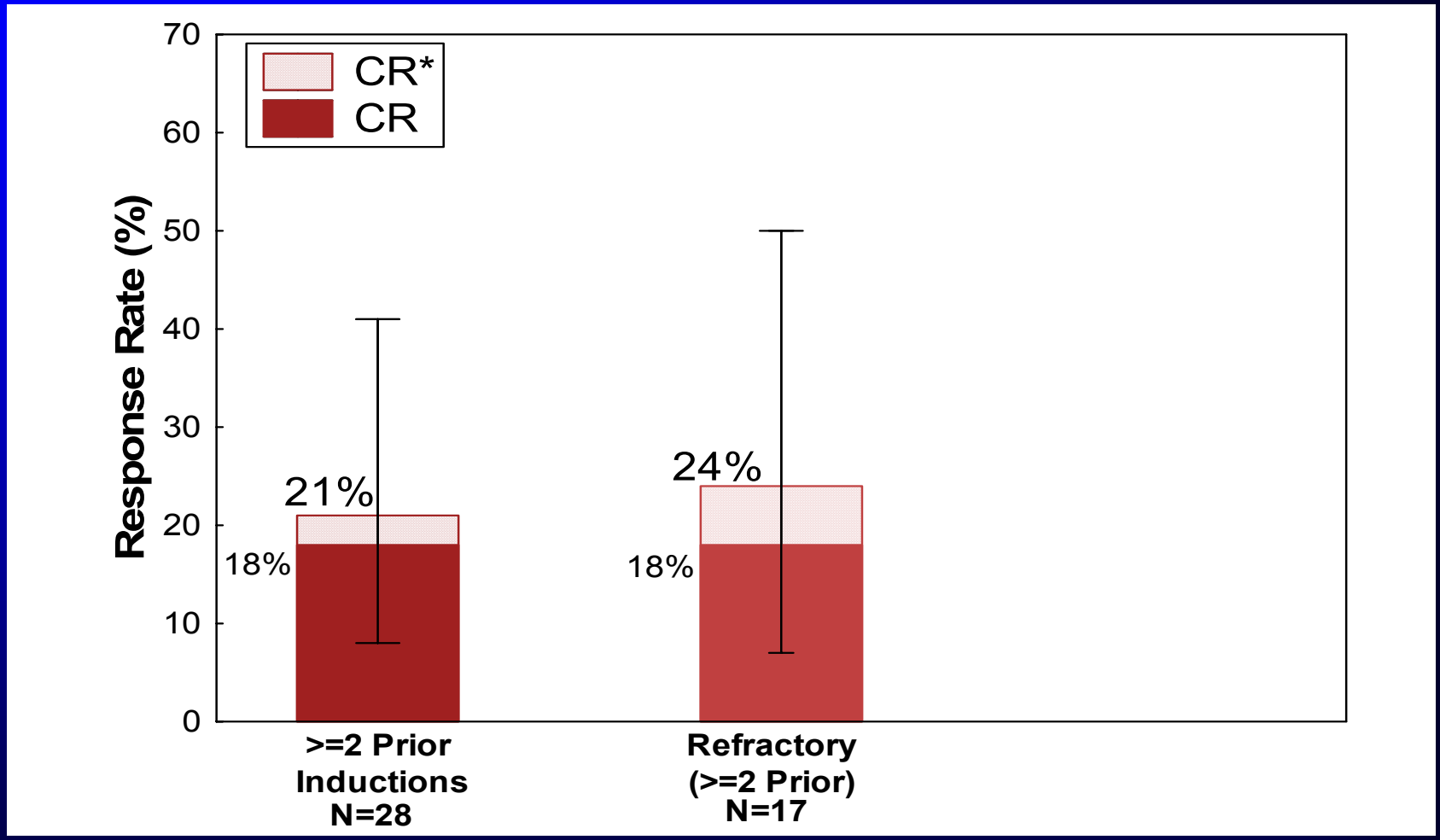
CR = complete response with full hematologic recovery
CR* = complete response without full hematologic recovery
CR plus CR* = total of patients achieving best response in either category

Adult: CALGB 19801 CR+CR* Rates



Brackets represent 95% confidence intervals for (CR+CR*)

Adult: CALGB 19801 CR+CR* Rates



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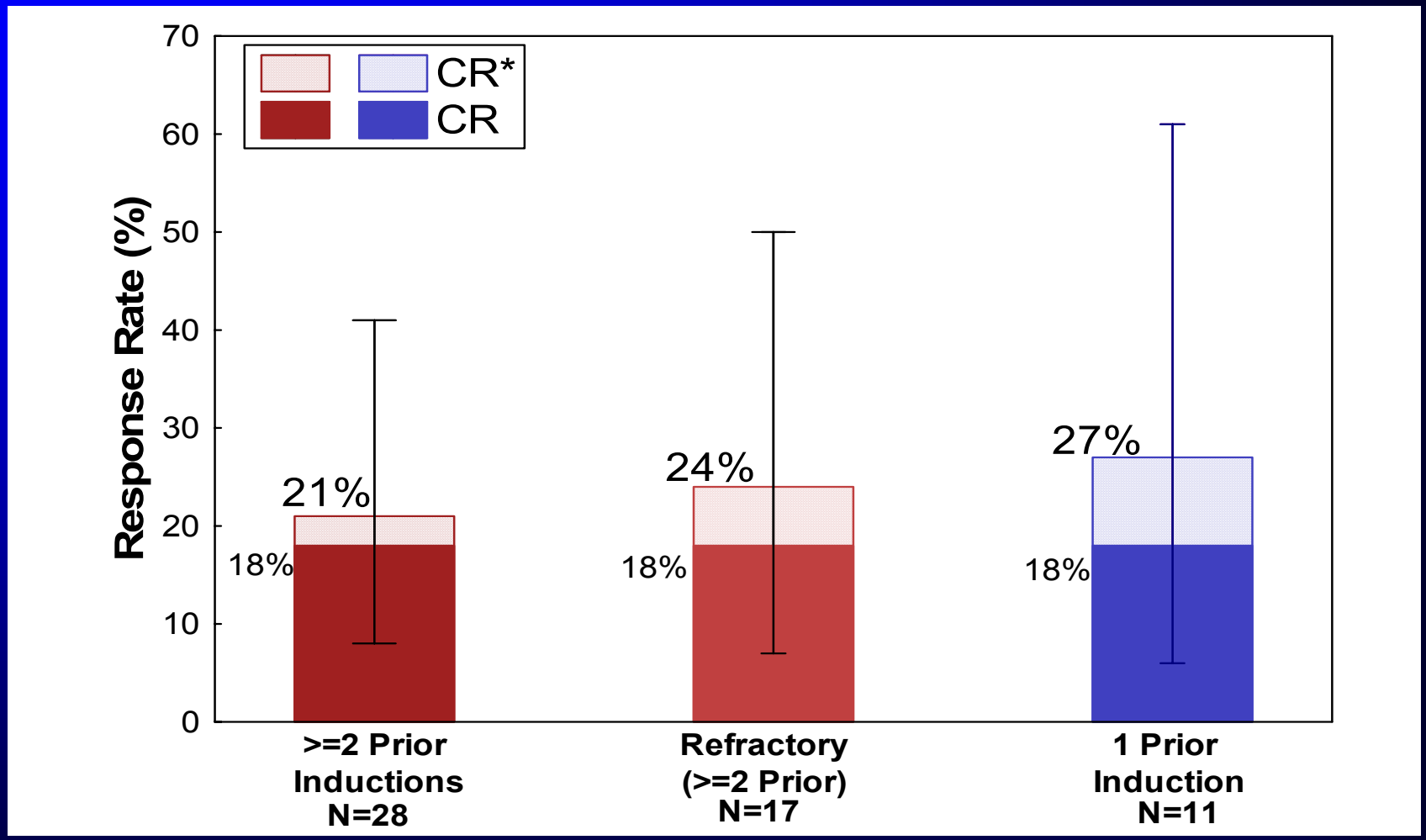
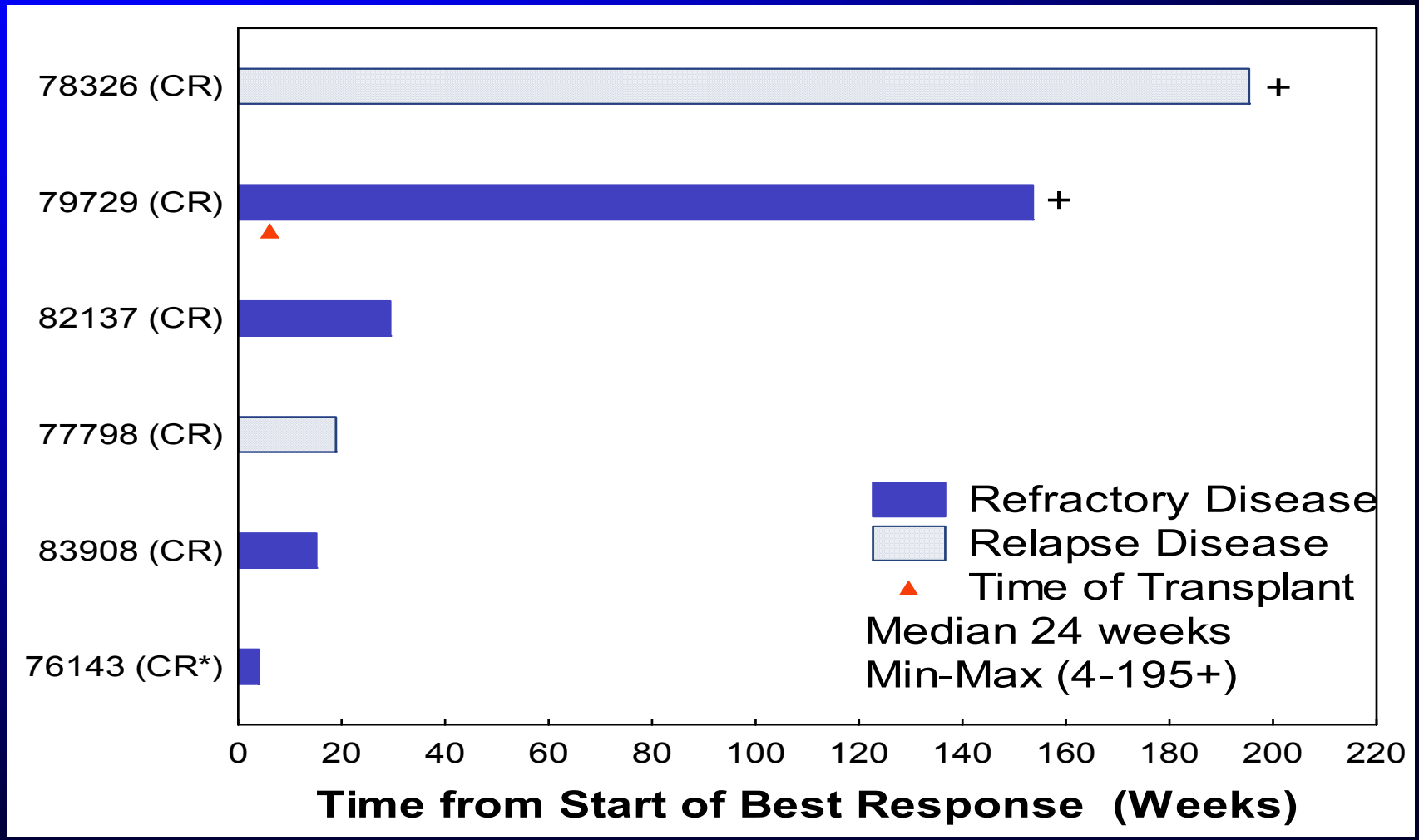
Adult: CALGB 19801 CR+CR* Rates



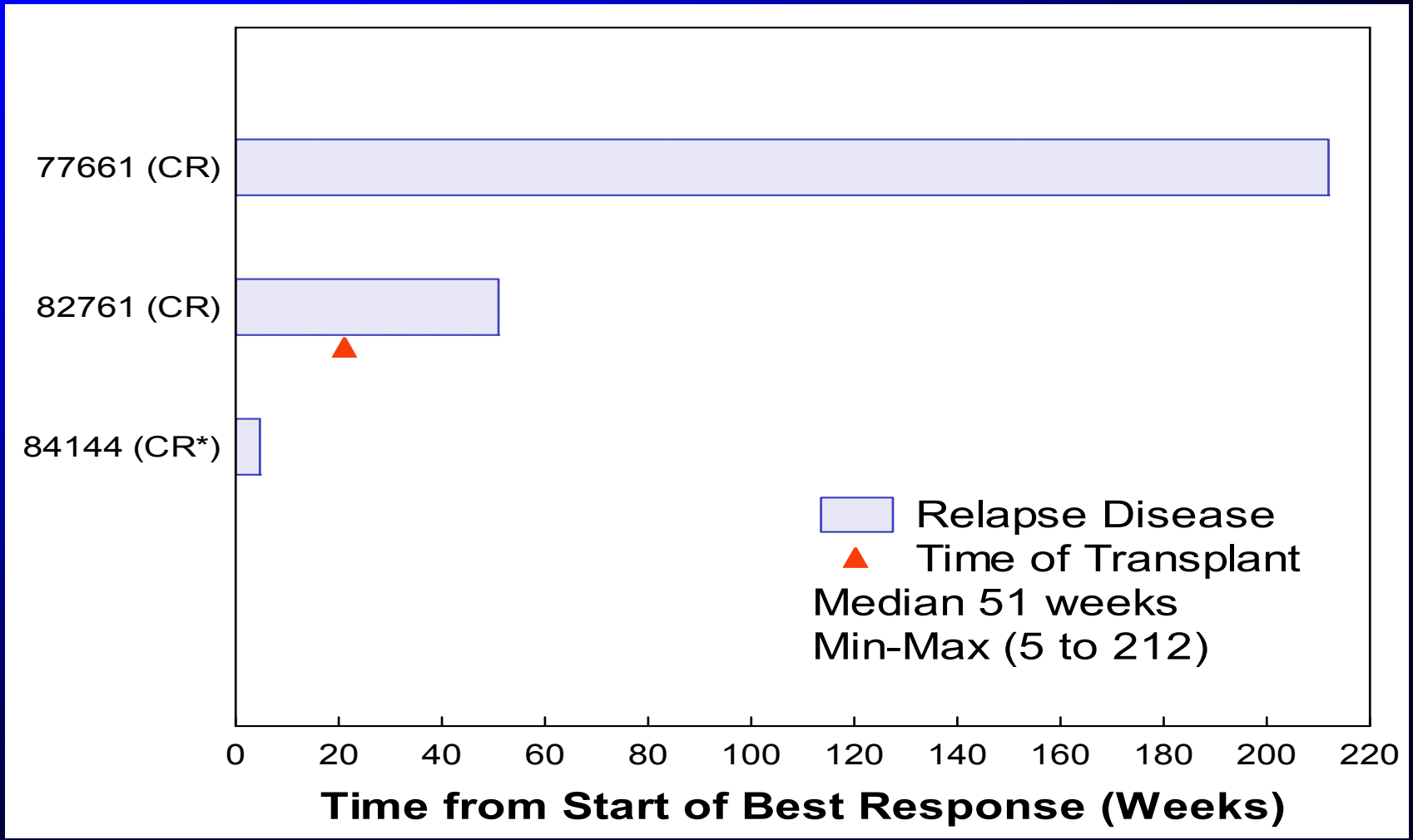
Brackets represent 95% confidence intervals for (CR+CR*)

Adult: CALGB 19801 Duration of Best Response (≥2 prior multi-agent inductions)

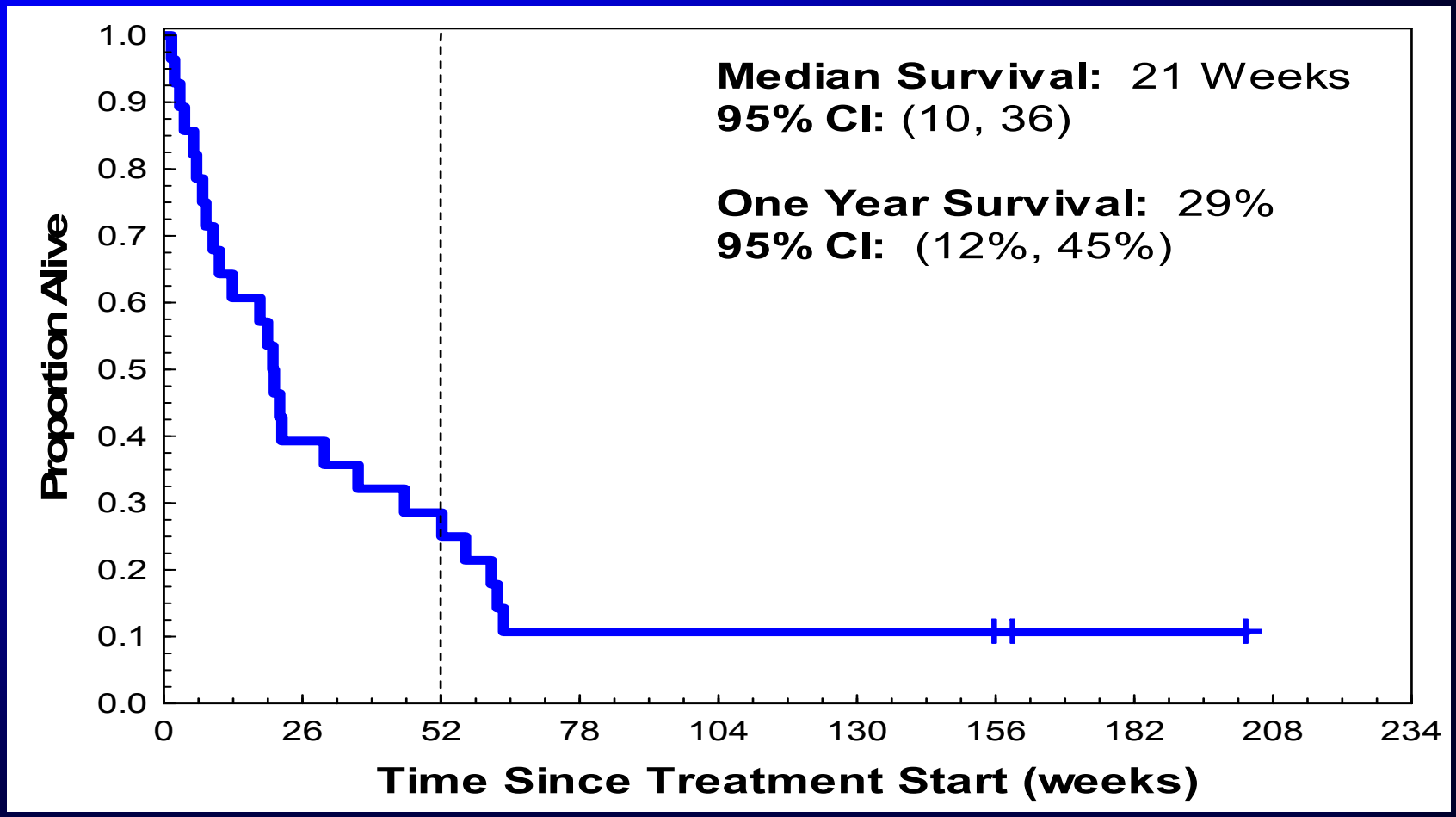


+ Response on-going at last evaluation

Adult: CALGB 19801 Duration of Best Response (1 prior multi-agent induction)



Adult: CALGB 19801 Overall Survival (≥ 2 Prior Multi-Agent Inductions)



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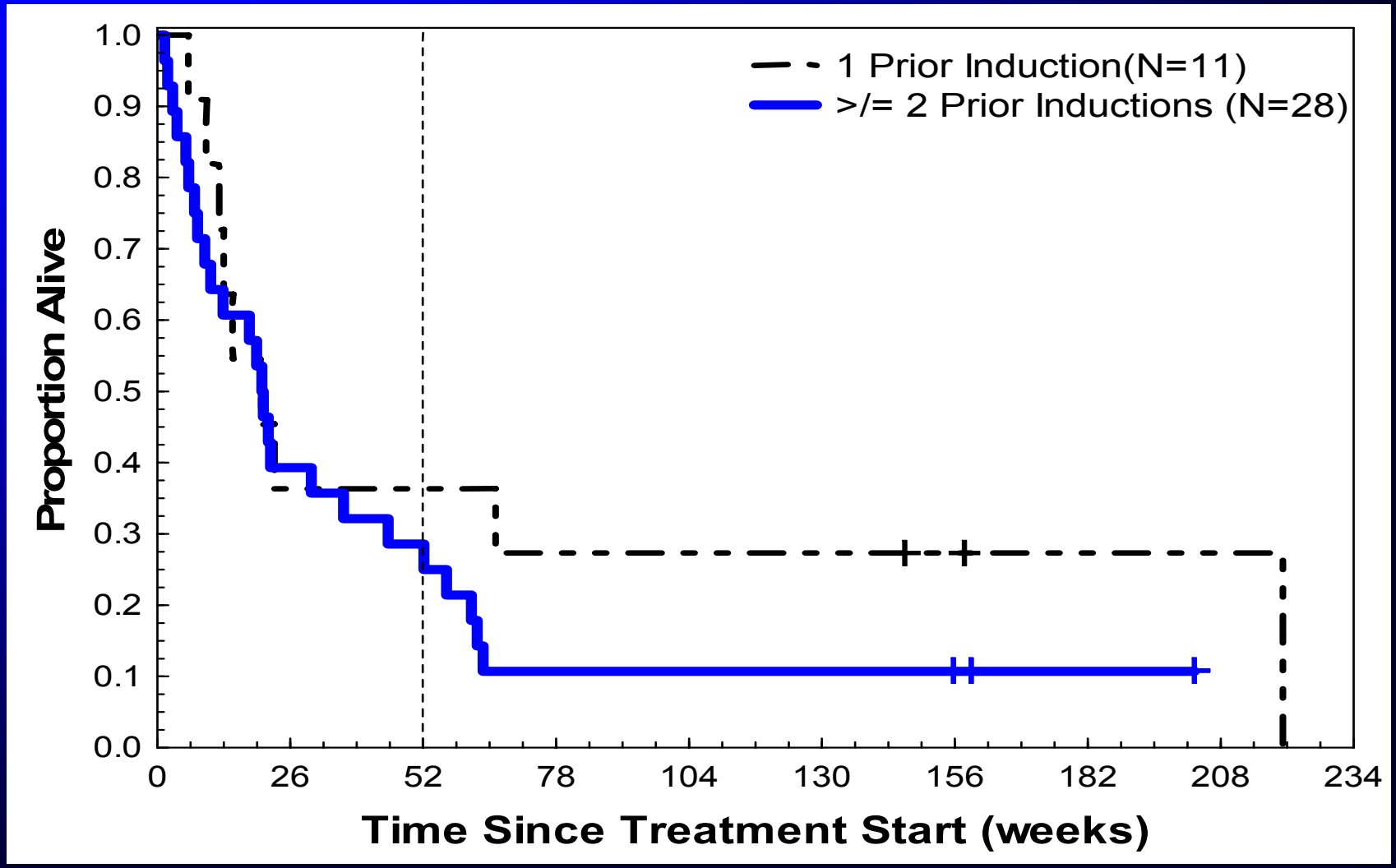
Adult: CALGB 19801 Overall Survival



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Pediatric: COG P9673

- Open-label, multicenter Phase II study
- Refractory or relapsed T-ALL or T-NHL
- Dose*: 650 mg/m^2 days 1-5, every 21 days
- Median: 11 years (range 3-20 years)
- 151 patients treated across 4 strata
  - At the recommended dose
    - 31 patients with 1 prior multi-agent induction
    - 39 patients with ≥2 prior multi-agent inductions
- Enrolled over 61 months

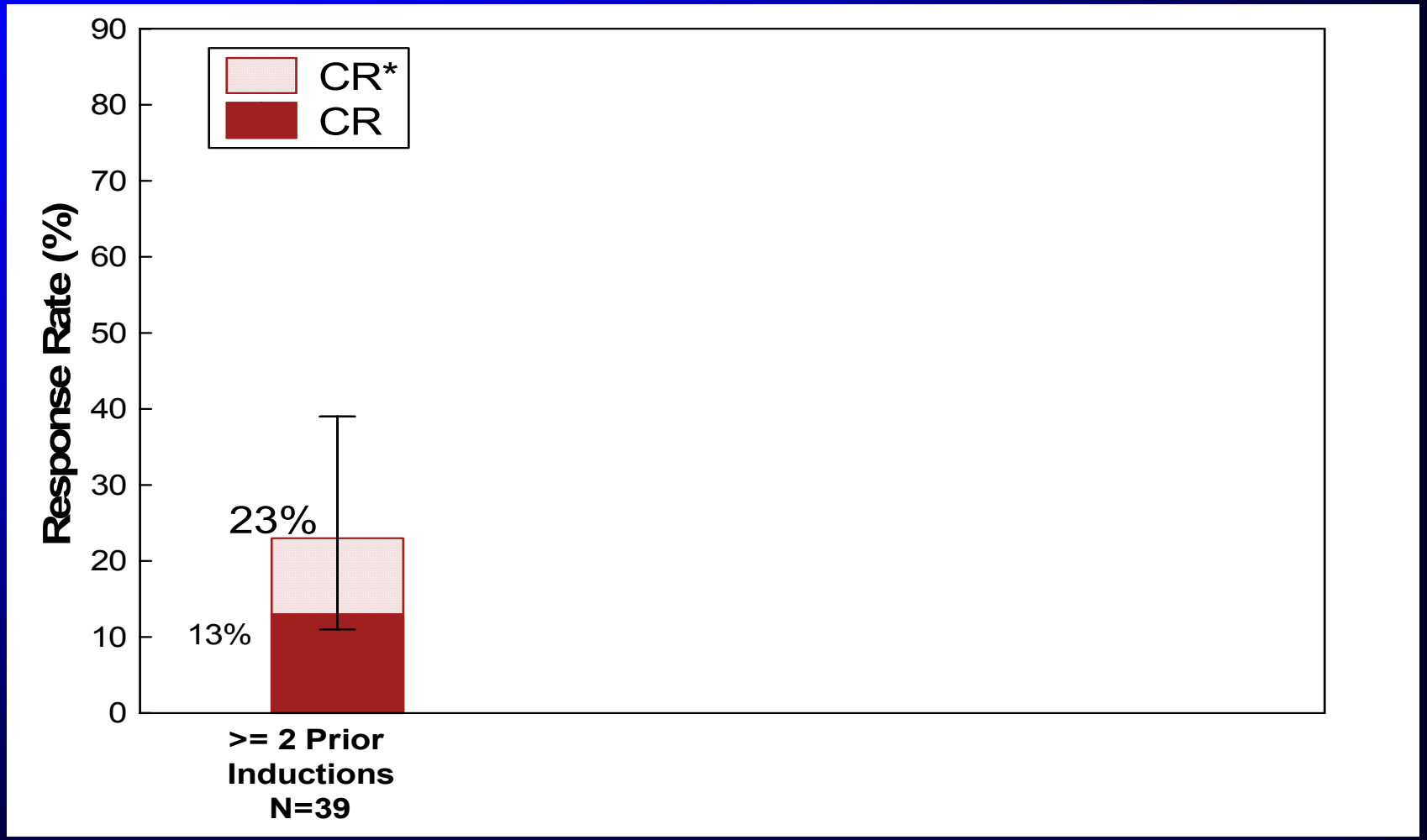
* Recommended Dose

Pediatric: COG P9673 Response Rate & Duration ≥ 2 Prior Inductions (N=39)

Response	CR	CR plus CR*
Response Rate	13%	23%
Median Duration of Response (weeks)	9	9
Duration of Response (weeks)	5 to 36	3 to 42

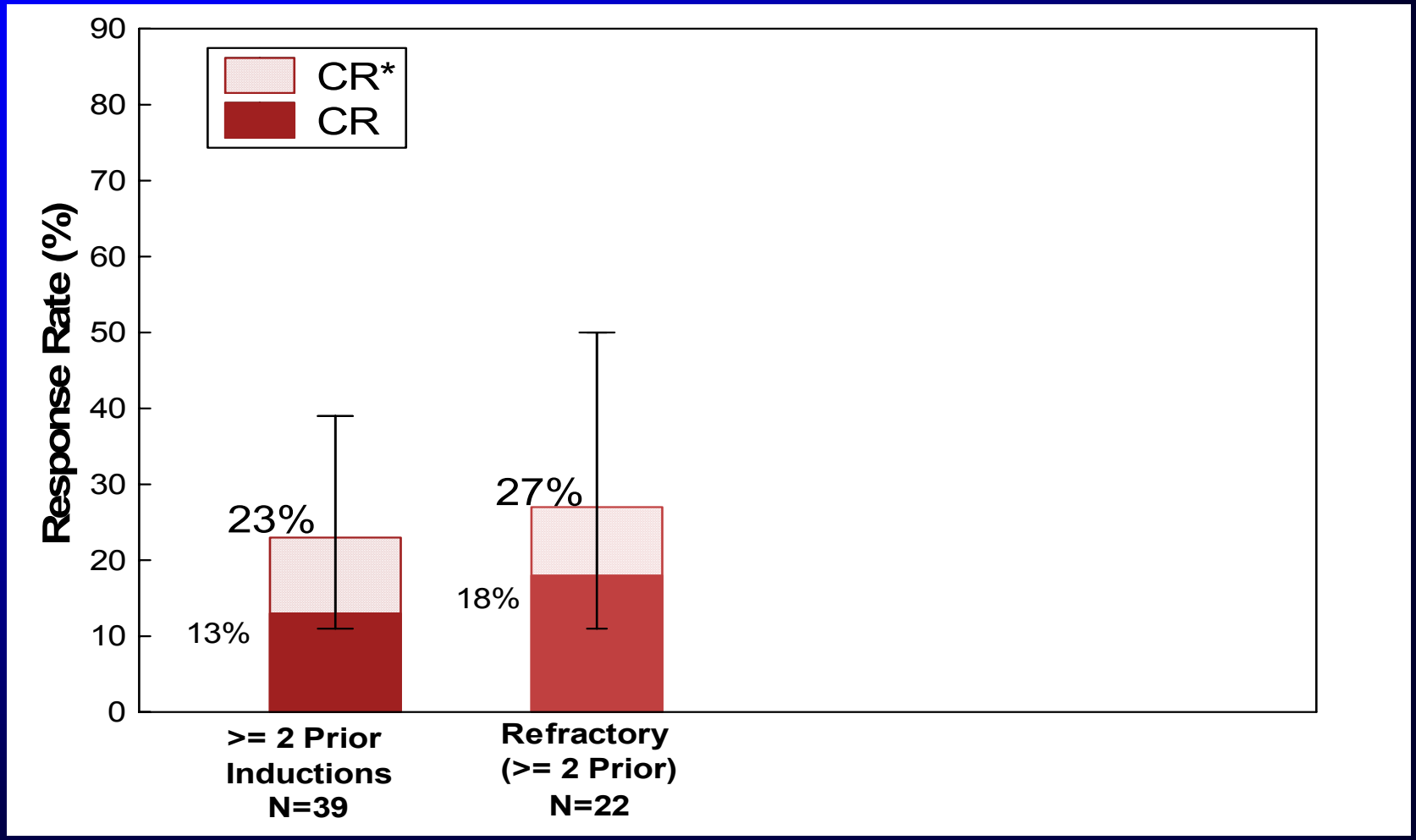
CR = complete response with full hematologic recovery
CR* = complete response without full hematologic recovery
CR plus CR* = total of patients achieving best response in either category

Pediatric: COG P9673 CR+CR* Rates



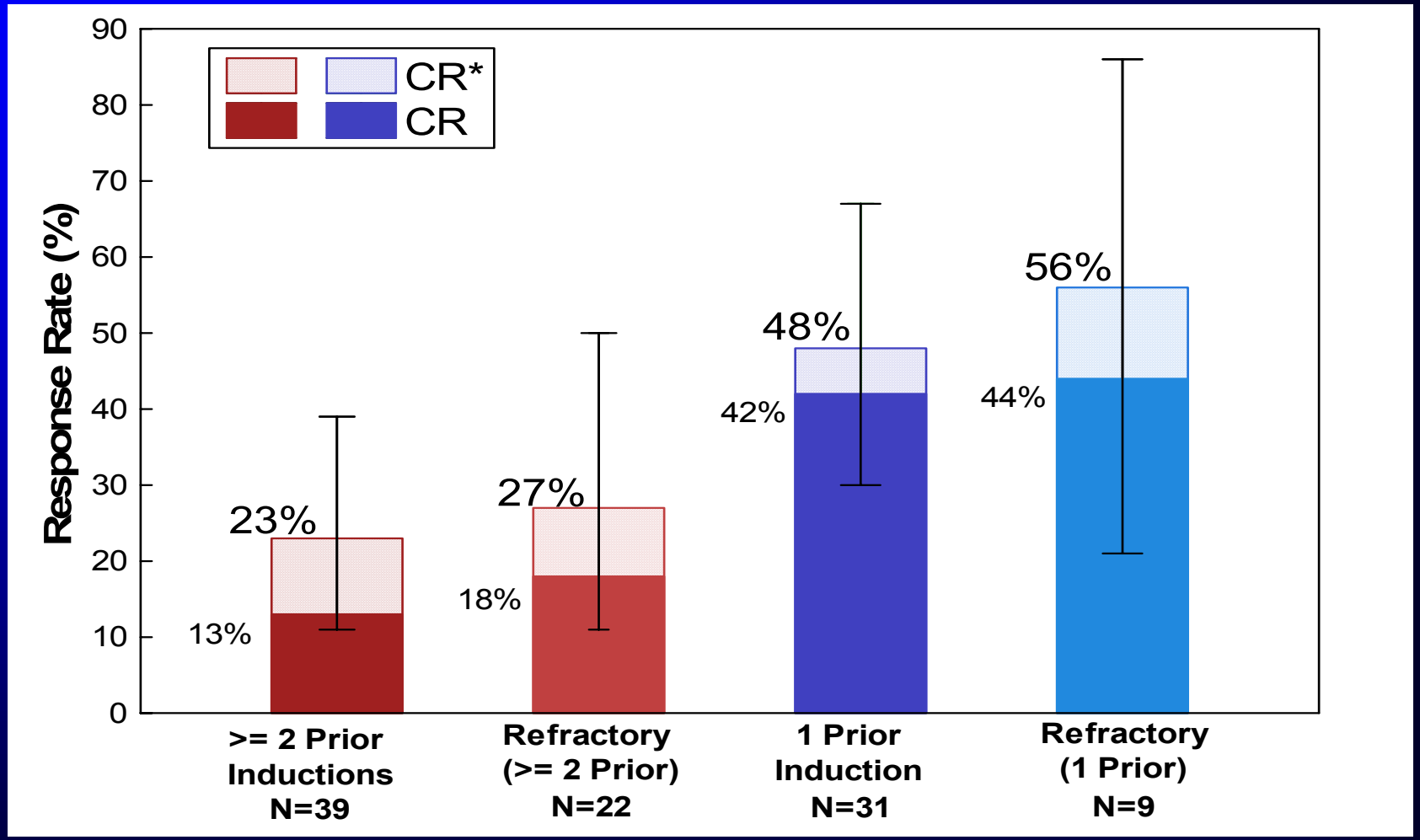
Brackets represent 95% confidence intervals for (CR+CR*)

Pediatric: COG P9673 CR+CR* Rates



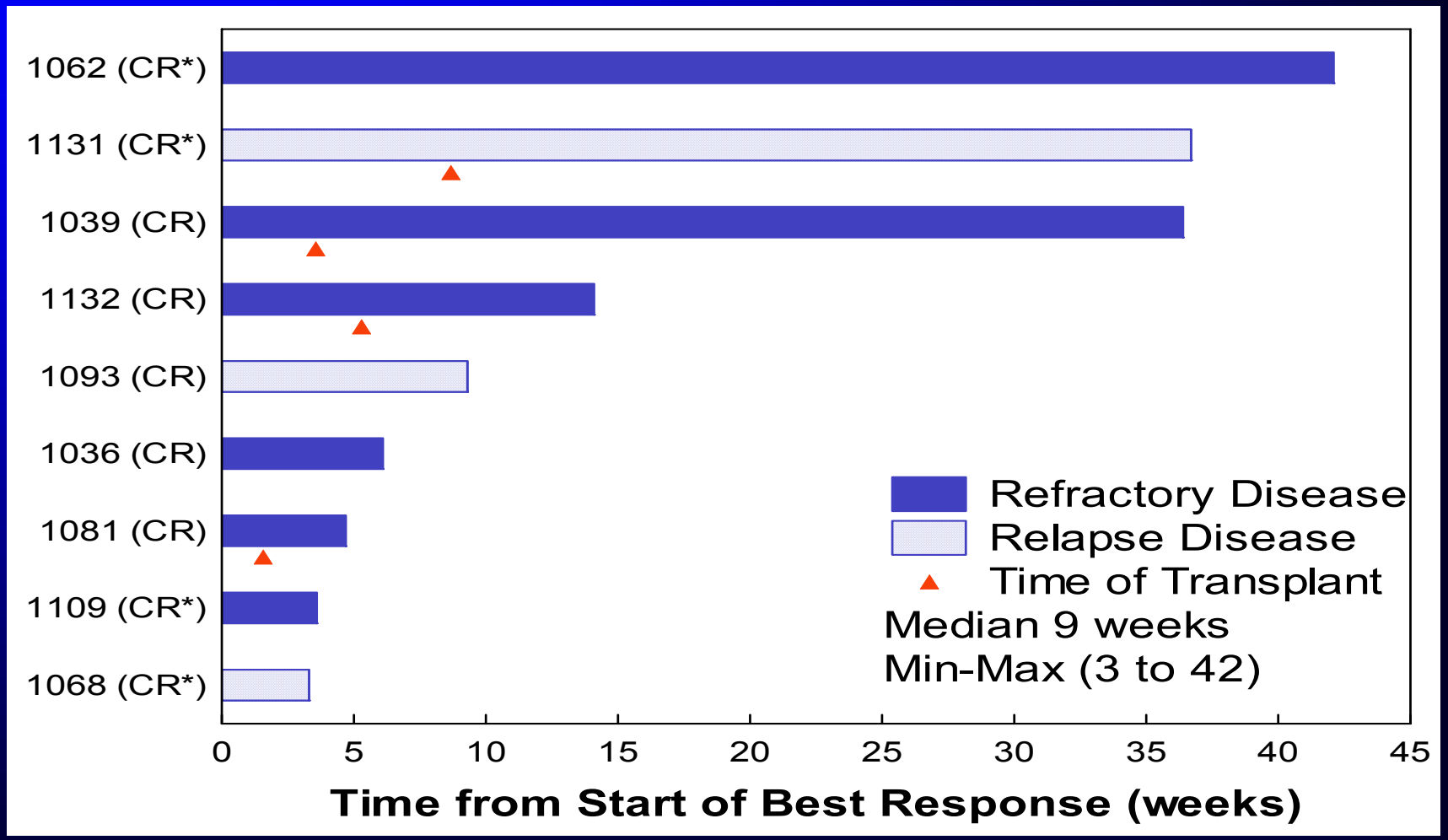
Brackets represent 95% confidence intervals for (CR+CR*)

Pediatric: COG P9673 CR+CR* Rates

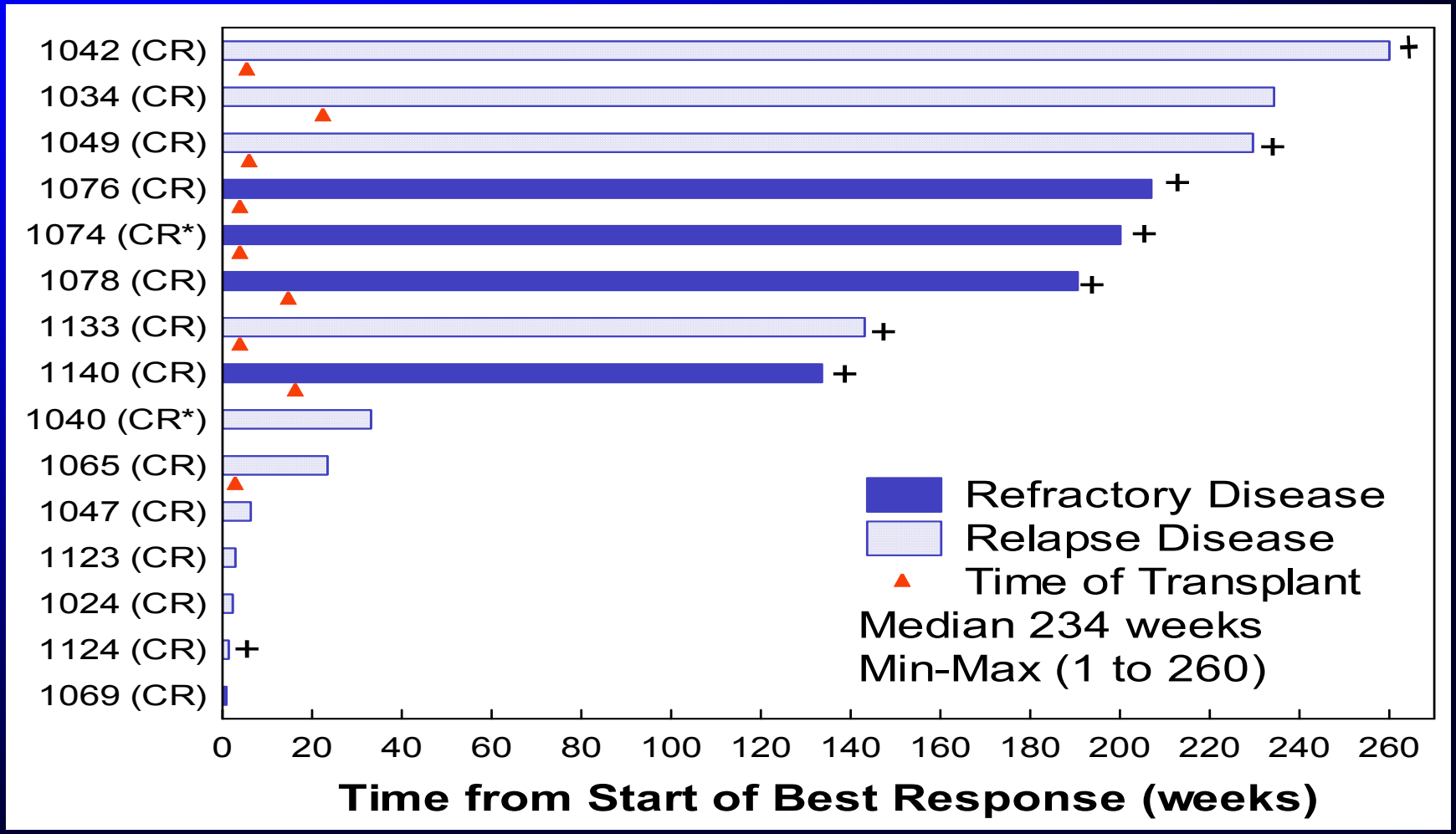


Brackets represent 95% confidence intervals for (CR+CR*)

Pediatric: COG P9673 Duration of Best Response (≥2 prior multi-agent inductions)

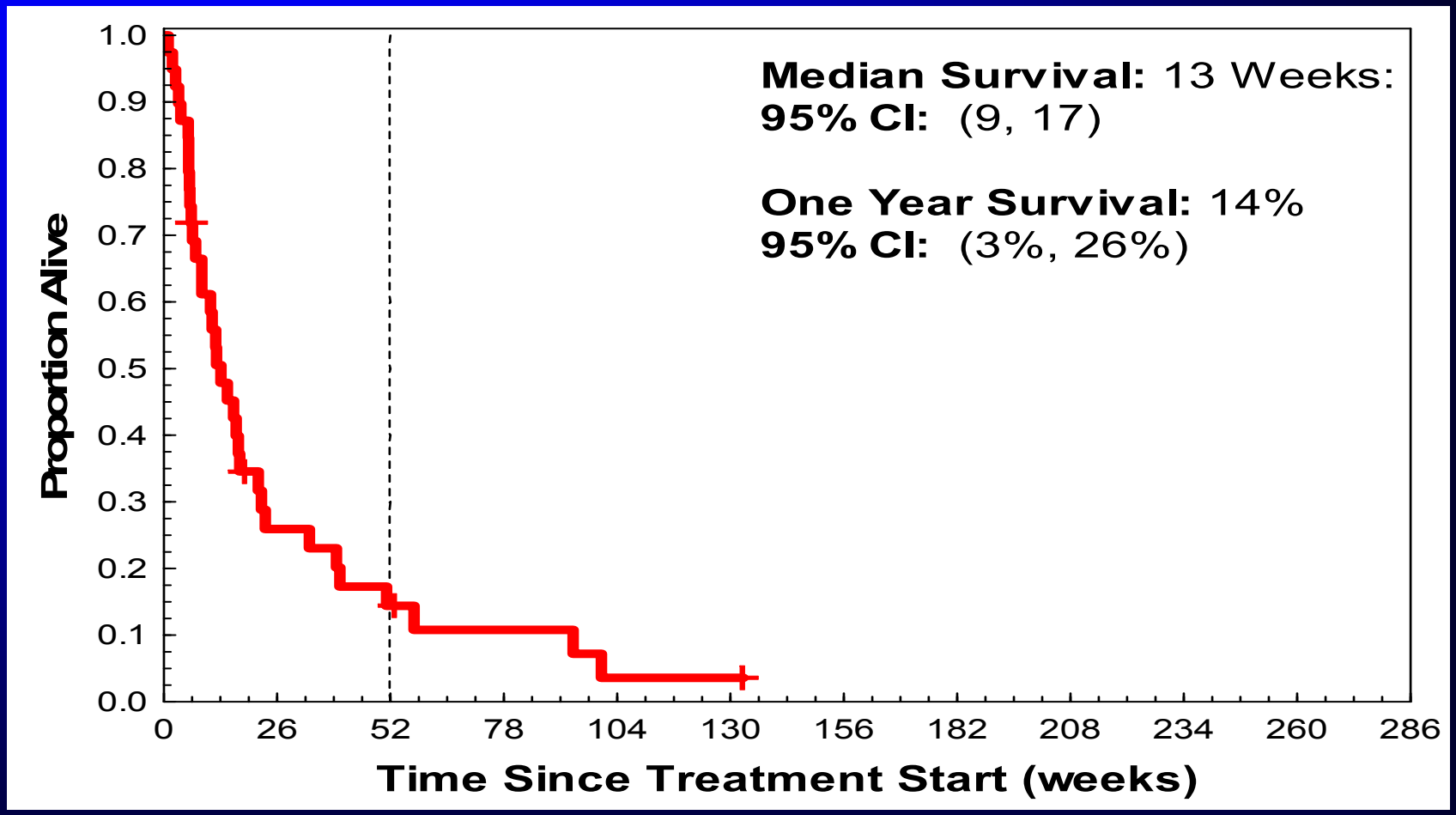


Pediatric: COG P9673 Duration of Best Response (1 prior multi-agent induction)



+ Response on-going at last evaluation

Pediatric: COG P9673 Overall Survival (≥ 2 prior multi-agent inductions)



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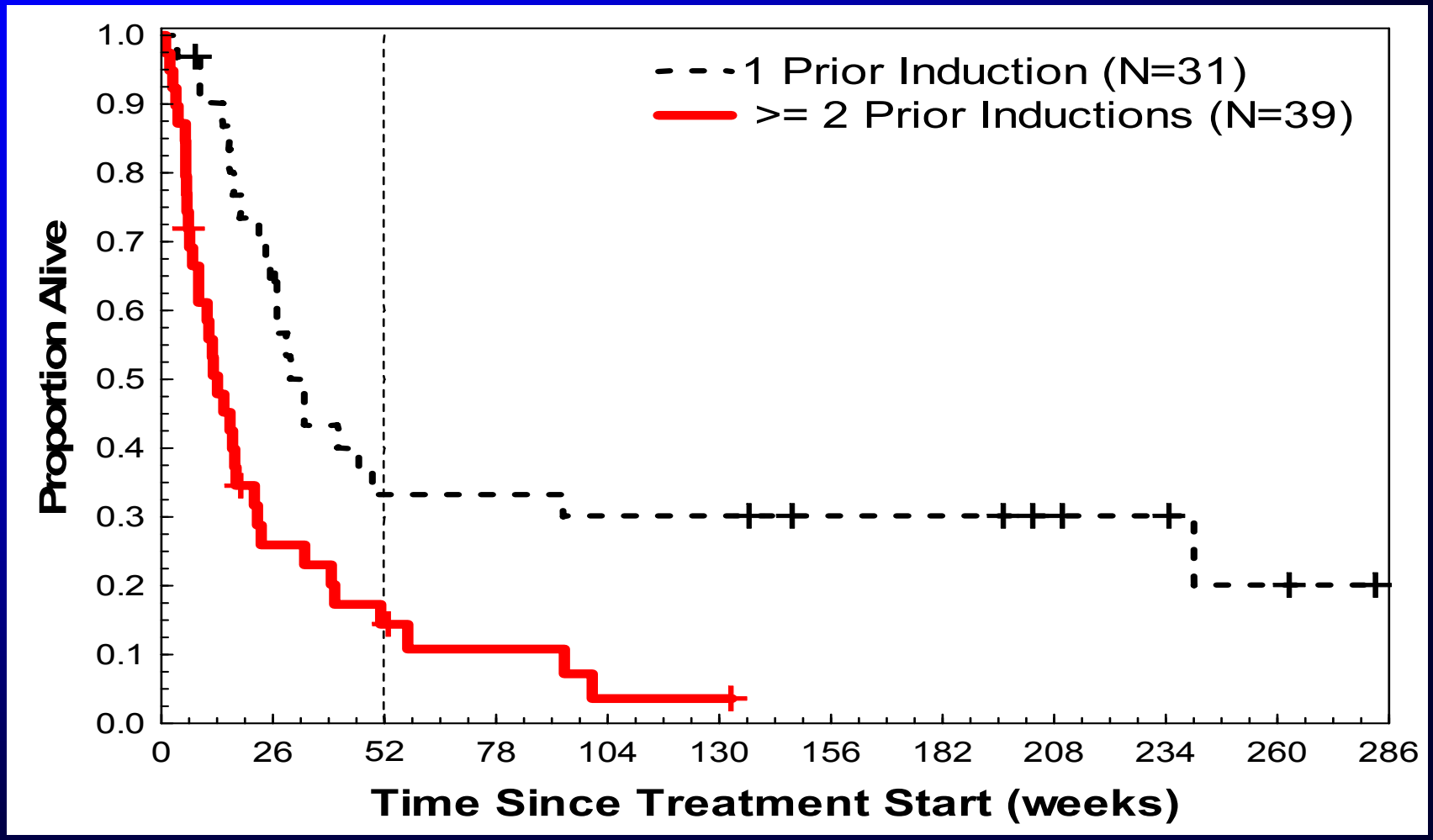
Pediatric: COG P9673 Overall Survival



+ Alive at last contact

Response Rate – Supportive Trials of Patients with Relapsed/Refractory T-ALL/T-LBL

Age Group	Study	N	CR %
Adult	TRC 9701 Special Exceptions (Univ Frankfurt)	24 16	13% 56%
Adult	PGAA1001 PGAA1002 PGAA1003	14 3 8	29% 0 0
Pediatric	PGAA1001 PGAA1002 PGAA1003	18 5 2	33% 40% 50%
Total		90	

Neutrophil Recovery Following Allogeneic Transplant

	Adult CALGB 19801[a]	Pediatric COG P9673[a]
Subjects with available data	n=6	n=21
Neutrophils (≥500/μL x3 days)	3 (50%)	20 (95%)

[a] Based on retrospective data collection. Data not available on all subjects.

Neutrophil Recovery Following Allogeneic Transplant

	Adult CALGB 19801[a]	Pediatric COG P9673[a]		Univ of Frankfurt[b]
Subjects with available data	n=6	n=21		n=18
Neutrophils (≥500/μL x3 days)	3 (50%)	20 (95%)		17 (94%)

[a] Based on retrospective data collection. Data not available on all subjects.

[b] Report provided by Investigator. Patients enrolled in Special Exceptions Program.

Efficacy Summary
≥ 2 Prior Multi-Agent Inductions

	Adult CALGB 19801	Pediatric COG P9673
CR plus CR*	21%	23%
Duration of CR plus CR*	4 to 195+ weeks	3 to 42 weeks
Median Overall Survival	21 weeks	13 weeks
1-year Survival	29%	14%

Efficacy Conclusions

Clinically meaningful benefit as shown by:

- Induction of complete remission
- Consistent rates of remission
  - Adult and pediatric patients
  - Patients with relapsed and refractory disease
  - Across Phase I and II studies
- Duration of response
- Documented successful transplantation
- One year survival

Safety

Mark Russo, M.D., Ph.D.
Group Director, Clinical Oncology, GSK

Safety Overview

- Safety populations
- Phase I experience
- Hematologic adverse events
- Non-hematologic adverse events
- Neurologic adverse events
- Mortality due to adverse events

Safety Populations

- 980 patients have received ARRANON
- Full safety database - 459 patients
- Adult dose of 1500 mg/m^2 on days 1,3,5
  - 36 CALGB19801 + 67 PGAA2003
  - 103 patients
- Pediatric dose of 650 mg/m^2 daily times 5
  - 84 patients COG P9673

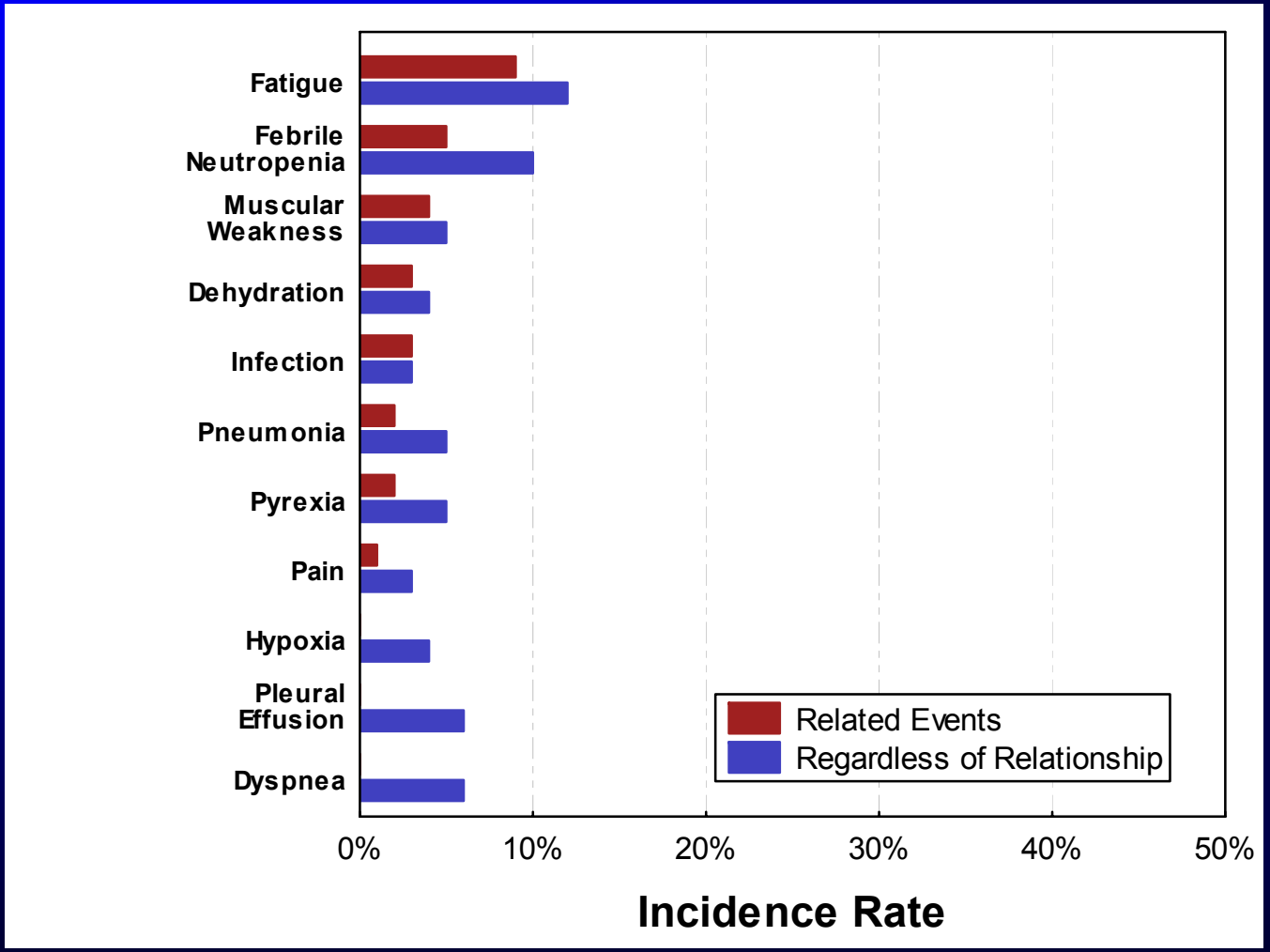
Phase I Experience

- 181 patients (141 Adult, 40 Pediatric)
- Dose Range: 104 mg/m^2 – 2900 mg/m^2
- Schedules tested: Daily X 5; Daily X 3; Days 1, 3, 5
- Neurotoxicity was dose-limiting
- Adult Phase II Day 1, 3, 5 – 2200 mg/m^2 decreased to 1500 mg/m^2
- Pediatric Phase II Daily X 5 – 1200 mg/m^2 decreased to 650 mg/m^2

Grade 4 Hematologic Adverse Events Regardless of Relationship

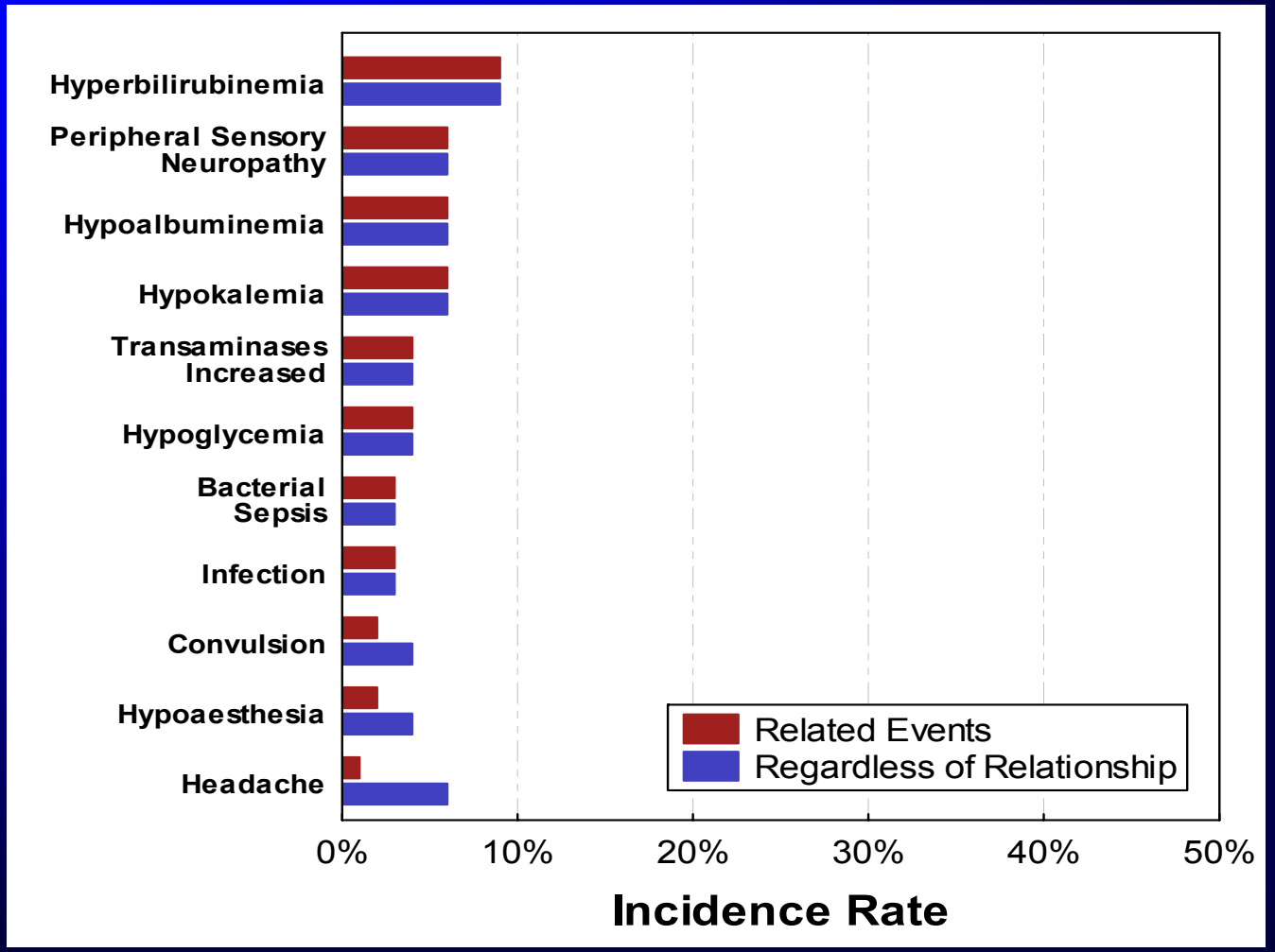
	Adult N=103	Pediatric N=84
Neutropenia	49%	62%
Anemia	14%	10%
Thrombocytopenia	22%	32%

Adult: Grade 3/4 Non-Hematologic Adverse Events (N=103)



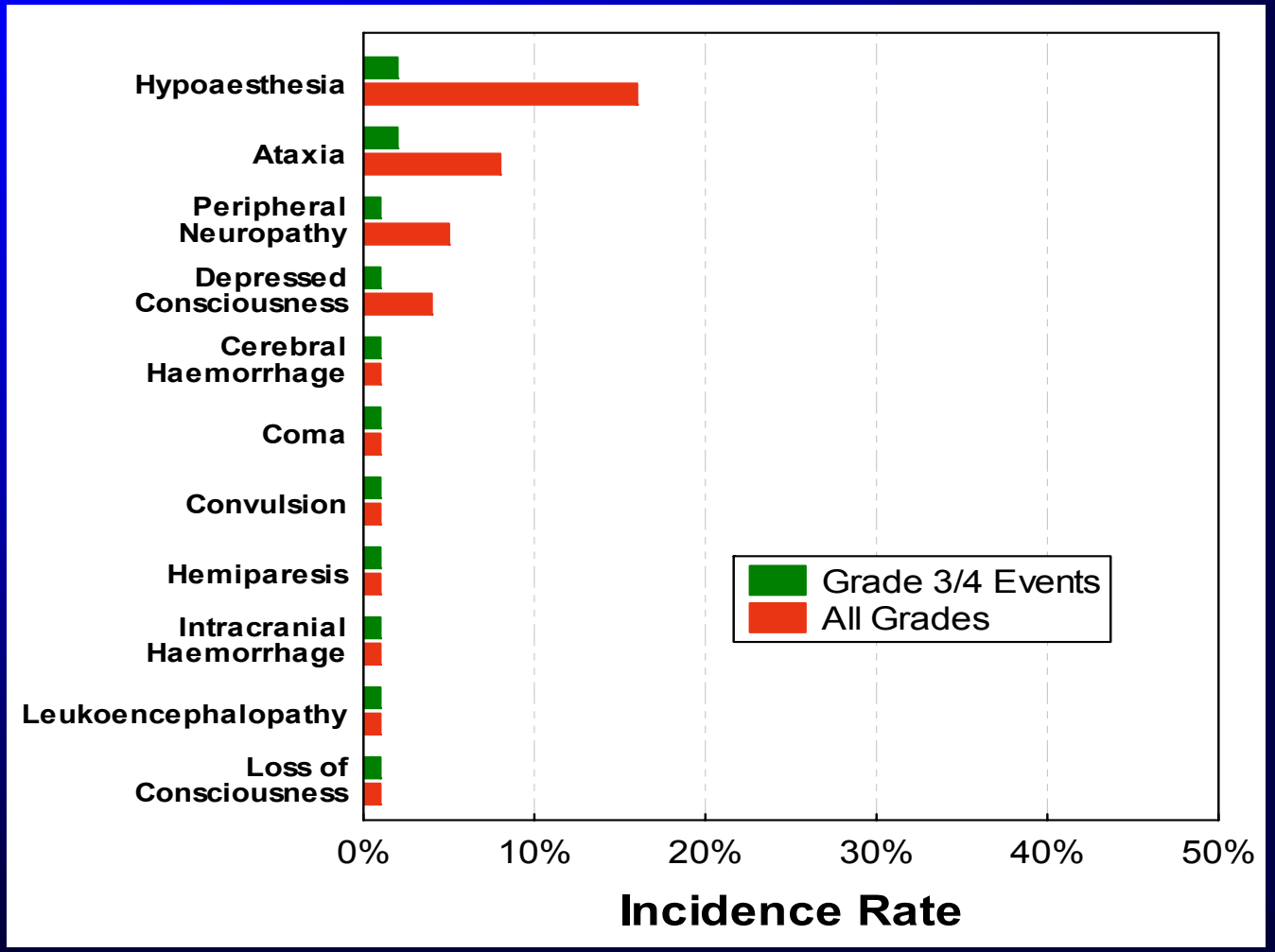
Includes all grade 3/4 events occurring in at least 3 subjects

Pediatric: Grade 3/4 Non-Hematologic Adverse Events (N=84)



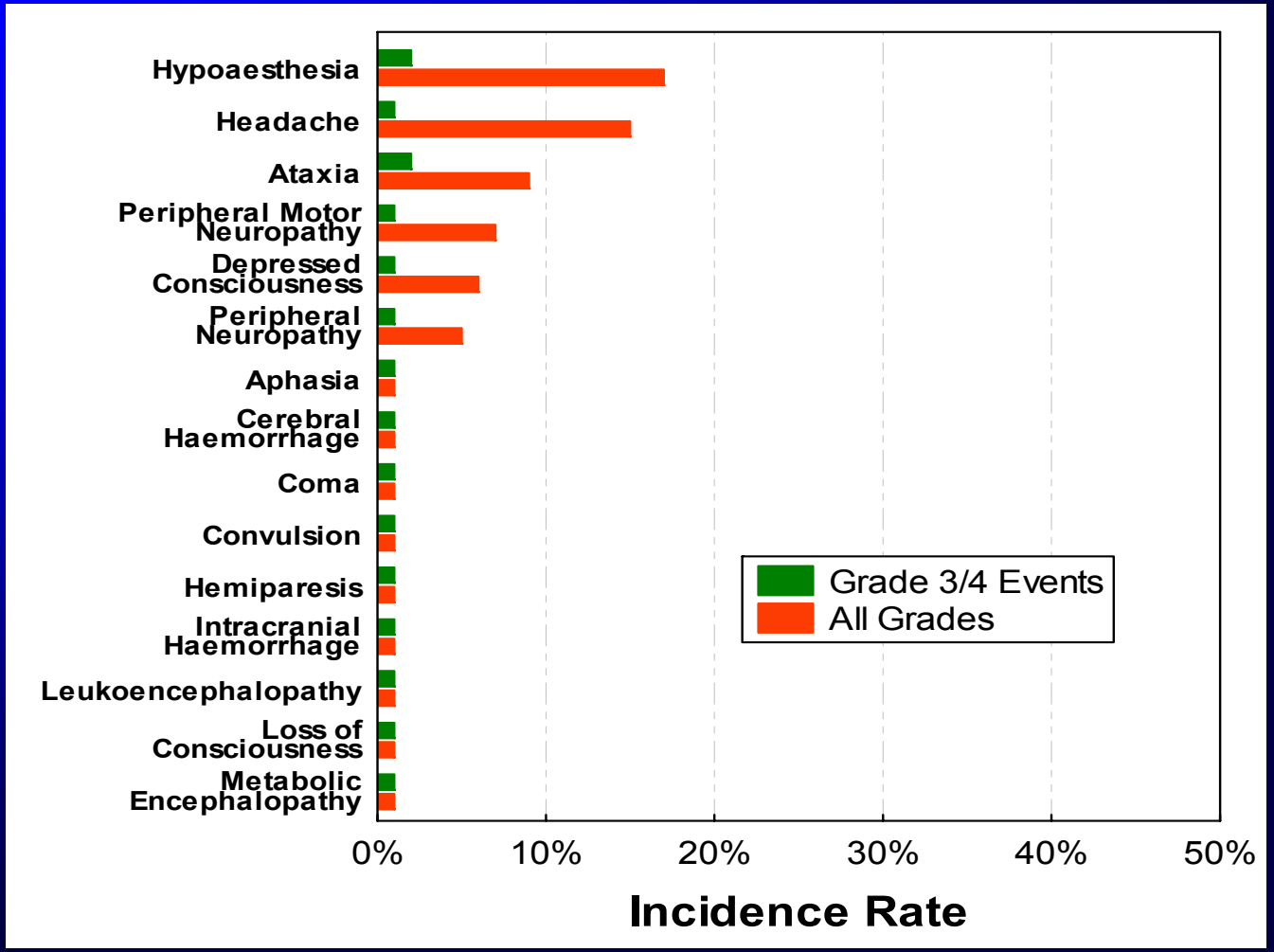
Includes all grade 3/4 events occurring in at least 3 subjects

Adult: Drug-related Neurologic Adverse Events (N=103)



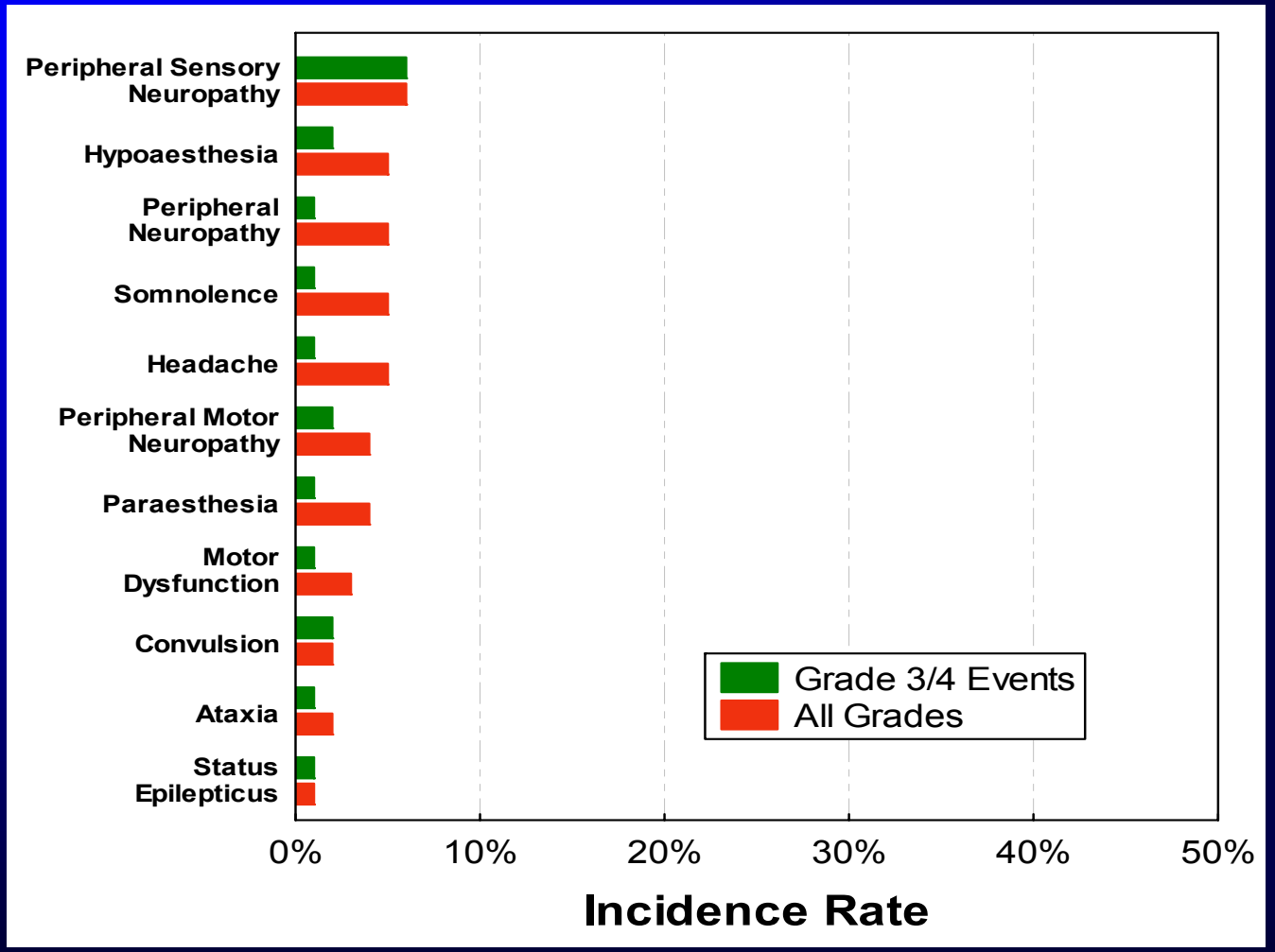
Includes all grade 3/4 neurologic events

Adult: Neurologic Adverse Events Regardless of Relationship (N=103)



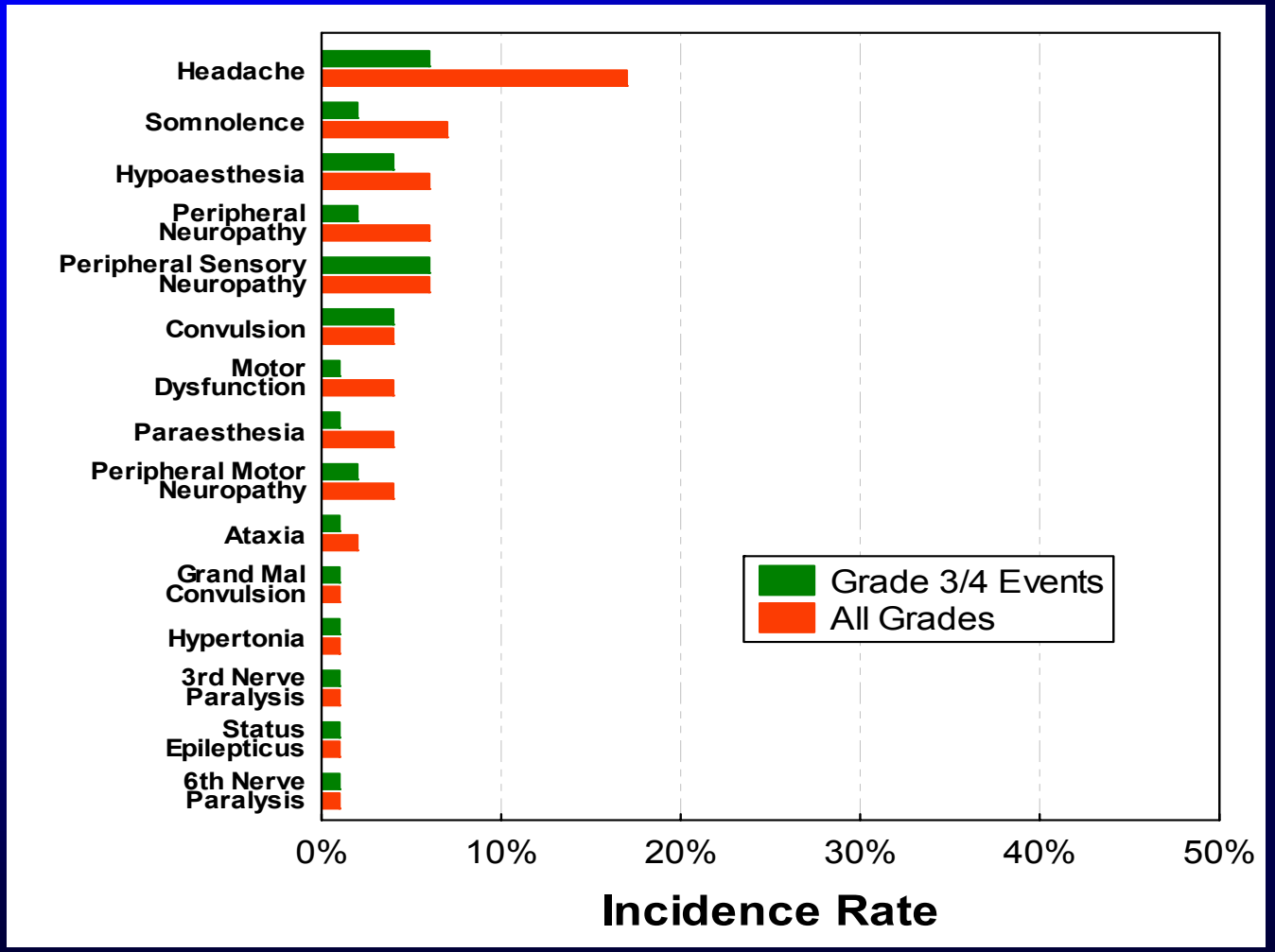
Includes all grade 3/4 neurologic events

Pediatric: Drug-related Neurologic Adverse Events (N=84)



Includes all grade 3/4 neurologic events

Pediatric: Neurologic Adverse Events Regardless of Relationship (N=84)



Includes all grade 3/4 neurologic events

Incidence of Neurologic Adverse Events Regardless of Relationship

	Grade 3	Grade 4
Adults (N=103)	10%	3%
Pediatric (N=84)	11%	8%

Resolution of Neurologic Adverse Events Regardless of Relationship

	Resolved	Unresolved*	Unknown
Adults (1500 mg/m^2) 217 events	47%	24%	28%
Pediatrics (650 mg/m^2) 80 events	63%	18%	20%

*includes 2 patients with fatal neurologic events (1 Adult, 1 Pediatric)

Clinical Presentation of Neurologic Adverse Events (1)

Somnolence

- Onset often on day of administration
- Drowsiness, increased sleep
- Usually reversible, within days
- Not clinically significant

Clinical Presentation of Neurologic Adverse Events (2)

Peripheral Neuropathies

- Onset generally after administration
- Mostly sensory
  - Numbness/dysesthesia of lower extremities
- Similar to that seen with vincristine and taxanes
- Occasionally motor
- Resolution may take several months
- Severe ascending polyneuropathy seen in 14 of 980 patients (1.5%)

Mortality Due to Adverse Events at Proposed Doses

- Nine in 187 patients (5%)
  - Six in adults, N=103
  - Three in pediatrics, N=84
- Two (1%) attributed to **ARRANON**
  - Coma
  - Status epilepticus

Safety Conclusions

- Hematologic events were most common, and manageable
- Neurologic events were frequent in this population
  - Most were grade 1 or 2
  - 13% G3/G4 for adults
  - 19% G3/G4 for pediatrics
- 1% of patients had fatal related adverse events
- Recommended doses have acceptable risk for this patient population

Role of ARRANON in Treatment

William L. Carroll, M.D.

Director, Pediatric Oncology, NYU
Chair, ALL Committee,
Children's Oncology Group

Evaluation of New Agents for T-ALL/T-LBL

Treatment Setting - Relapsed/Refractory Disease

- Heavily pretreated patients
- Historically treatment is usually individualized based on response to prior therapy
- Stem cell transplantation is often the intention of treatment, chemotherapy used to induce remission

Rationale - Clinical Trials

- Evaluate ability to induce complete remission in heavily pretreated patients
- Randomized studies not possible in relapsed or refractory setting
- Integrate most promising compounds that provide clinical benefit into front-line therapy

Patients with Relapsed or Refractory T-ALL/T-LBL

ARRANON

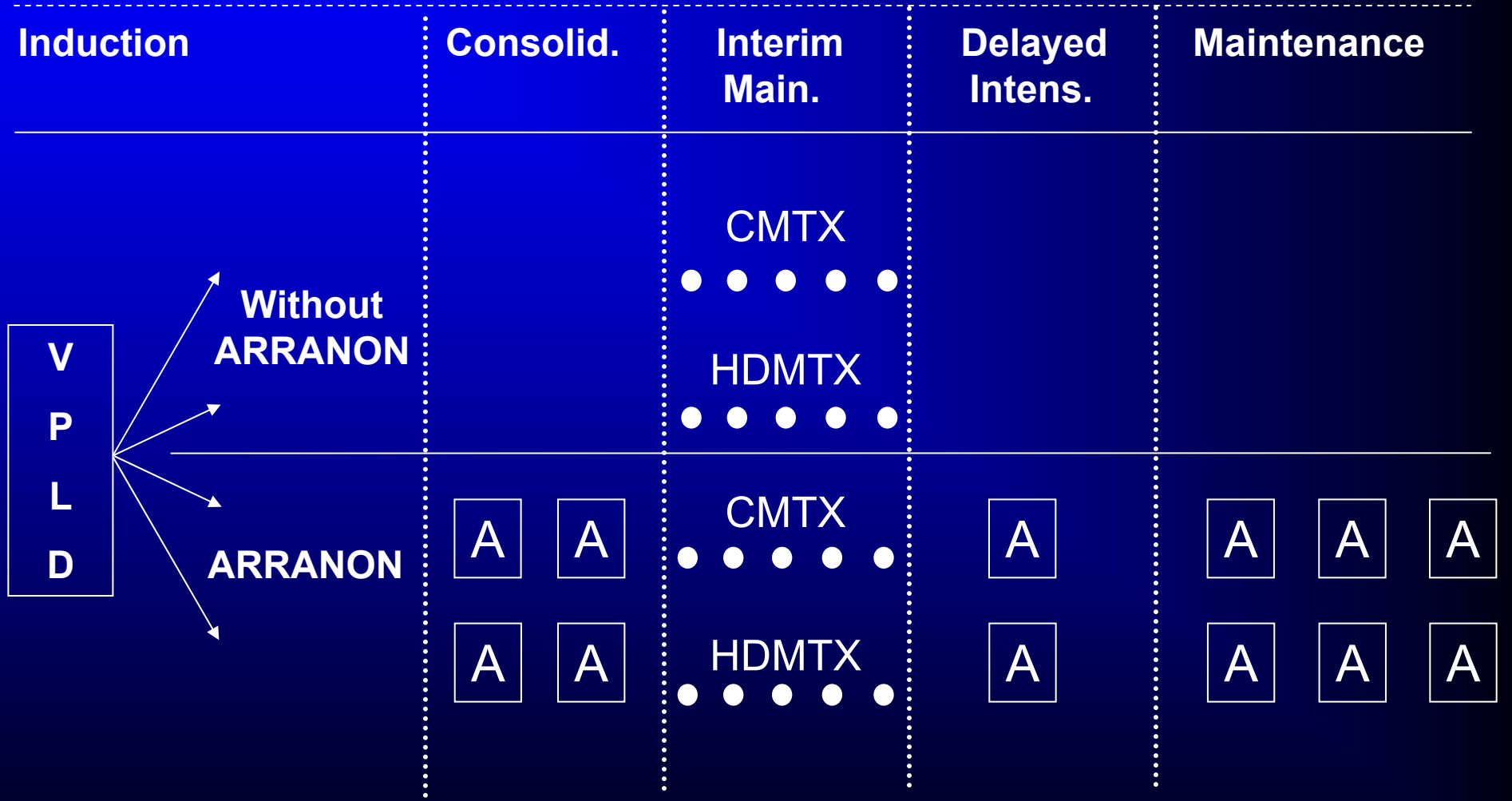
- Provides clinical benefit in patients with:
  - Two or more prior inductions
    - Notable CR rates, especially for the treatment setting
  - One prior induction
    - Single agent activity at least equal to that provided by aggressive multi-agent regimens
- Safety profile in patients with:
  - Relapsed or refractory disease
    - Acceptable adverse event profile
  - Newly diagnosed disease
    - Proven ability to combine with multi-agent therapy AALL00P2 (new diagnosis higher risk T ALL)

Phase III Randomized Trial – COG AALL0434

- Randomized, multi-center, cooperative group trial (COG)
- N=640 patients with T-ALL, aged 1-30 years
- Study design
  - Modified BFM regimen (based on legacy CCG-1961C and identical to current AALL0232 study for higher risk B precursor ALL)
  - Randomized to (high and intermediate risk patients):
    - with or without ARRANON
    - high dose MTX vs escalating IV MTX (aka Capezzi MTX)
- Primary endpoint: EFS at 4 years
- Safety Phase: first 20 consecutive high risk patients
- Efficacy phase: interim analyses at 20%, 40%, 60%, 80%, and 100% of the expected total # events

AALL0434 Efficacy Phase
High and Intermediate Risk Patients

Backbone Regimen: BFM (CCG 1961C)



Phase III Randomized Trial – AALL0434

- **ARRANON** administration
  - 650 mg/m^2 for five consecutive days
  - Consolidation, delayed intensification and maintenance
- Assessment of:
  - Event free survival
  - Minimal residual disease post consolidation

ARRANON – Role in Treatment

- **ARRANON** provides
  - clinical benefit, and
  - acceptable risk to benefit profile
- **ARRANON** is an effective treatment for patients with relapsed or refractory T-ALL/T-LBL

Conclusions

Peter Ho, M.D., Ph.D.
VP, Discovery Medicine Oncology, GSK

Conclusions

- T-ALL/T-LBL ≥ 2nd relapse or refractory disease
  - Poor prognosis and no standard of care
- **ARRANON:** Acceptable safety profile
  - Expected & manageable non-neurological (incl. hematologic) adverse events for indicated population
  - Neurological adverse events
    - Low grade events are common
    - Grade 3 / 4 events are less common, but require prescriber attention

Conclusions

- **ARRANON:** Clinically meaningful benefit as single agent in T-cell ALL/LBL
  - Consistent demonstration of CR
    - Second and third line patients
    - Refractory patients
    - Children and adults
  - CR durable and allowed time for transplantation
  - Demonstrable survival at one year
- Overall favorable benefit - risk profile for the proposed population of relapsed or refractory patients

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