Update in Pediatric malignancies

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Outlines

- Hematologic malignancy
  - Acute lymphoblastic leukemia
    - CAR T cell
    - Bispecific antibody
  - Acute myeloid leukemia
    - FLT3 inhibitor
  - Chronic myeloid leukemia
    - Children and adolescence recommendation
- Solid tumor
  - Target therapy in pediatric solid tumor

Childhood cancer incidence in Thailand

Childhood cancer incidence and survival in Thailand: A comprehensive population-based registry analysis, 1990–2011

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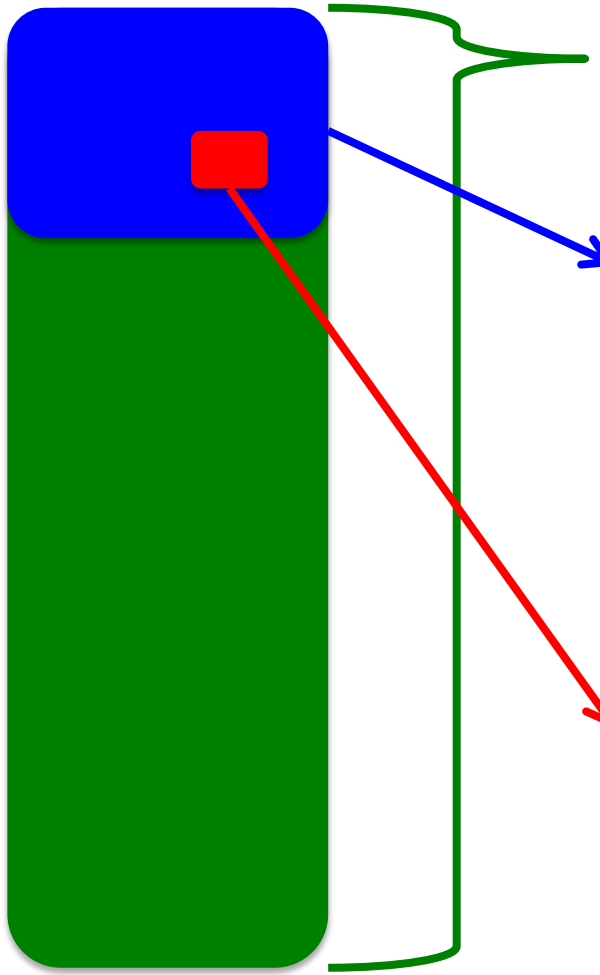
Pediatr Blood Cancer. 2019;66:e27428.
https://doi.org/10.1002/pbc.27428

- The ASR of all childhood cancers was 98.5 per million person years with 91.0 per million person-years in 1990–2000 and 106.2 per million person-years in 2001–2011.
- The top three cancer groups were leukemias, brain tumors, and lymphomas.
- The 5-year survival for all childhood cancers significantly improved from 39.4% in 1990–2000 to 47.2% in 2001–2011 ($P < 0.01$).

TABLE 2 Age-specific and age-standardized incidence rates (ASRs) for ICCC groups and subgroups

		Age at diagnosis[b]				Decade of diagnosis[a]				Sex[a]			
ICCC group	Overall[a]	0–4 y	5–9 y	10–14 y	15–19 y	1990–2000	2001–2011	IRR	95% CI	Male	Female	IRR	95% CI
I. Leukemia	36.1	55.9	31.4	27.7	23.3	33.4	38.9	1.2	1.0, 1.3	40.8	31.2	0.7	0.7, 0.8
ALL	22.2	37.2	22.8	14.9	8.9	21.2	23.2	1.1	1.0, 1.3	25.8	18.5	0.7	0.6, 0.8
AML	7.8	9.5	5.4	8.0	7.9	6.3	9.2	1.4	1.1, 1.8	8.2	7.4	0.9	0.7, 1.1
Unspecified	4.8	8.4	2.6	3.2	4.2	4.8	4.9	1.0	0.7, 1.3	5.2	4.4	0.8	0.6, 1.1
II. Lymphoma	10.3	6.4	9.8	10.7	15.5	9.5	11.1	1.2	1.0, 1.5	13.6	6.8	0.5	0.4, 0.6
Hodgkin lymphoma	2.0	0.6	2.5	2.4	3.1	1.5	2.5	1.7	1.1, 2.7	3.1	1.0	0.3	0.2, 0.5
Non-Hodgkin lymphoma	5.2	1.9	5.1	6.0	9.0	4.2	6.2	1.5	1.1, 2.0	6.5	3.8	0.6	0.4, 0.8
Burkitt lymphoma	0.9	1.2	1.4	0.5	0.4	0.9	1.0	1.1	0.6, 2.2	1.5	0.3	0.2	0.1, 0.5
Unspecified	1.4	0.9	0.6	1.6	2.7	1.7	1.0	0.6	0.3, 1.0	1.8	0.9	0.5	0.3, 0.9
III. Brain and spinal neoplasms	12	12.3	14.6	12	8.9	11.1	13.0	1.2	1.0, 1.4	12.7	11.4	0.9	0.7, 1.0
Astrocytomas	3.1	2.7	3.2	3.0	3.7	2.8	3.5	1.3	0.9, 1.9	3.1	3.2	1.0	0.7, 1.4
PNETs and medulloblastoma	2.8	3.8	3.4	2.8	0.5	2.8	2.7	1.0	0.6, 1.5	3.1	2.4	0.7	0.5, 1.1
Unspecified	5.0	4.3	6.7	5.0	3.9	4.9	5.1	1.1	0.8, 1.4	5.3	4.6	0.8	0.6, 1.1
IV. Neuroblastoma	3.2	8.2	2.0	0.5	0.6	3.5	2.9	0.8	0.6, 1.2	2.7	3.7	1.3	0.9, 1.9
V. Retinoblastoma	2.7	8.5	0.6	0.1	0.0	2.5	3.0	1.2	0.8, 1.9	2.7	2.8	1.0	0.6, 1.6
VI. Renal tumors	3.2	9.0	1.5	0.2	0.5	2.5	4.0	1.6	1.0, 2.4	3.2	3.3	1.0	0.7, 1.5
VII. Hepatic tumors	2.2	3.3	1.4	0.9	2.9	2.2	2.2	1.0	0.6, 1.5	2.9	1.5	0.5	0.3, 0.8
VIII. Malignant bone tumors	4.5	1.1	2.0	7.7	8.7	4.4	4.7	1.1	0.8, 1.4	5.3	3.8	0.7	0.5, 0.9
IX. Soft tissue sarcomas	4.8	5.3	2.7	4.3	6.8	4.3	5.2	1.3	0.9, 1.7	4.5	5.1	1.1	0.8, 1.5
Rhabdomyosarcoma	1.8	3.2	1.2	1.4	1.2	2.0	1.7	0.9	0.5, 1.5	1.9	1.7	0.9	0.5, 1.5
Other specified	1.7	1.2	1.0	1.4	3.6	1.3	2.1	1.5	0.9, 2.5	1.3	2.1	1.6	1.0, 2.6
X. Gonadal and germ cell neoplasms	6.2	3.8	2.4	6.7	13.0	5.5	6.8	1.2	0.9, 1.6	3.8	8.6	2.2	1.7, 2.9
XI. Carcinomas and epithelial neoplasms	7.2	1.7	2.4	7.2	20.0	6.5	8.0	1.2	1.0, 1.6	6.1	8.3	1.3	1.1, 1.7
XII. Other and unspecified neoplasms	6.0	8.0	2.3	4.3	9.2	5.6	6.4	1.2	0.9, 1.5	6.7	5.3	0.8	0.6, 1.0
All cancer groups	98.5	123.7	73.1	82.2	109.4	91.0	106.2	1.2	1.1, 1.3	104.8	91.8	0.8	0.8, 0.9

Thailand population in 2019



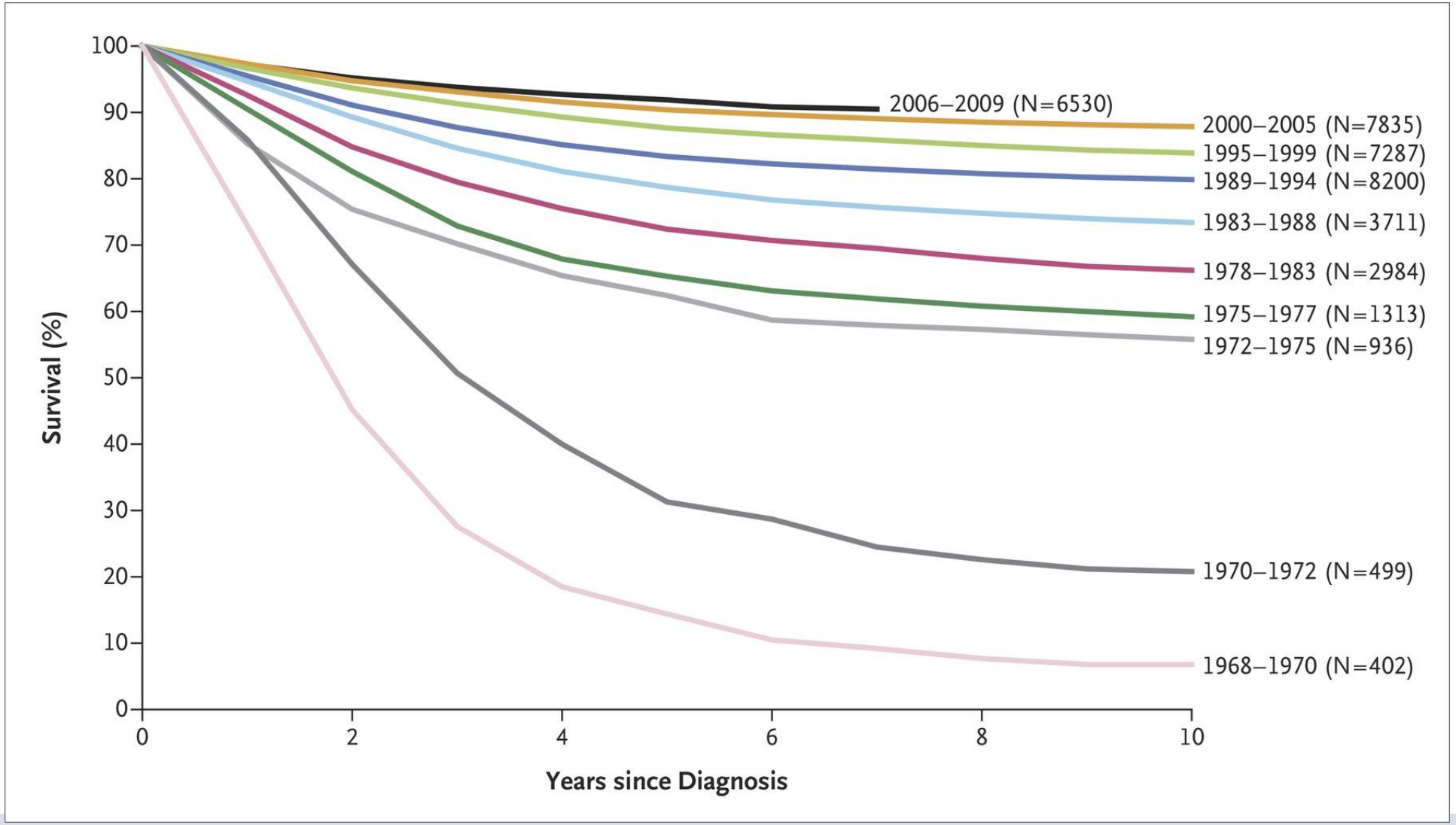
- Total population 69 M
- **Age 0-21 years 17 M**
  - Age-adjusted Incidence Rates (ASR) for childhood cancer (2014-2016)

    = *78.25 per million*
- ***1330*** *children are diagnosed with cancer each year*

Thai Pediatric Oncology Group
ชมรมโรคมะเร็งเด็กแห่งประเทศไทย

Acute lymphoblastic leukemia

Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009

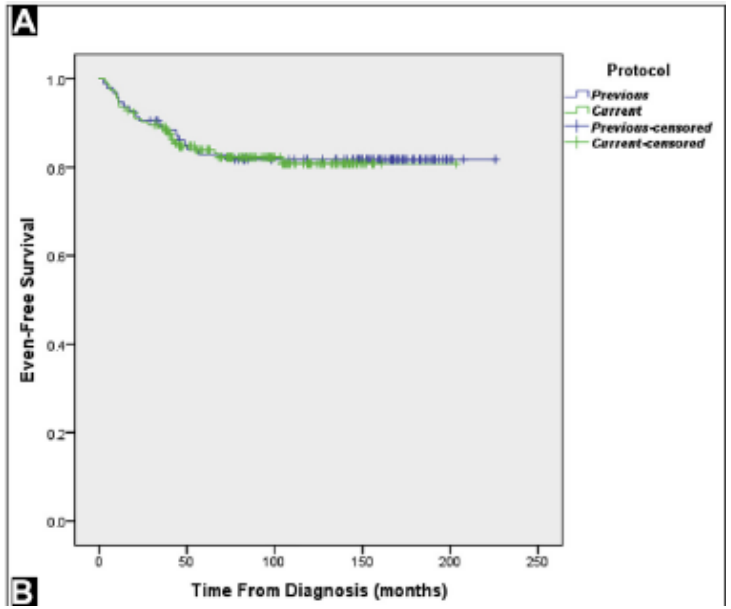


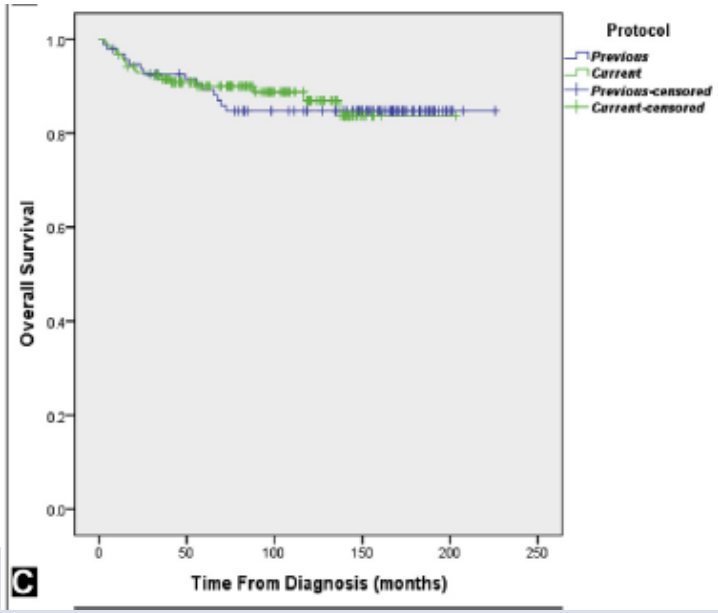
Hunger SP, *et al*. *NEJM* 2015

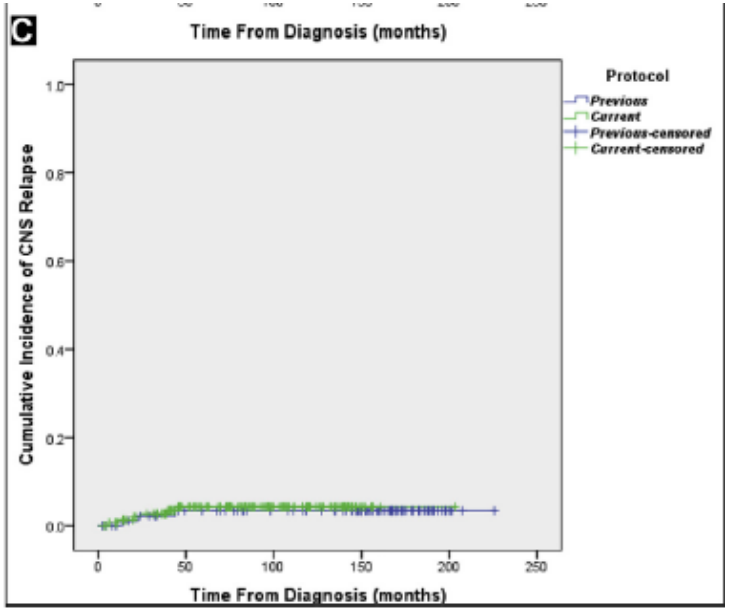
Long-Term Outcomes of Modified St Jude Children's Research Hospital Total Therapy XIIIB and XV Protocols for Thai Children With Acute Lymphoblastic Leukemia

Pacharapan Surapolchai,[1] Usanarat Anurathapan,[2] Arpatsorn Sermcheep,[2] Samart Pakakasama,[2] Nongnuch Sirachainan,[2] Duantida Songdej,[2] Pongpak Pongpitcha,[2] Suradej Hongeng[2]

Clinical Lymphoma, Myeloma & Leukemia, Vol. 19, No. 8, 497-505 © 2019





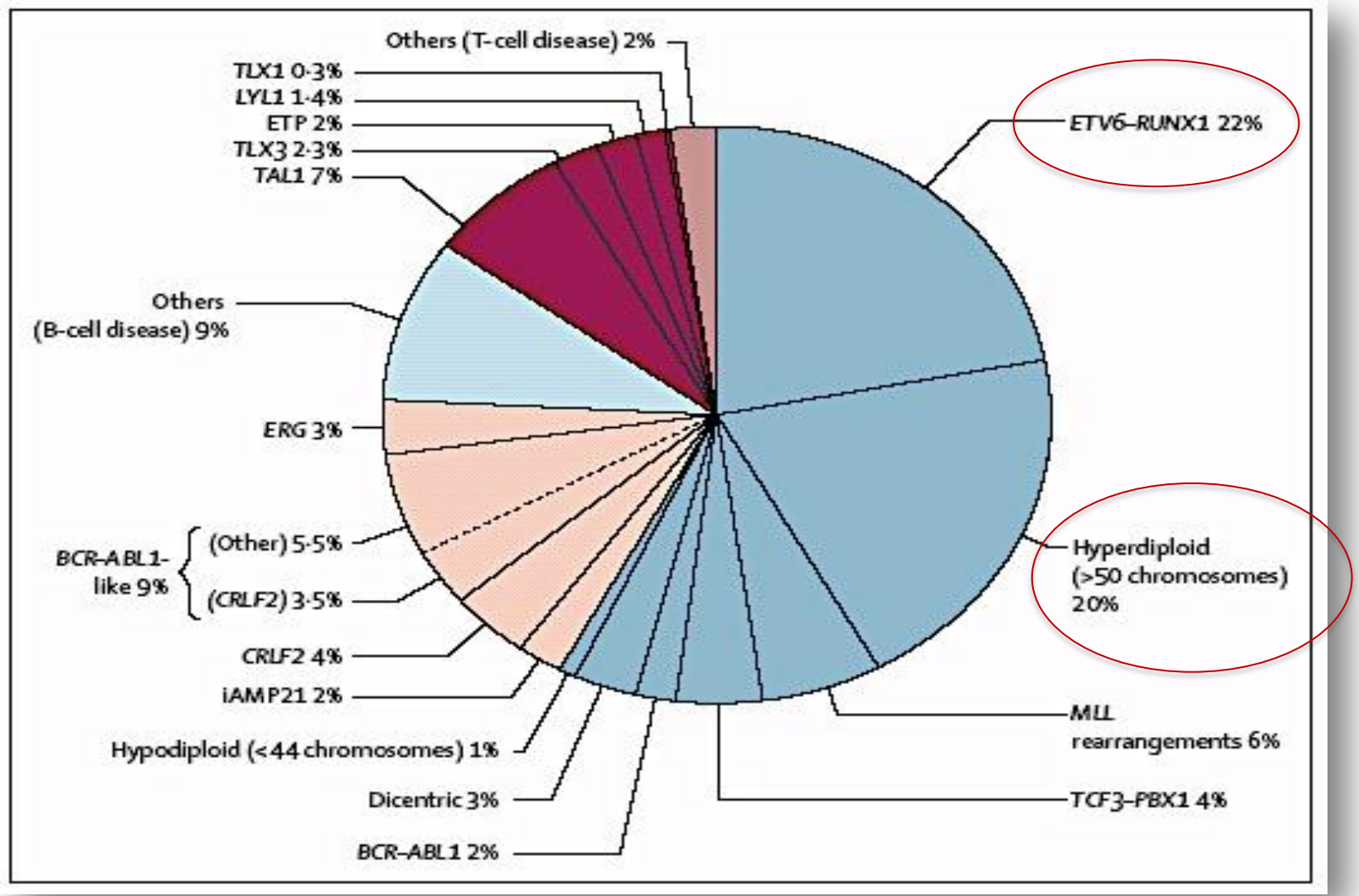


ALL: Risk based therapy

Standard Risk (SR)	High Risk (HR)	Very High Risk (VHR)
Clinical criteria ■ Pre-B ALL ○ Age 1-9 and ○ WBC < 50,000 Molecular criteria (optional) ■ Day 29 BM MRD < 0.01% ■ No unfavorable molecular feature	Clinical criteria ■ T-ALL ■ Pre-B ALL ○ Age 10-13 or ○ WBC >= 50,000 ■ Testicular disease ■ Steroid pretreatment Molecular criteria (optional) ■ Day 29 BM MRD >= 0.01% with favorable cytogenetic: ETV-6/RUNX-1 or double trisomy 4,10	Clinical criteria ■ Pre-B ALL ○ Age >= 14 ■ CNS-3 ■ Induction failure (M2 or M3 at day 29) Molecular criteria (optional) ■ Day 29 BM MRD >= 0.01 with no favorable cytogenetic ■ Unfavorable molecular feature ○ iAMP 21 ○ MLL arrangement ○ Hypodipliody (< 44 chromsome or DNA index < 0.81) ○ Ph-chromsome (follow Ph-ALL protocol)

MRD day19 in standard risk pre B ALL and MRD post consolidation in T cell might play a major role in future

Cytognetics and molecular genetic abnormalities in Pediatric ALL



Inaba H et al. The Lancet, vol 381, 1 June 2013

MRD in ALL

- Become standard of care in terms of risk classification
- MRD identified "*high risk*" in patients with good risk genetic lesion
  - Trisomy 4,10, *ETV6/RUNX1*
- MRD identified "*low risk*" in patients with poor risk genetic lesion
  - iAmp21, ETP-ALL
- Identify risk of relapse in patient undergoing BMT
- No role of MRD in Burkitt leukemia

Comparison of MRD detection technique

Technique	Detection limit	Applicability
Morphology and cytochemistry	10^{-1}–10^{-2}	All leukemias
Cytogenetics	10^{-1}–10^{-2}	Leukemias with microscopically detectable numeric or structural aberrations (only cells in mitosis)
Fluorescence *in situ* hybridization	10^{-1}–10^{-2}	Leukemias with known numeric or structural aberrations (interphase cells)
Flow cytometry for DNA content	10^{-1}–10^{-2}	About 30% of B-precursor ALL; < 5% of T-ALL
Flow cytometry for leukemia-associated immunophenotype	10^{-3}–10^{-4}	50–90% of ALL
PCR techniques		
DNA level		
Rearranged immunoglobulin and T-cell receptor genes	10^{-3}–10^{-6}	90% of ALL
Chromosomal aberrations with known breakpoints	10^{-4}–10^{-6}	10–20% of T-ALL, > 5% of B-ALL
RNA level		
Chromosomal aberrations resulting in leukemia-specific fusion genes and fusion mRNA	10^{-3}–10^{-5}	10–15% of B-precursor ALL

Cause of death in childhood ALL

- Overall survival in B-cell ALL is around 80-90%
- The most common cause of death are relapsed disease and infection
- In relapsed/refractory disease need salvage therapy for achieving remission before undergo hematopoietic stem cell transplantation (HSCT)

Pediatric ALL cases in Thailand

1330 cases are newly diagnosed with cancer per year

20% of all cancer in PEDS is ALL

(85% is B-cell type vs. 15% is others)

We have ~226 cases with newly diagnosed B-cell ALL per year

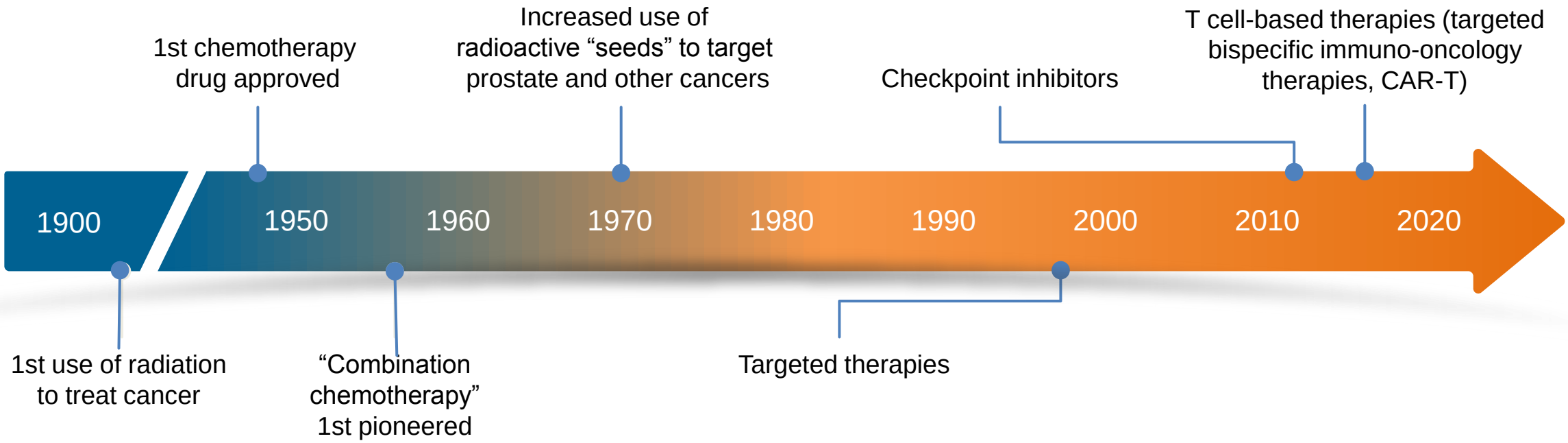
10–15% of ALL patients experience a relapse[1]

20-30 cases are a relapse disease per year

[1]*Leukemia* 2018

A Shift Toward Targeted Approaches Has Redefined the Therapeutic Landscape for Cancer[1,2]

Major Milestones in Cancer Treatment[1,2]

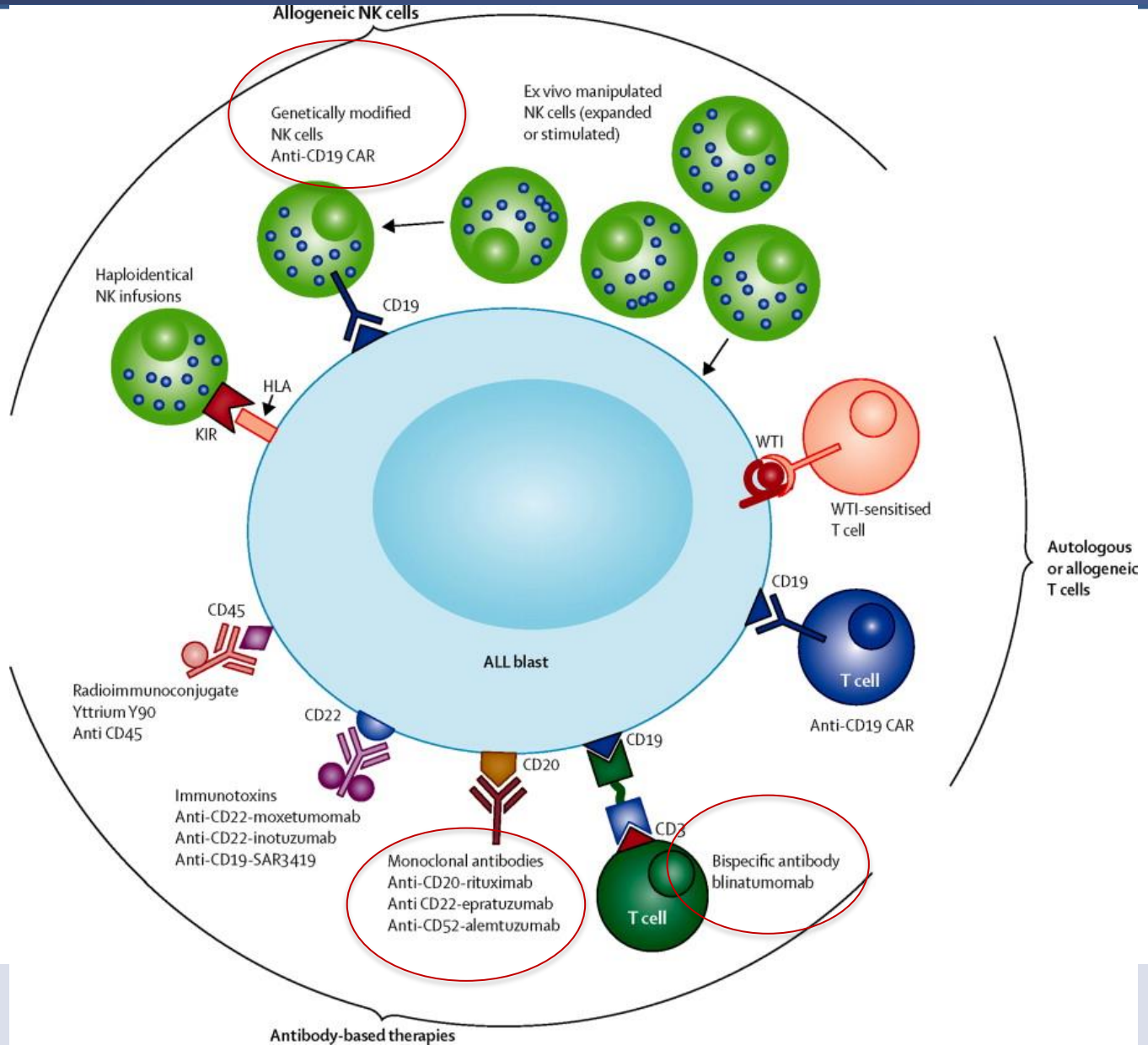


- Targeted approaches have advanced the therapeutic landscape toward individualized care[1]

CAR-T, chimeric antigen receptor T cell.

1. ASCO. Cancer progress timeline. https://www.asco.org/research-progress/cancer-progress-timeline/major-milestones-against-cancer. Accessed April 17, 2019.
2. CRI. Timeline of progress in immunotherapy. https://www.cancerresearch.org/immunotherapy/timeline-of-progress. Accessed April 17, 2019.

Immunological approaches under investigation for childhood relapsed ALL

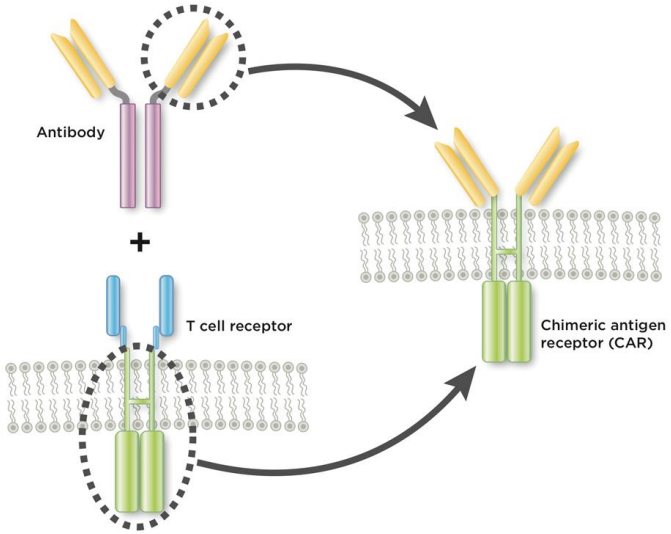


Lancet. 2013

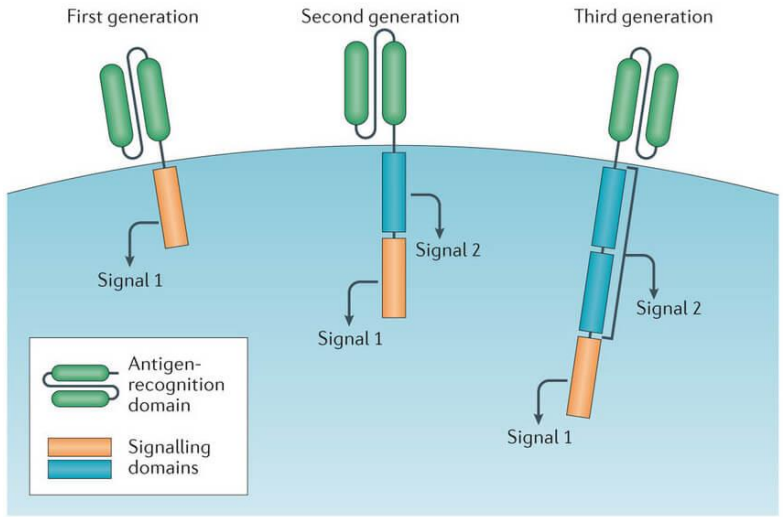
FDA approval of a CAR therapy in 2017

- The drug, called tisagenlecleucel (brand name Kymriah), is manufactured by the pharmaceutical company Novartis.
- Children and young adults with relapsed/refractory ALL will be eligible to receive this therapy.

Cost 475,000 USD per cycle

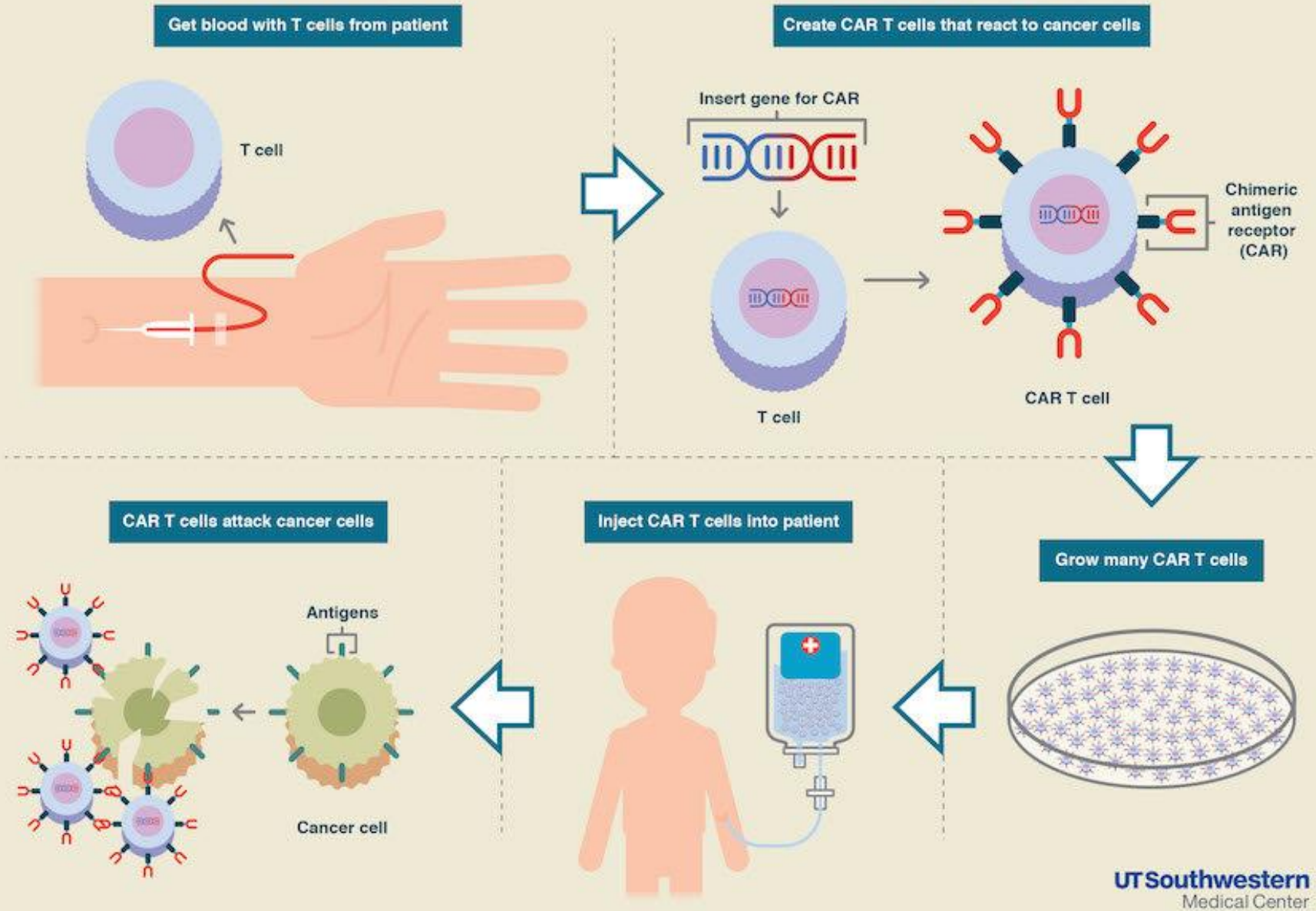


A chimeric antigen receptor, or CAR, joins together part of an antibody and part of a T cell receptor.



Nature Reviews | Clinical Oncology

CAR T-cell Therapy



First Author and Reference	Program CAR	Population	Response	CRS	Neurologic Toxicity
		ALL			
Maude [4]	PENN 4-1BB	n = 30 (r/rALL) Pediatrics and adults	CR = 90%	100% CRS 27% severe	43% total
Maude [5]	Novartis Multicenter 4-1BB	n = 75 Pediatrics and AYA	CR = 81% MRDNeg = 81%	77% total	13% grade 3
Park [7]	MSKCC CD28	n = 53 Adults	CR = 83% MRDNeg = 67%	85% total 26% severe (1 grade 5)	42% grades 3-4
Lee [3]	NCI CD28	n = 21 Pediatrics and AYA	CR = 67%	76% CRS 28% severe	29% total
Turtle [10]	Seattle 4-1BB	n = 30 Adults	CR = 93%	83% CRS	50% severe
Gardner [1]	Seattle 4-1BB	Pediatrics and AYA n = 45	CR = 93% MRDNeg = 93%	93% CRS 23% severe	49% total 21% grades 3-4
NHL and CLL					
Schuster [9]	PENN 4-1BB	n = 28 (DLBCL/FL)	CR = 57%	57% CRS 18% severe	11% severe
Schuster [12]	Novartis Multicenter 4-1BB	n = 93 (DLBCL)	CR = 40%	58% CRS 9% severe	12% ≥ grade 3
Neelapu [6]	KITE Multicenter CD-28	n = 111 (DLBCL /TFL/PMBCL)	CR = 54%	93% CRS 13% severe	28% ≥ grade 3
Abramson [11]	Juno Multicenter 4-1BB	n = 91 (DLBCL/FL/PMBCL/MCL)	CR = 46%	35% CRS 1% severe	Total 35% 12% ≥ grade 3
Kochenderfer [2]	NCI CD28	n = 15 (NHL/CLL)	CR = 53% PR = 27%	27% severe	40% total
Porter [8]	PENN 4-1BB	n = 14 (CLL)	CR = 29% PR = 29%	64% total 28% severe	43% total 1/14 grade 4

N. Frey, D. Porter / Biol Blood Marrow Transplant 25 (2019) e123-e127

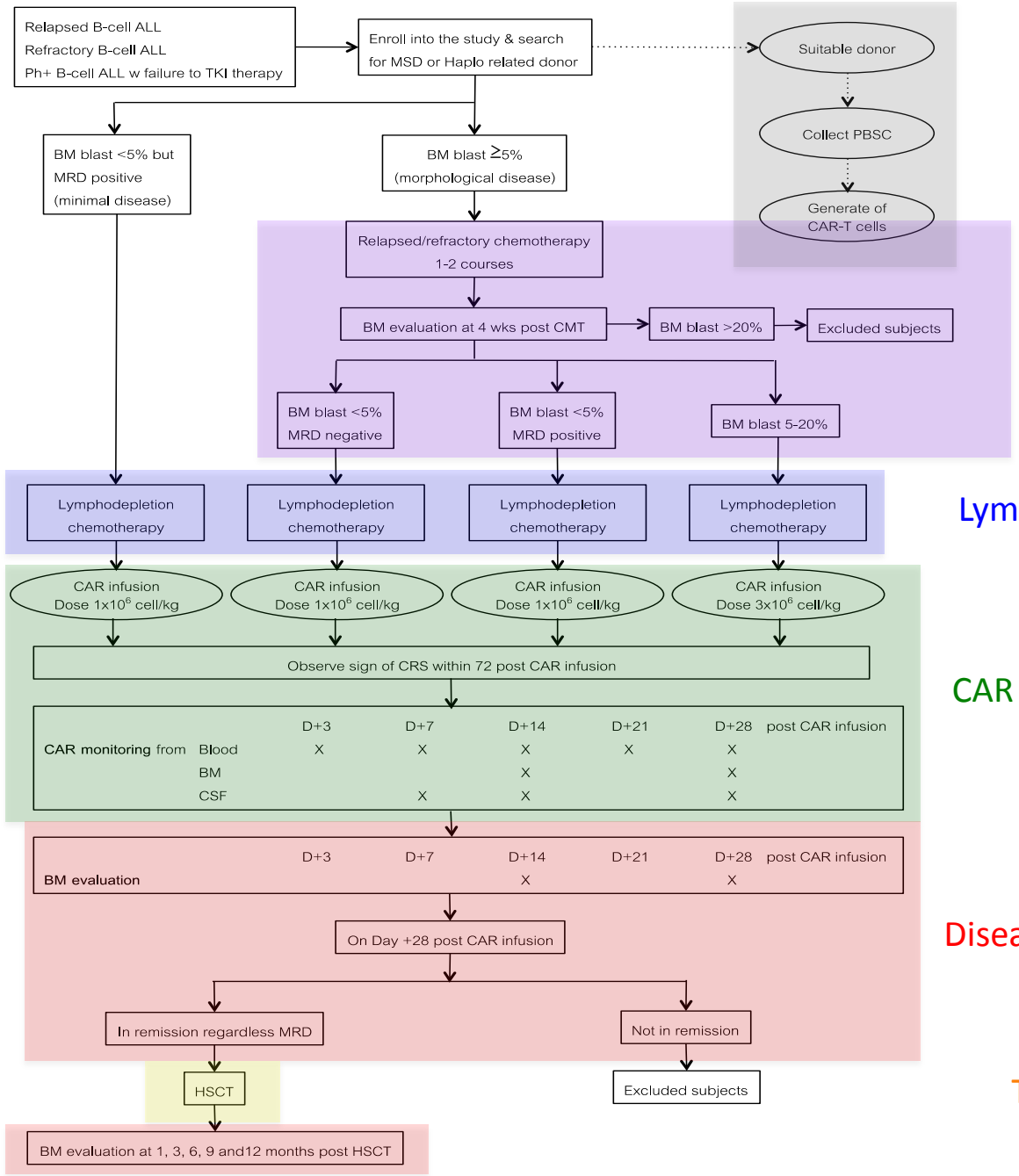
CAR T cell therapy in Thailand

- **Phase II clinical trial**

  new treatment for a certain type of cancer works ? and safety ?

- **Single arm**
- **Pediatrics group only**
- **CAR T-cell**
- **Relapsed/refractory B-cell ALL**
- **Multicenter:** Siriraj hospital and Ramathibodi hospital

Study design



LAB

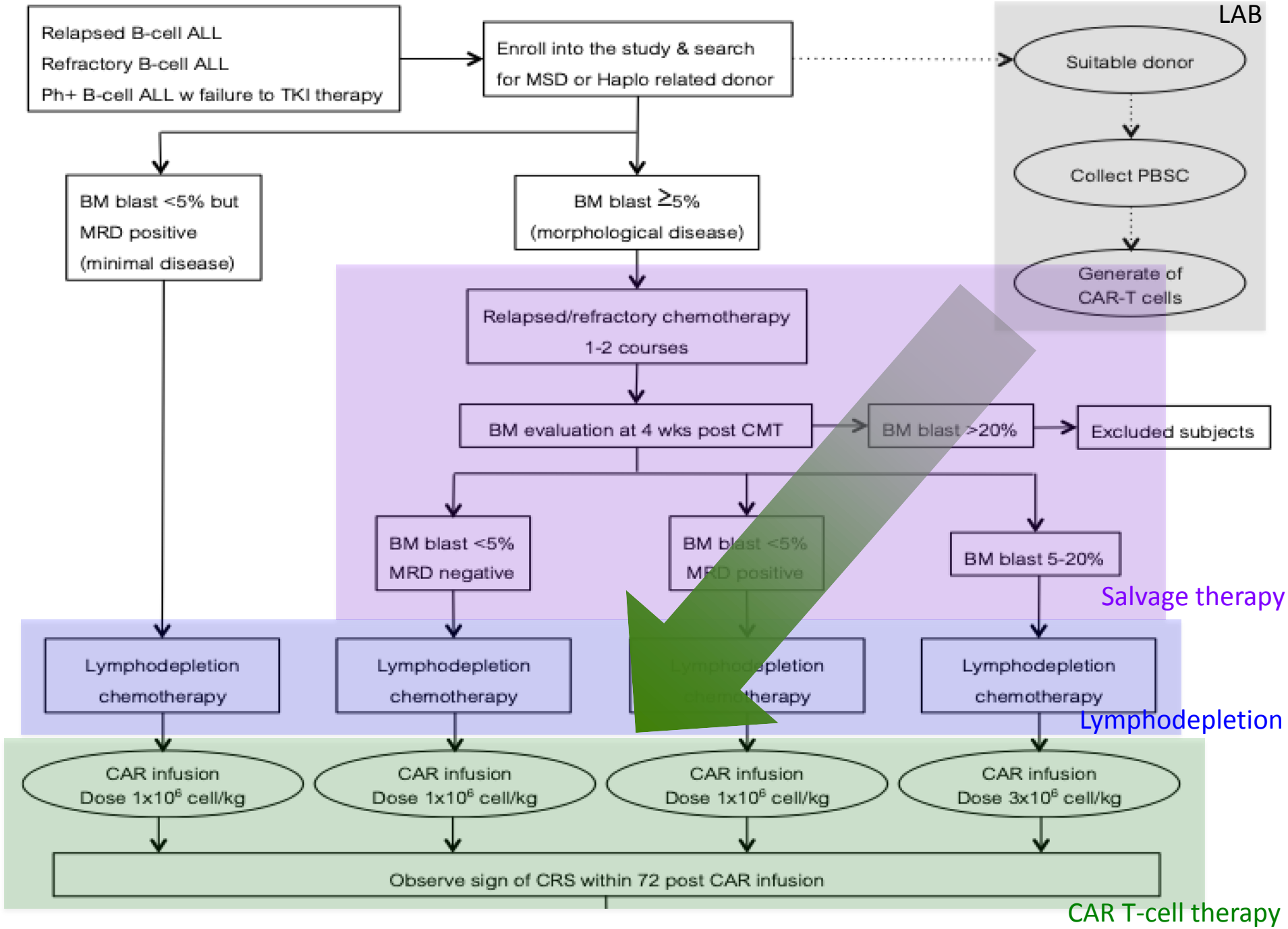
Salvage therapy

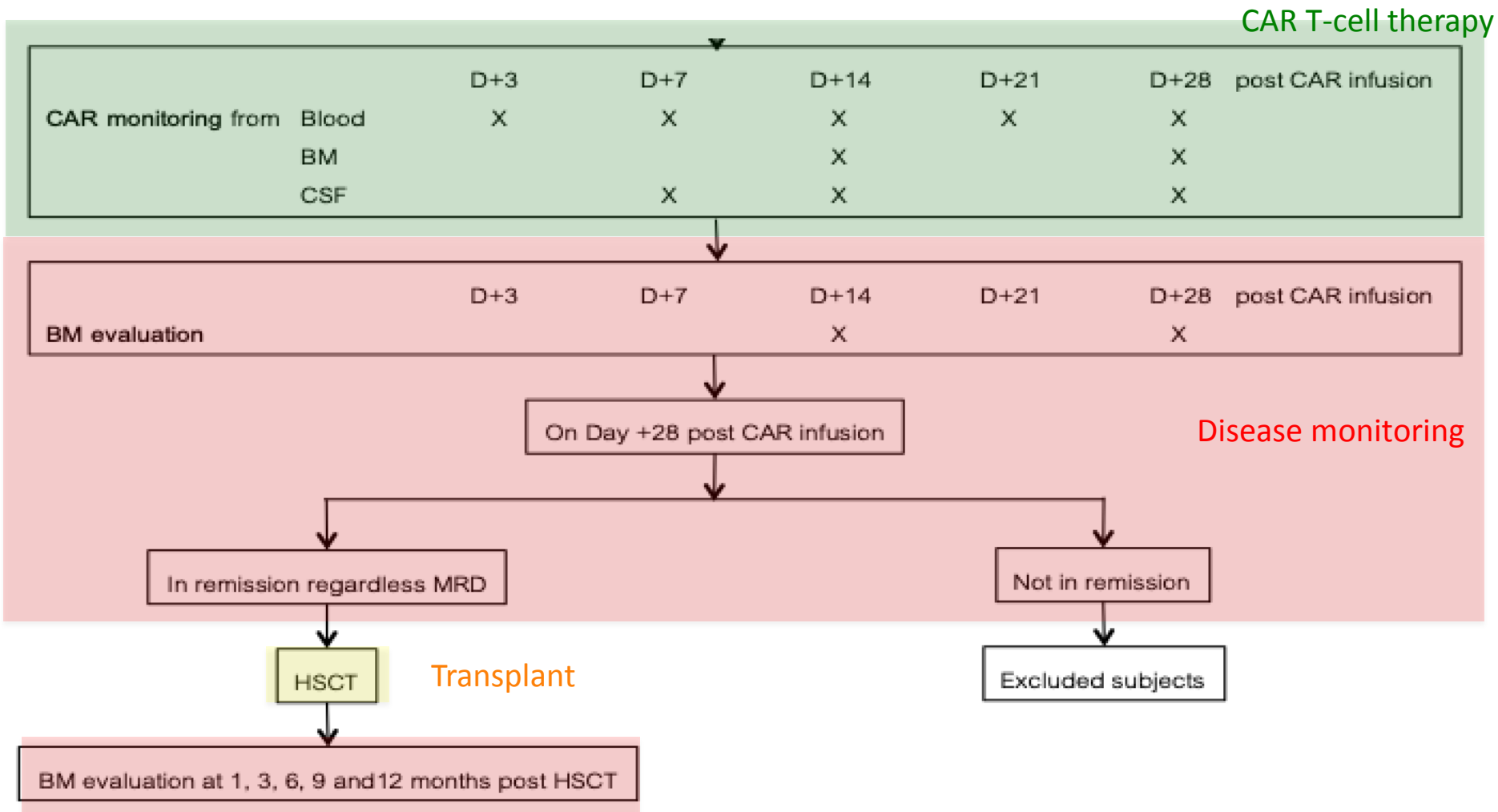
Lymphodepletion

CAR T-cell therapy

Disease monitoring

Transplant

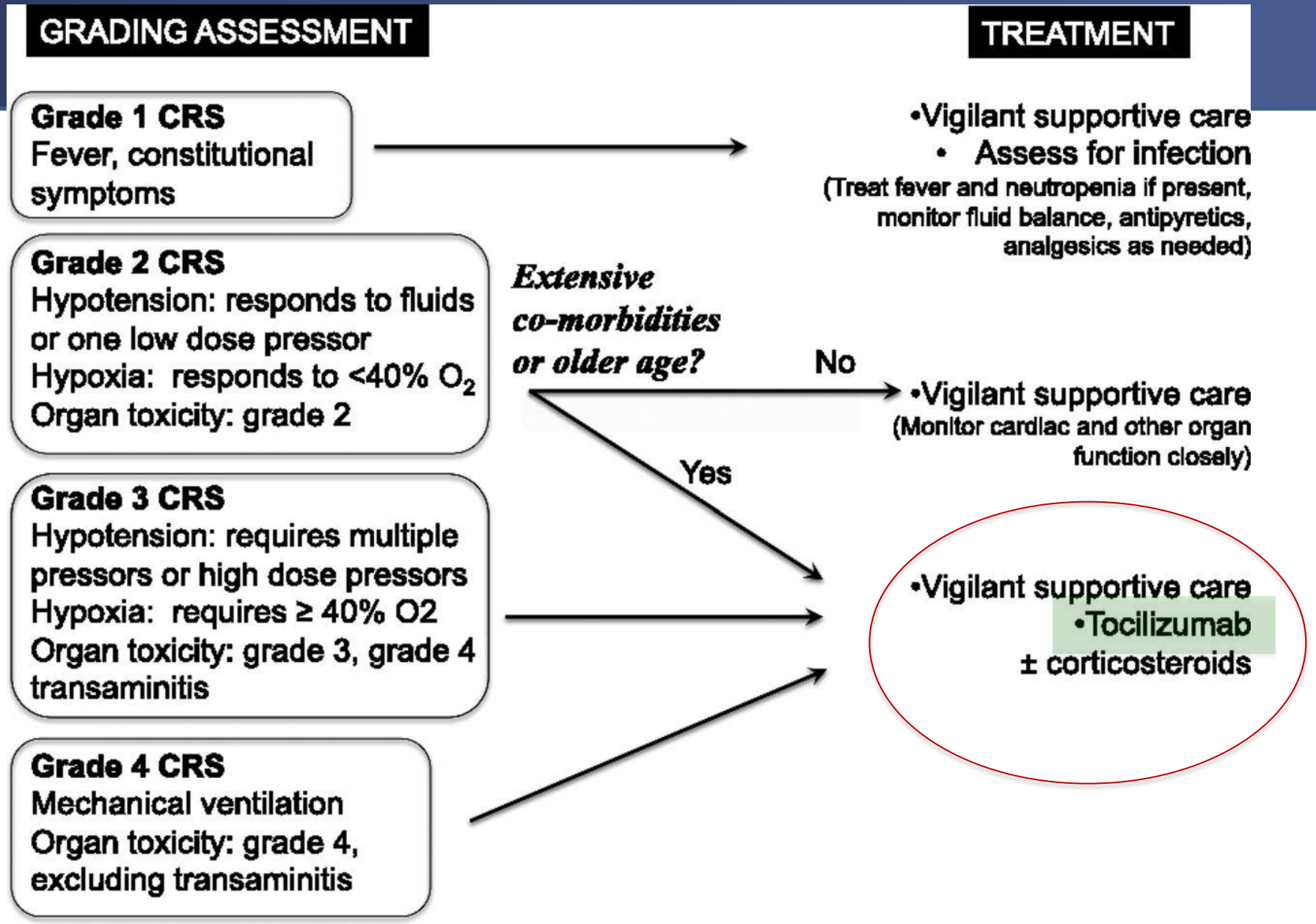

Relapsed B-cell ALL
Refractory B-cell ALL
Ph+ B-cell ALL w failure to TKI therapy
Enroll into the study & search for MSD or Haplo related donor
LAB
Suitable donor
Collect PBSC
Generate of CAR-T cells
BM blast <5% but MRD positive (minimal disease)
BM blast ≥5% (morphological disease)
Relapsed/refractory chemotherapy 1-2 courses
BM evaluation at 4 wks post CMT
BM blast >20%
Excluded subjects
BM blast <5% MRD negative
BM blast <5% MRD positive
BM blast 5-20%
Salvage therapy
Lymphodepletion chemotherapy
Lymphodepletion chemotherapy
Lymphodepletion chemotherapy
Lymphodepletion chemotherapy
Lymphodepletion
CAR infusion Dose 1x10⁶ cell/kg
CAR infusion Dose 1x10⁶ cell/kg
CAR infusion Dose 1x10⁶ cell/kg
CAR infusion Dose 3x10⁶ cell/kg
Observe sign of CRS within 72 post CAR infusion
CAR T-cell therapy


CAR T-cell therapy
D+3 D+7 D+14 D+21 D+28 post CAR infusion
CAR monitoring from Blood X X X X X
BM X X
CSF X X X
D+3 D+7 D+14 D+21 D+28 post CAR infusion
BM evaluation X X
On Day +28 post CAR infusion
Disease monitoring
In remission regardless MRD
Not in remission
HSCT
Transplant
Excluded subjects
BM evaluation at 1, 3, 6, 9 and12 months post HSCT

Cytokine release syndrome (CRS)

- It usually develops within first 2 weeks, peak at 72 hr after CAR infusion.
- Autoimmune toxicity, so-called “on target, off-tumor toxicity,” results from antigen-specific attack on host tissues when the targeted tumor associated antigen is expressed on nonmalignant tissue.

- Biological marker: Monitoring CRP, IL-6


GRADING ASSESSMENT
TREATMENT
Grade 1 CRS
Fever, constitutional symptoms
•Vigilant supportive care
• Assess for infection
(Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed)
Grade 2 CRS
Hypotension: responds to fluids or one low dose pressor
Hypoxia: responds to <40% O_2
Organ toxicity: grade 2
Extensive co-morbidities or older age?
No
•Vigilant supportive care
(Monitor cardiac and other organ function closely)
Yes
Grade 3 CRS
Hypotension: requires multiple pressors or high dose pressors
Hypoxia: requires ≥ 40% O2
Organ toxicity: grade 3, grade 4 transaminitis
•Vigilant supportive care
•Tocilizumab
± corticosteroids
Grade 4 CRS
Mechanical ventilation
Organ toxicity: grade 4, excluding transaminitis

Blood. 2014

Blinatumomab Use in Pediatric Patients With Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia

Indication in Thailand (May 2019)

1.MRD-positive B-cell Precursor ALL

B-cell Precursor ALL ในผู้ใหญ่และเด็กที่อยู่ในภาวะโรคสงบอย่างสมบูรณ์ครั้งแรกหรือครั้งที่สองโดยที่มีปริมาณยีนที่ผิดปกติจำนวนน้อย ๆ (minimal residual disease, MRD) มากกว่าหรือเท่ากับ 0.1%

2. Relapsed or refractory B-cell Precursor ALL ในผู้ใหญ่ และเด็ก

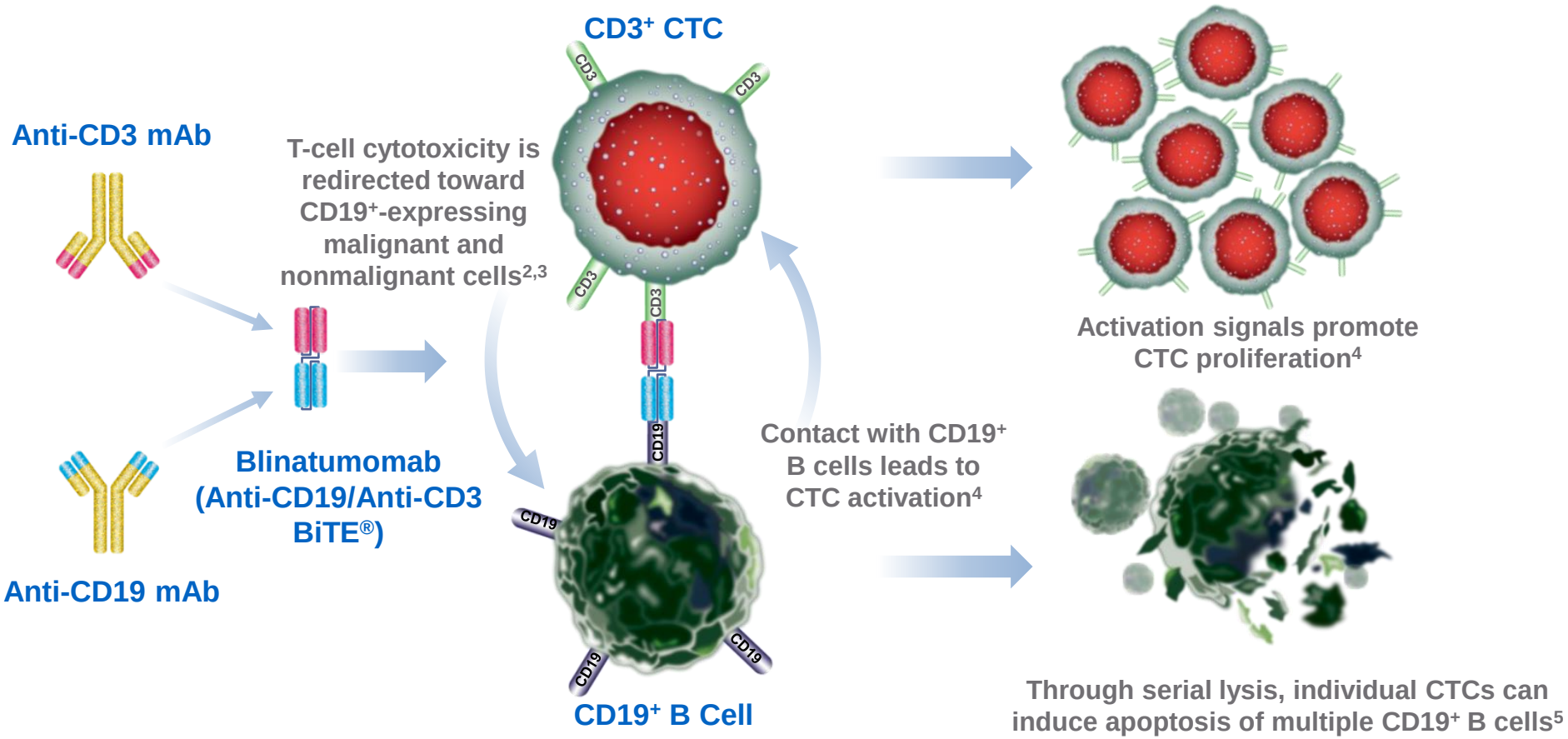
Blinatumomab Offers a Treatment Option for Pediatric Patients With R/R ALL[1,2]

- Targeted treatments are needed to overcome disease resistance and to augment or replace non-specific chemotherapy regimens, even in children with chemosensitive ALL[1]
- Immunotherapy constitutes an important anti-leukemic treatment strategy[1]
- CD19 is highly expressed throughout B-cell development and is present on > 90% of B-cell lineage cancers[3-5]
- Blinatumomab is a BiTE® antibody construct designed to direct CTCs to CD19-expressing cancer cells[1,6]
- Blinatumomab has been found to be effective in the treatment of R/R ALL in adult and pediatric populations[1,2,7]

ALL, acute lymphoblastic leukemia; BiTE®, bispecific T-cell engager; CD, cluster of differentiation; CTC, cytotoxic T cell; R/R, relapsed/refractory.

1. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389. 2. Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA. 3. Raponi S, et al. *Leuk Lymphoma*. 2011;52:1098-1107. 4. Hoelzer D, et al. *Blood Rev*. 2012;26:25-32. 5. Nagorsen D, et al. *Exp Cell Res.* 2011;317(9):1255-1260. 6. Bargou R, et al. *Science*. 2008;321:974-977. 7. Kantarjian H, et al. *N Engl J Med*. 2017;376:836-847.

Blinatumomab: BiTE® Antibody Construct Designed to Bridge CTCs to CD19-Expressing B Cells, Resulting in Cell Death[1]



BiTE®, bispecific T-cell engager; CD, cluster of differentiation; CTC, cytotoxic T cell; mAb, monoclonal antibody.

1. Baeuerle PA, et al. *Cancer Res.* 2009;69:4941-4944. 2. Bargou R, et al. *Science.* 2008;321:974-977. 3. Topp MS, et al. *Lancet Oncol*. 2015;16:57-66.
4. Klinger M, et al. *Blood.* 2012;119:6226-6233. 5. Hoffmann P, et al. *Int J Cancer.* 2005;115:98-104.

Study MT103-205

NCT01471782

Phase 1/2 Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

An Open-Label, Multicenter, Single-Arm, Phase 1/2 Study[1,2]

MT103-205

Phase 1 (rolling six design) N = 49
Dosing finding

Dose Escalation (n = 23)*

Cohort 1
5 µg/m²/day
(n = 5)

↓

Cohort 2
15 µg/m²/day
(n = 7)

↓

Cohort 3
30 µg/m²/day
(n = 5)

↓

Cohort 4
15/30 µg/m²/day
(n = 6)

Endpoints

Primary
- MTD (max dose with ≤ 1 of 6 patients in a cohort experiencing a DLT)

Secondary
- AE incidence
- PK

PK Expansion (n = 26)

Recommended dose (n = 26)

5/15 µg/m²/day
cIV infusion
4 weeks on,
2 weeks off
Up to five cycles

Intensive PK
(n = 26)
Age groups:
< 2 years (n = 8)
2–6 years† (n = 9)
7–17 years† (n = 9)

Phase 2 (Simon-like two-stage design) N = 44
Efficacy and safety at recommended dose

Recommended dose (n = 44)

5/15 µg/m²/day
cIV infusion
4 weeks on,
2 weeks off
Up to five cycles

Age groups:
< 2 years (n = 2)
2–6 years (n = 11)
7–17 years (n = 31)

Endpoints

Primary
- Rate of CR within the first two cycles (CR = no evidence of circulating blasts or extramedullary disease and < 5% blasts in bone marow)

Secondary
- AE incidence
- Proportion undergoing alloHSCT after treatment
- Relapse-free survival, overall survival, time to relapse, duration of CR

Exploratory
- Rate of MRD response

*Only patients 2–17 years of age were enrolled.
†Patients in the two older age groups (2–6 years, 7–17 years) were evaluated first, before the enrollment of patients < 2 years of age was permitted.
AE, adverse event; alloHSCT, allogeneic hematopoietic stem cell transplantation; cIV, continuous intravenous; CR, complete remission; DLT, dose-limiting toxicity; MRD, minimal residual disease; MTD, maximum tolerated dose; PK, pharmacokinetics.

1. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389. 2. von Stackelberg A, et al. *J Clin Oncol*. 2016; supplementary material (online).

Key Eligibility Criteria for Enrolled Patients[1,2]

Inclusion criteria

- B-cell precursor ALL with > 25% bone marrow blasts
- Age 0–18 years (2–17 years only in the phase 1 dose escalation)
- R/R ALL disease:
  - Second or later bone marrow relapse; any marrow relapse after alloHSCT; or refractory to other treatments
    - Patients in first relapse must have failed to achieve a CR following full standard re-induction chemotherapy regimen of at least 4 weeks duration
    - Patients who had not achieved a first remission must have failed a full standard induction regimen
- Karnofsky or Lansky (age < 16 years) performance status ≥ 50%

Exclusion criteria

- Active acute or extensive chronic GVHD after alloHSCT
- Active CNS or testicular involvement

ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; CNS, central nervous system; CR, complete remission; CRS, cytokine release syndrome; GVHD, graft-versus-host disease; R/R, relapsed/refractory.

1. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389. 2. von Stackelberg A, et al. *J Clin Oncol*. 2016; supplementary material (online).

Blinatumomab Maximum Tolerated Dose[1,2] Was 15 µg/m²/day

Cohort	Blinatumomab µg/m²/day	Patients, n	Dose-limiting toxicities, n
1	5	5	0
2	15	7	1 Grade 4 CRS deemed related to grade 4 GI hemorrhage
3	30	5	2 Grade 4 CRS;[a] Grade 4 CRS deemed related to grade 5 cardiac failure
4	15/30[b]	6	1 Grade 5 respiratory failure with cardiac arrest following hypotonia and muscle weakness[c]

- To mitigate the risk of CRS, a stepwise dose[b] of blinatumomab 5/15 µg/m²/day was recommended

[a]Successfully treated with tocilizumab.
[b]Stepwise dosing of 15 µg/m²/day for the first 7 treatment days, followed by 30 µg/m²/day thereafter.
[c]Respiratory failure with cardiac arrest occurred after 7 days of infusion with blinatumomab at 15 µg/m²/day had been completed (the 30-µg/m²/day dose was not administered). The patient experienced febrile neutropenia and pneumonia shortly before blinatumomab infusion start.
CRS, cytokine release syndrome; GI, gastrointestinal; MTD, maximum tolerated dose.
1. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.
2. von Stackelberg A, et al. *J Clin Oncol*. 2016; supplementary material (online).

Recommended Dose Confirmed in Phase 1 Was Applied to Phase 2

Based on the phase 1 dose-escalation phase, the recommended blinatumomab dose for children with R/R B-cell precursor ALL was:

5 µg/m^2/day
for the first 7 days

followed by

15 µg/m^2/day
starting at day 8

ALL, acute lymphoblastic leukemia; R/R, relapsed/refractory.

von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Patients Achieved Hematologic Response With Blinatumomab

Hematologic response	Patients in phase 2 n = 44[a]			All patients at recommended dose n = 70[a]		
	n	%	95% CI	n	%	95% CI
CR within the first two cycles	14	32	19–48	27	39	27–51
CR within the first two cycles by baseline bone marrow blast count						
< 50% blasts at baseline	5/12	42	15–72	10/18	56	31–79
≥ 50% blasts at baseline	9/32	28	14–47	17/52	33	20–47
Nonresponders (did not achieve CR)						
Partial remission	3	7	–	4	6	–
Blast-free hypoplastic or aplastic bone marrow	0	0	–	2	3	–
Progressive disease	8	18	–	10	14	–
No response	14	32	–	21	30	–
No response assessment[b]	5	11	–	6	9	–
Relapse or death following CR[c]	10	71	–	7	26	–

[a]All patients treated at the recommended dose in phase 1 or 2. [b]Patients died (n = 5) or withdrew consent (n = 1) before the first response assessment.
[c]Relapse during the efficacy follow-up (no chemotherapy or alloHSCT between end of blinatumomab treatment and relapse).
alloHSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; CR, complete remission.
von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Molecular Response in Patients Who Achieved Complete Remission With Blinatumomab

	Patients in phase 2 n = 44[a]			All patients at recommended dose n = 70[a]			Patients < 2 years at recommended dose n = 10[a]		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
MRD response in patients who achieved CR within the first two cycles[b]									
MRD response	8/14	57	29–82	14/27	52	32–71	3/6	50	12–88
Complete MRD response	8/14	57	29–82	14/27	52	32–71	3/6	50	–
No MRD response	6/14	43	–	12	44	–	3/6	50	–
No data available	0	0	–	1	4	–	0	0	–

Of 27 responders, 52% achieved a complete molecular response, 48% by day 15 of cycle 1

[a]All patients treated at the recommended dose in phase 1 or 2.
[b]MRD response was assessed by flow cytometry; MRD response was defined as < 10^{-4} detectable blasts; complete MRD response was defined as no detectable blasts.
CI, confidence interval; CR, complete remission; MRD, minimal residual disease.
von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Relapse-Free Survival Among Patients Who Achieved Complete Remssion[1,2]

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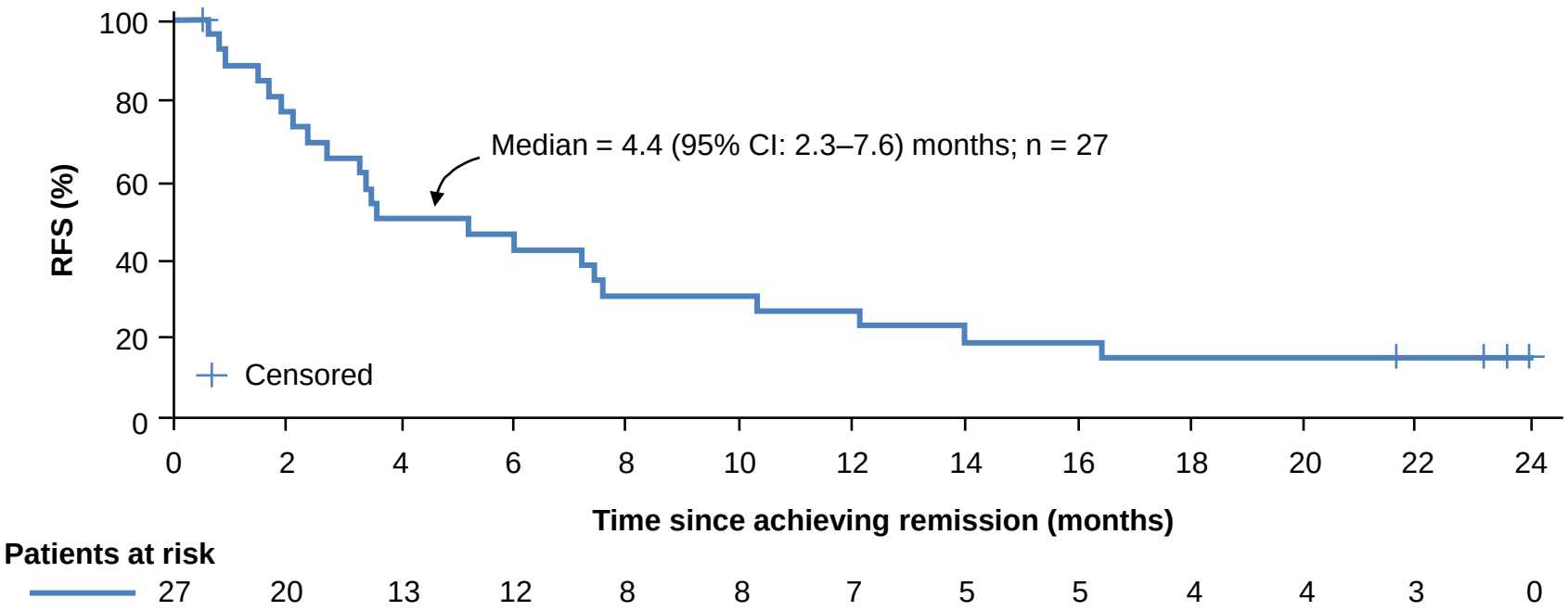
Kaplan–Meier Analysis of RFS* in 27 Responders Who Received Blinatumomab at the Recommended Dose



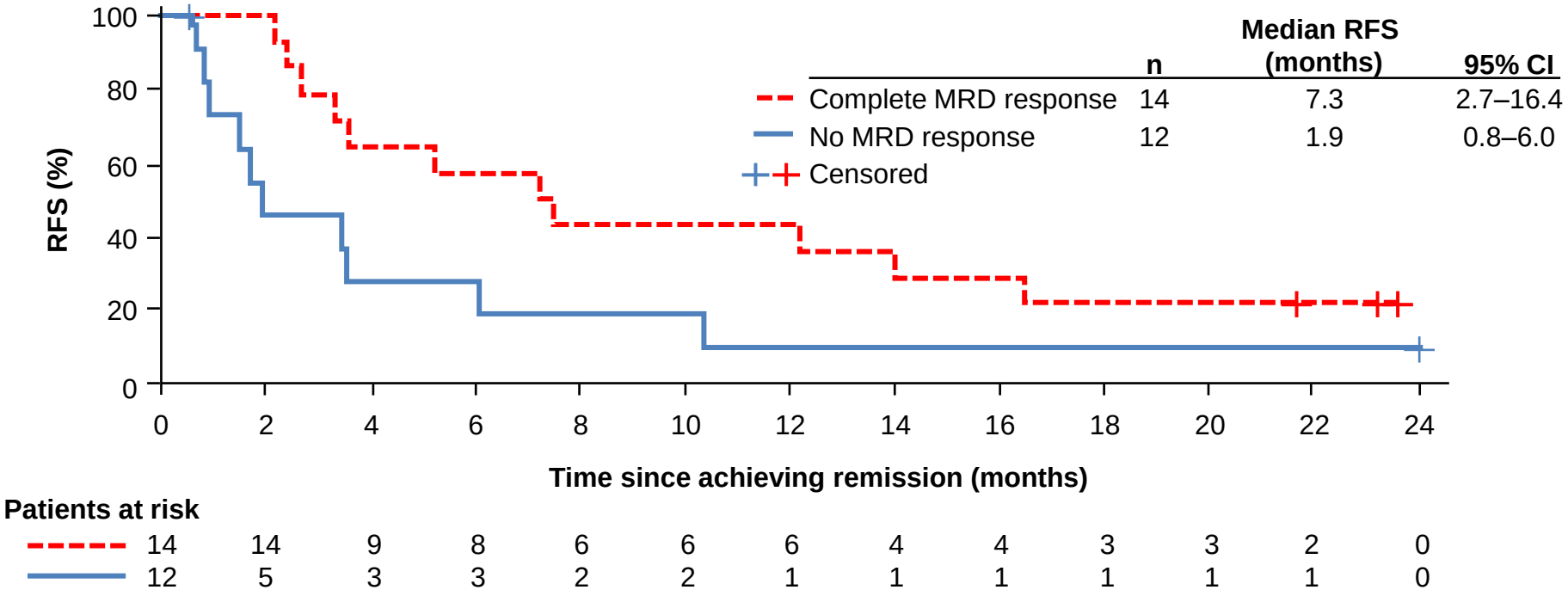
Median RFS among responders was 4.4 months with an RFS rate of 42% at 6 months (median follow-up 23.1 months)

*RFS was calculated from the time of first achieved remission to the first documented relapse or death due to any cause.
CI, confidence interval; CR, complete remission; RFS, relapse-free survival.
1. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389. 2. von Stackelberg A, et al. *J Clin Oncol*. 2016; supplementary material (online).

Relapse-Free Survival Among Patients Who Achieved Complete Molecular Response

MT103-205

Kaplan–Meier Analysis of RFS Among Patients With CR According to MRD Response*



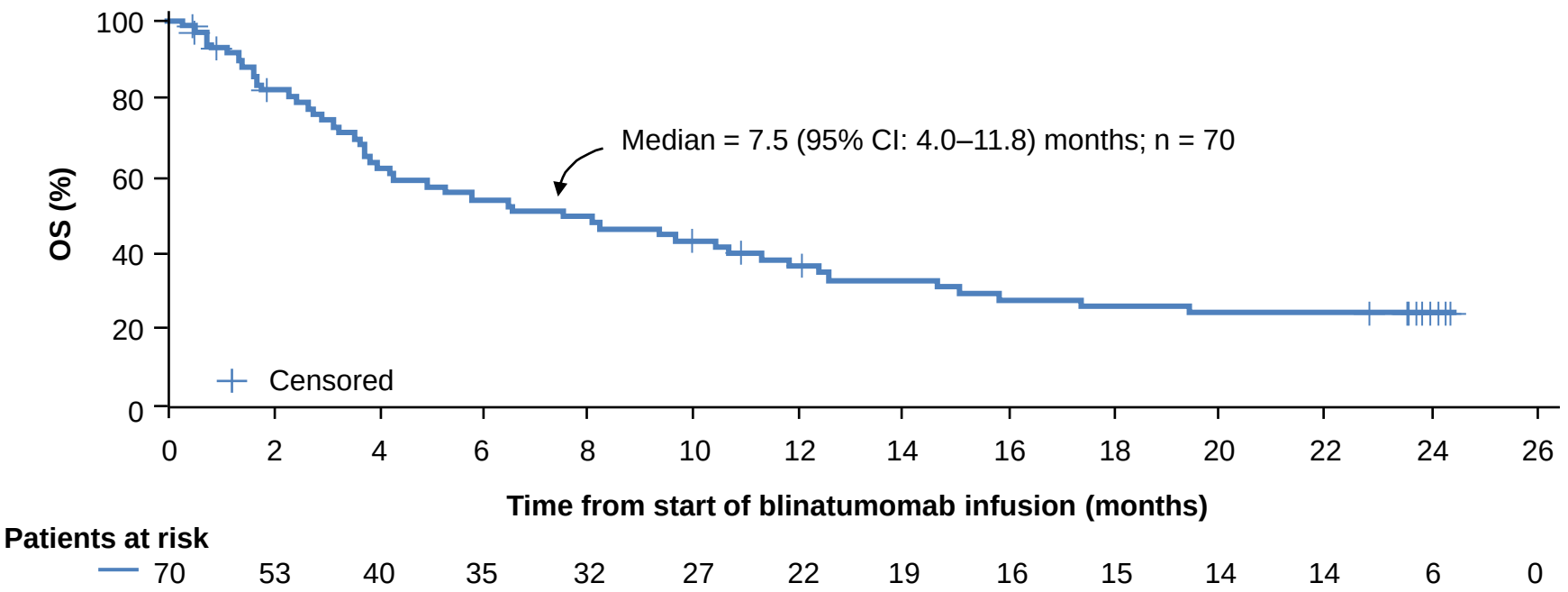
- Patients with complete molecular response experienced longer RFS than those without complete molecular response (7.3 vs 1.9 months)

*All patients who received the recommended dose in phase 1 or 2.
CI, confidence interval; CR, complete remission; MRD, minimal residual disease; RFS, relapse-free survival.
von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Overall Survival Among Patients Who Received Blinatumomab

MT103-205

Kaplan–Meier Analysis of OS in Patients Who Received Blinatumomab at the Recommended Dose



- Of all patients who received blinatumomab at the recommended dose, median OS was 7.5 months

Data are based on the 2-year follow-up. Median follow-up was 23.8 months.
CI, confidence interval.
von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Adverse Events in Patients Who Received Blinatumomab

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	All patients n = 70[a]
Patients with AEs, n (%)	70 (100)
AEs of worst grade ≥ 3 occurring in ≥ 5% of patients, n (%)	61 (87)
Anemia	25 (36)
Thrombocytopenia	15 (21)
Febrile neutropenia	12 (17)
Hypokalemia	12 (17)
Neutropenia	12 (17)
Alanine aminotransferase increased	11 (16)
Platelet count decreased	10 (14)
Pyrexia	10 (14)
Neutrophil count decreased	9 (13)
Aspartate aminotransferase increased	8 (11)
Leukopenia	7 (10)
White blood cell count decreased	7 (10)
CRS	4 (6)
Hypertension	4 (6)

- Among the 70 patients who received blinatumomab, the most common AEs, regardless of causality and grade, were pyrexia (80%), anemia (41%), nausea (33%), and headache (30%)

[a]All patients who received the recommended dose in phase 1 or 2.
AE, adverse event; CRS, cytokine release syndrome.
von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Fatal Adverse Events in Patients Who Received Blinatumomab[1,2]

	All patients n = 70[a]
Fatal AEs on study[b]	6 (7)
Multiorgan failure[c]	2 (3)
Sepsis[c]	1 (1)
Fungal infection	1 (1)
Respiratory failure[c]	1 (1)
Thrombocytopenia	1 (1)

- Ten (14%) patients interrupted and four (6%) permanently discontinued treatment because of AEs
  - Two permanent discontinuations were considered treatment-related (grade 3 and 4 CRS), and one each was due to multiorgan failure and fungal infection

Out of 70 patients, six had fatal AEs; three patients died after alloHSCT following blinatumomab-induced remission

[a]All patients who received the recommended dose in phase 1 or 2.
[b]Does not include two deaths due to disease progression, including one patient who died of recurrent leukemia. These deaths were reported by the investigators as AEs.
[c]Patient died after alloHSCT following blinatumomab-induced remission (only one of the patients with multiorgan failure).
AE, adverse event; alloHSCT, allogeneic hematopoietic stem cell transplantation; CRS, cytokine release syndrome.
1. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389. 2. von Stackelberg A, et al. *J Clin Oncol*. 2016; supplementary material (online).

Some Patients Treated With Blinatumomab Developed Cytokine Release Syndrome

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	All patients n = 70[a]
Patients with CRS, n (%)	
Any grade	8 (11)
Worst grade 3	3 (4)
Worst grade 4	1 (1)
Worst grade 5	0
Temporarily interrupted treatment because of CRS	2 (3)[b]
Discontinued treatment because of CRS	2 (3)[c]
Patients with CRS by age group, n (%)	
< 2 years (n = 10)	2 (3)
Worst grade 3 or 4	0
2–6 years (n = 20)	2 (3)
Worst grade 3 or 4	2 (3)
7–17 years (n = 40)	4 (6)
Worst grade 3 or 4	2 (3)
Duration of grade ≥ 3 CRS, n (%)	
> 3 to ≤ 7 days	2 (3)
> 7 to ≤ 14 days	1 (1)
> 14 days	1 (1)
Median (95% CI) days	6.5 (5.0–16.0)

[a]All patients who received the recommended dose in phase 1 or 2. [b]All grade 3. [c]One grade 3 and one grade 4 event.
CI, confidence interval; CRS, cytokine release syndrome.
von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Some Patients Treated With Blinatumomab Experienced Neurologic/Psychiatric Events

MT103-205

	All patients n = 70[a]
Patients with neurologic/psychiatric events of any grade regardless of relation to treatment, n (%)	17 (24)
Tremor	4 (6)
Dizziness	3 (4)
Somnolence	3 (4)
Convulsion	2 (3)
Paresthesia	2 (3)
Encephalopathy	1 (1)
Neuralgia	1 (1)
Ataxia	1 (1)
Atonic seizure	1 (1)
Cerebrospinal fluid leakage	1 (1)
Depressed level of consciousness	1 (1)
Dysgeusia	1 (1)
Hypoesthesia	1 (1)
Nystagmus	1 (1)
Syncope	1 (1)
Confusional state	1 (1)
Mental disorder	1 (1)

13% of patients had neurologic events, primarily tremor and dizziness, that were considered treatment related; these events were of grade 2 and resolved upon treatment discontinuation

[a]All patients who received the recommended dose in phase 1 or 2.

von Stackelberg A, et al. *J Clin Oncol*. 2016; supplementary material (online).

Conclusions

- **Phase 1**
  - MTD established as 15 µg/m^2/day
  - Recommended stepwise dosing of 5/15 µg/m^2/day to reduce the risk of CRS
- **Phase 2**
  - Blinatumomab showed anti-leukemic activity in heavily pretreated pediatric patients with R/R B-cell precursor ALL, including patients < 2 years old and those with unfavorable cytogenetics
  - For patients who received the recommended dose, the rate of complete remission within the first two cycles was 39%, with most responders achieving complete molecular response
  - Median relapse-free survival among patients achieving CR was 4.4 months with an RFS rate of 42% at 6 months
  - Median overall survival for patients who received blinatumomab at the recommended dose was 7.5 months
  - AEs associated with blinatumomab treatment were consistent with previous experience
  - Most of the grade ≥ 3 AEs were cytopenias and blood chemistry changes

This study supported further evaluation of blinatumomab in children with B-cell precursor ALL, including those with first-relapse or newly diagnosed disease at high risk of treatment failure because of significant MRD burden or unfavorable cytogenetics

AE, adverse event; ALL, acute lymphoblastic leukemia; CR, complete remission; CRS, cytokine release syndrome; MRD, minimal residual disease; MTD, maximum tolerated dose; R/R, relapsed/refractory.

von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Study 20130320 (RIALTO)

NCT02187354

Blinatumomab Use in Pediatric Patients With Relapsed/Refractory B-Cell Precursor Acute Lymphoblastic Leukemia From an Open-Label, Multicenter, Expanded-Access Study

Objectives[1,2]

Primary

- To estimate the **incidence of treatment-emergent and treatment-related AEs** in pediatric and adolescent patients with R/R ALL during treatment with blinatumomab

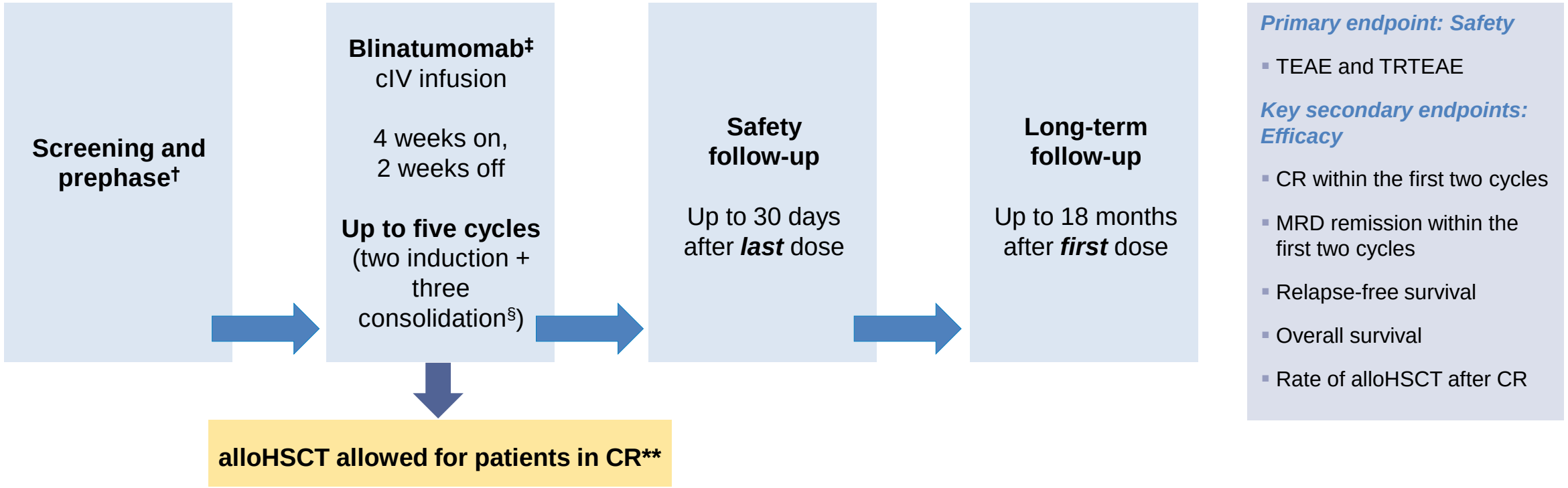
Secondary

- To describe key **efficacy outcomes**, including incidence of:
  - CR
  - MRD response
  - Relapse-free survival
  - Overall survival
  - Rate of alloHSCT after CR

AE, adverse event; ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; MRD, minimal residual disease; R/R, relapsed/refractory.

1. Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.
2. NCT02187354. Available at: https://clinicaltrials.gov/ct2/show/NCT02187354. Accessed November 27, 2018.

An Open-Label, Multicenter, Expanded-Access Study in Pediatric Patients With R/R ALL*



Primary endpoint: Safety

- TEAE and TRTEAE

Key secondary endpoints: Efficacy

- CR within the first two cycles
- MRD remission within the first two cycles
- Relapse-free survival
- Overall survival
- Rate of alloHSCT after CR

*This analysis focuses on the 98 pediatric and adolescent patients enrolled into the expanded-access study. †Prephase period is permitted for the administration of dexamethasone or hydroxyurea to reduce tumor burden and the incidence of tumor lysis syndrome. For patients with blasts > 50% at screening, dexamethasone is mandatory as prephase medication. ‡Dosing: If < 25% blasts at screening: 15 μg/m^2/day; if ≥ 25% blasts at screening: 5 μg/m^2/day on days 1−7 in cycle 1, then 15 μg/m^2/day thereafter. §If patients achieve CR within first two cycles. **Complete remission defined as no evidence of circulating blasts or extramedullary disease and < 5% blasts in bone marrow; CR was subclassified on the basis of recovery of peripheral blood counts.

alloHSCT, allogeneic hematopoietic stem cell transplantation; cIV, continuous intravenous; CR, complete remission; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; R/R ALL, relapsed/refractory acute lymphoblastic leukemia; TEAE, treatment-emergent adverse event; TRTEAE, treatment-related treatment-emergent adverse event.

Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.

Key Eligibility Criteria for Enrolled Patients[1,2]

Inclusion criteria

- CD19-positive B-cell precursor ALL with ≥ 5% bone marrow blasts or < 5% blasts and MRD level ≥ 10^{-3}
- Age > 28 days and < 18 years
- R/R disease:
  - Second or later bone marrow relapse; any marrow relapse after alloHSCT; or refractory to other treatments (chemotherapy/alloHSCT)
- Adequate liver function defined as:
  - ALT ≤ 135 IU/L in the European Union and Switzerland
  - ALT < 5 times the upper limit of normal for age in the USA
- Prior treatment with blinatumomab was allowed, provided the patient was not blinatumomab-refractory or intolerant, and leukemic cells were CD19 positive

Exclusion criteria

- Clinically relevant CNS pathology
- Chemotherapy within 2 weeks, radiotherapy within 4 weeks, or immunotherapy within 6 weeks of the start of treatment
- Grade 2 to 4 acute GVHD or active chronic GVHD
- Immunosuppressive agents to prevent or treat GVHD within 2 weeks of the start of treatment

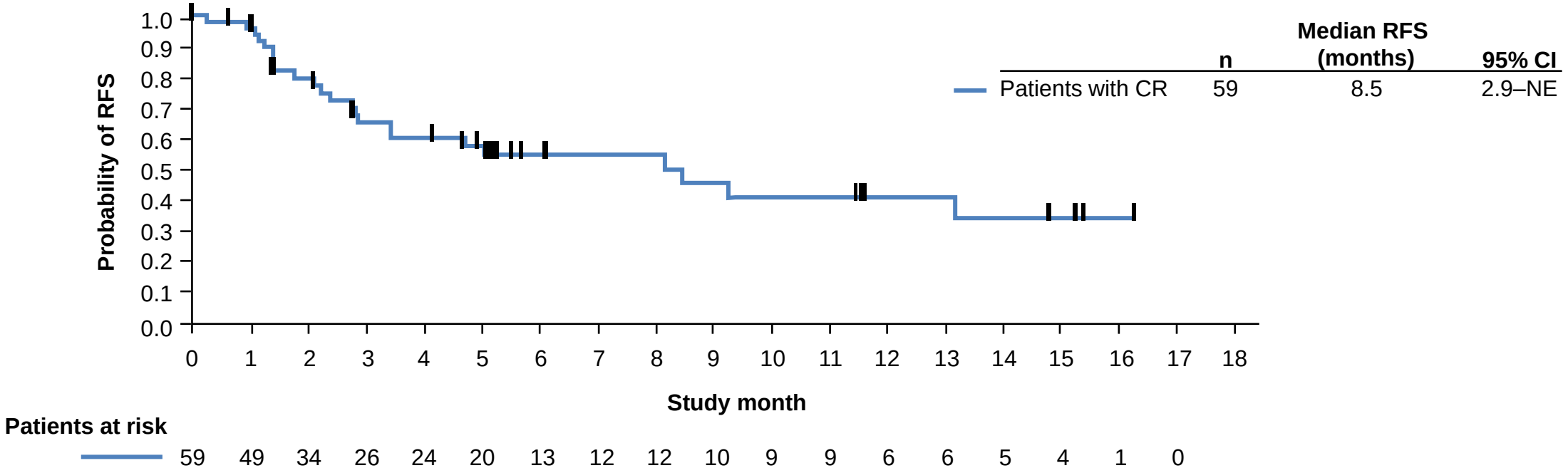
ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; ALT, alanine transaminase (serum glutamic pyruvic transaminase); CD, cluster of differentiation; CNS, central nervous system; GVHD, graft-versus-host disease; MRD, minimal residual disease; R/R, relapsed/refractory.

1. Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA. 2. NCT02187354. Available at: https://clinicaltrials.gov/ct2/show/NCT02187354. Accessed November 27, 2018.

Relapse-Free Survival in Patients Who Received Blinatumomab

N=98

Kaplan–Meier Analysis of Relapse-Free Survival With Blinatumomab

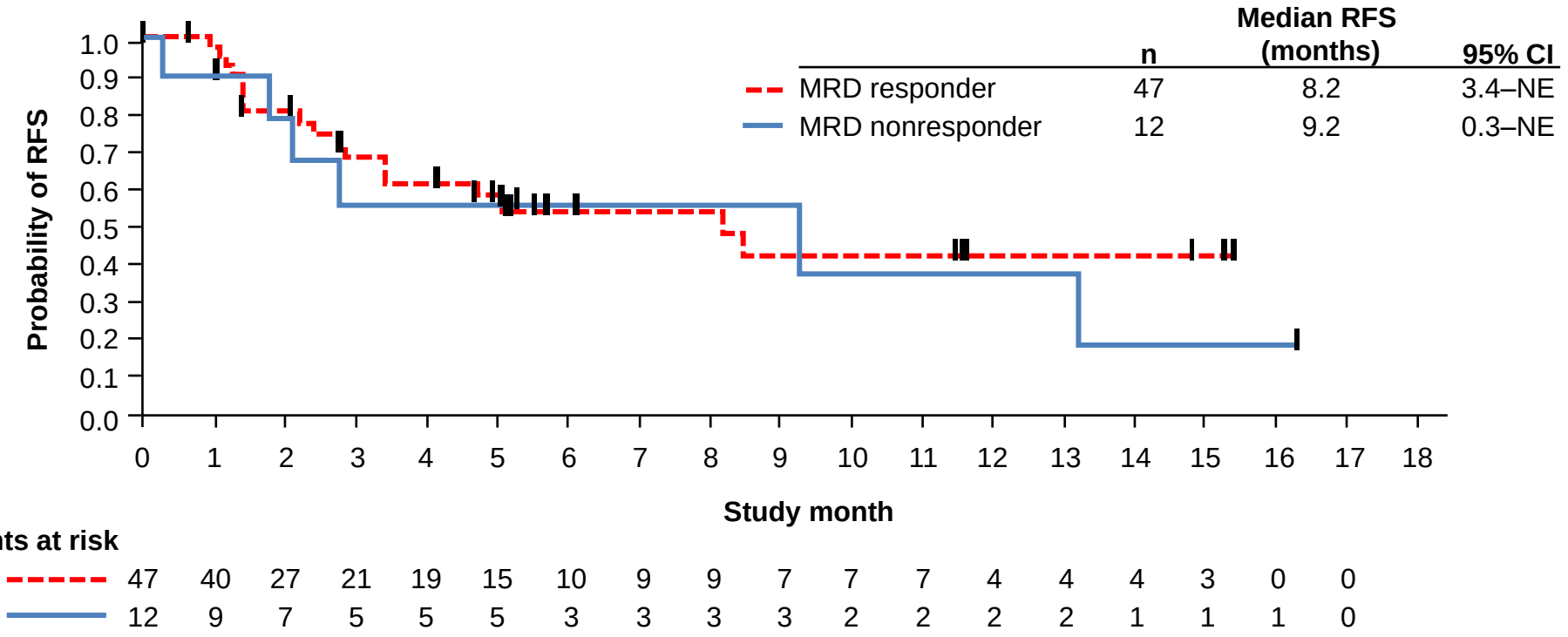


Patients who received blinatumomab achieved a median RFS of 8.5 months

RFS is based only on responders and calculated from time of CR.
CI, confidence interval; CR, complete remission; NE, not estimable; RFS, relapse-free survival .
Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.

Relapse-Free Survival Among Patients Who Achieved Complete Molecular Response

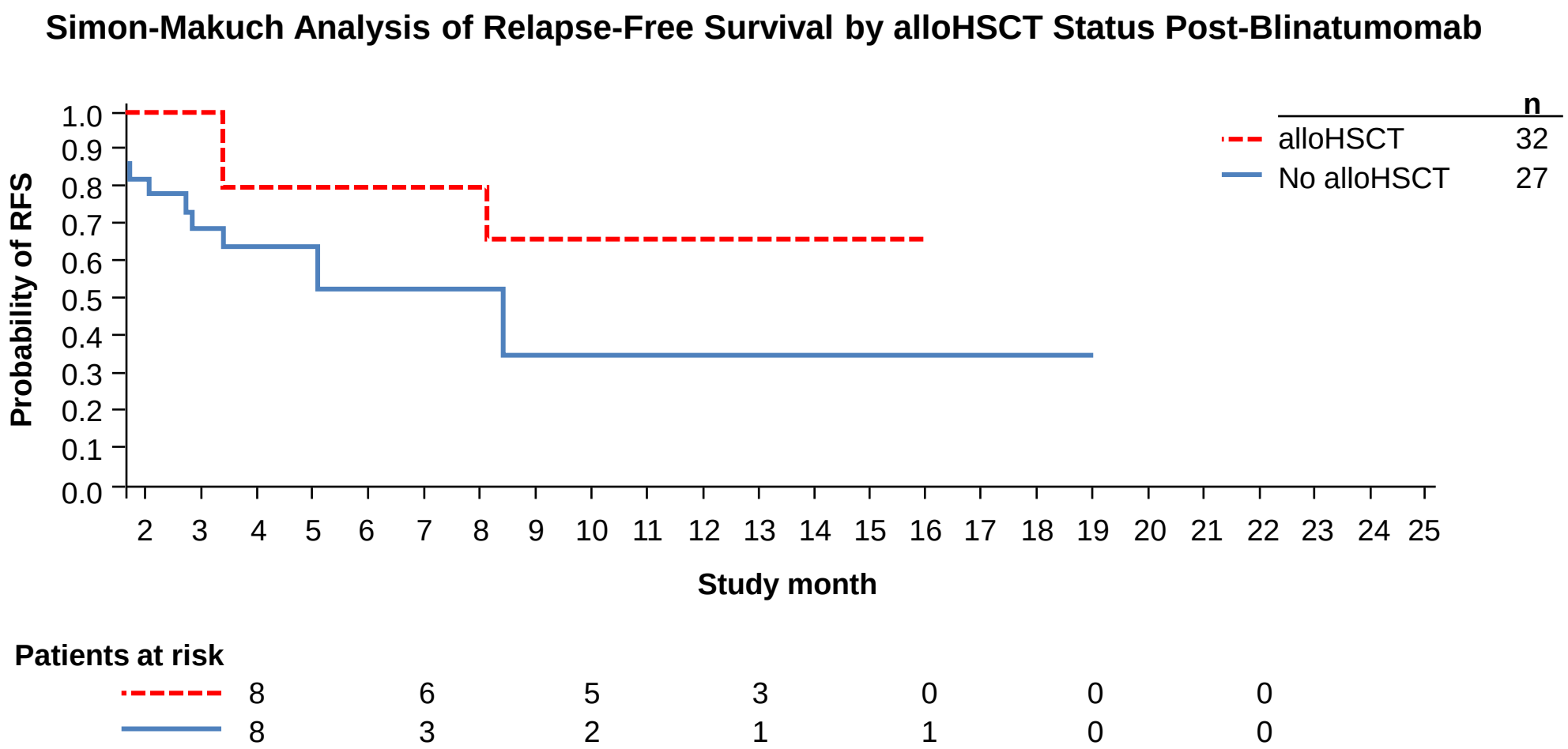
Kaplan–Meier Analysis of Relapse-Free Survival With Blinatumomab by MRD Response Status



Patients who achieved an MRD response had a median RFS of 8.2 months

RFS by MRD response is based only on responders and calculated from time of CR by Kaplan–Meier method.
CI, confidence interval; CR, complete remission; MRD, minimal residual disease; NE, not estimable; RFS, relapse-free survival.
Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.

Relapse-Free Survival by Baseline alloHSCT in Patients Who Received Blinatumomab



Simon-Makuch method using a 42-day landmark.
alloHSCT, allogeneic hematopoietic stem cell transplantation; RFS, relapse-free survival.
Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.

Overall Survival Among Patients Who Received Blinatumomab

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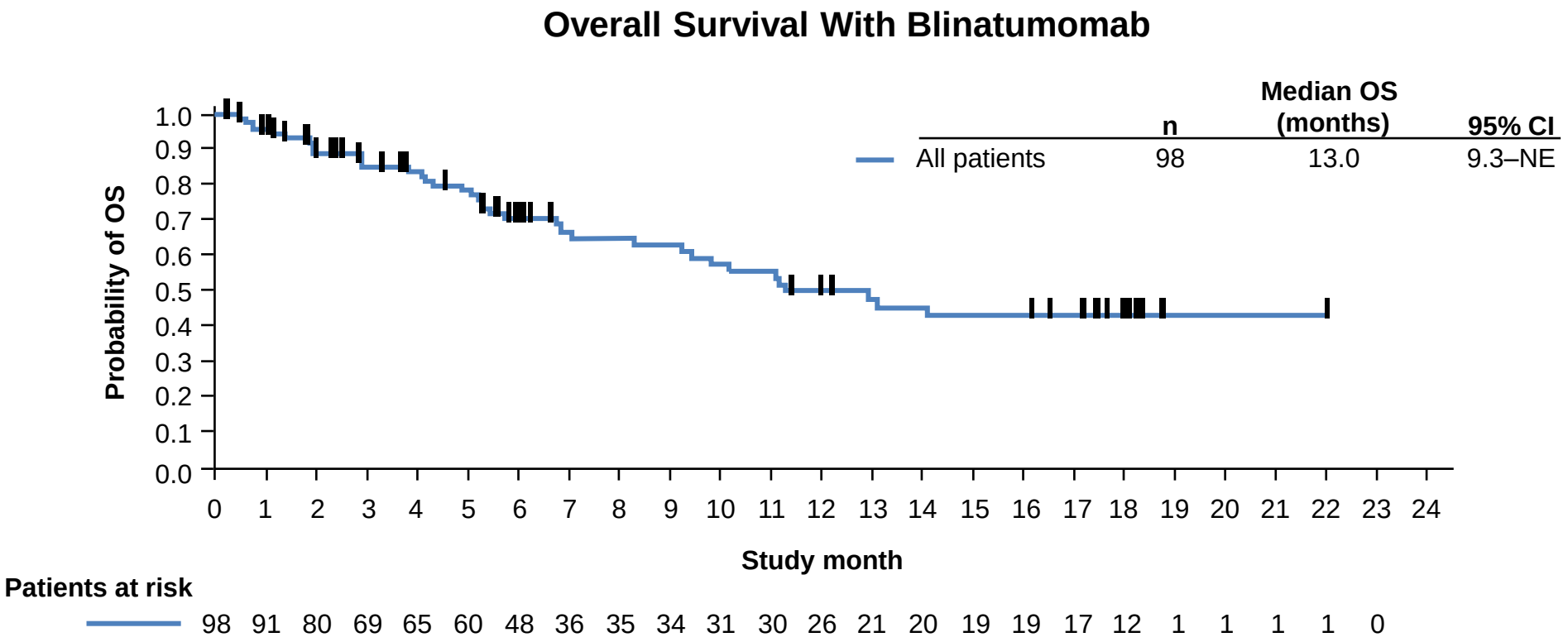

Patients treated with blinatumomab had a median OS of 13 months

alloHSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; CR, complete remission; MRD, minimal residual disease; NE, not estimable; OS, overall survival.

Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.

Overall Survival Among Patients Who Achieved Complete Molecular Response

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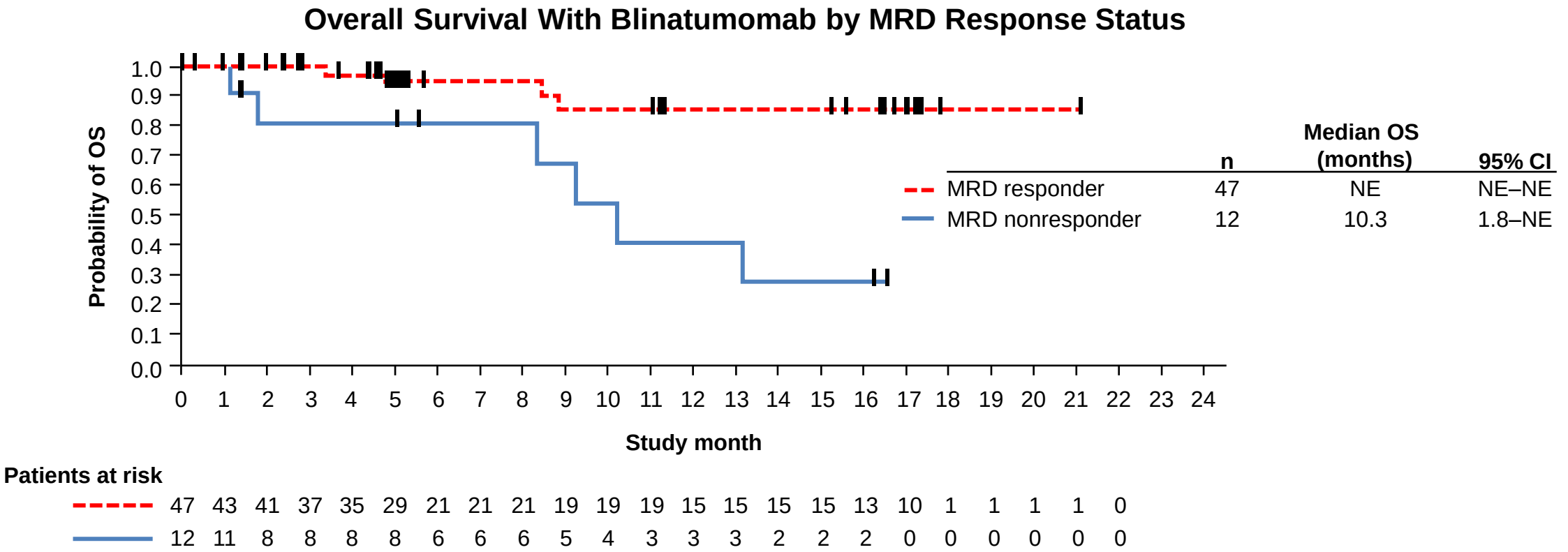

Median OS was not reached in patients who achieved a MRD response

OS by MRD response is based on responders and calculated from time of CR by Kaplan–Meier method.
alloHSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; CR, complete remission; MRD, minimal residual disease; NE, not estimable; OS, overall survival.
Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.

Overall Survival by Baseline alloHSCT Status in Patients Who Received Blinatumomab

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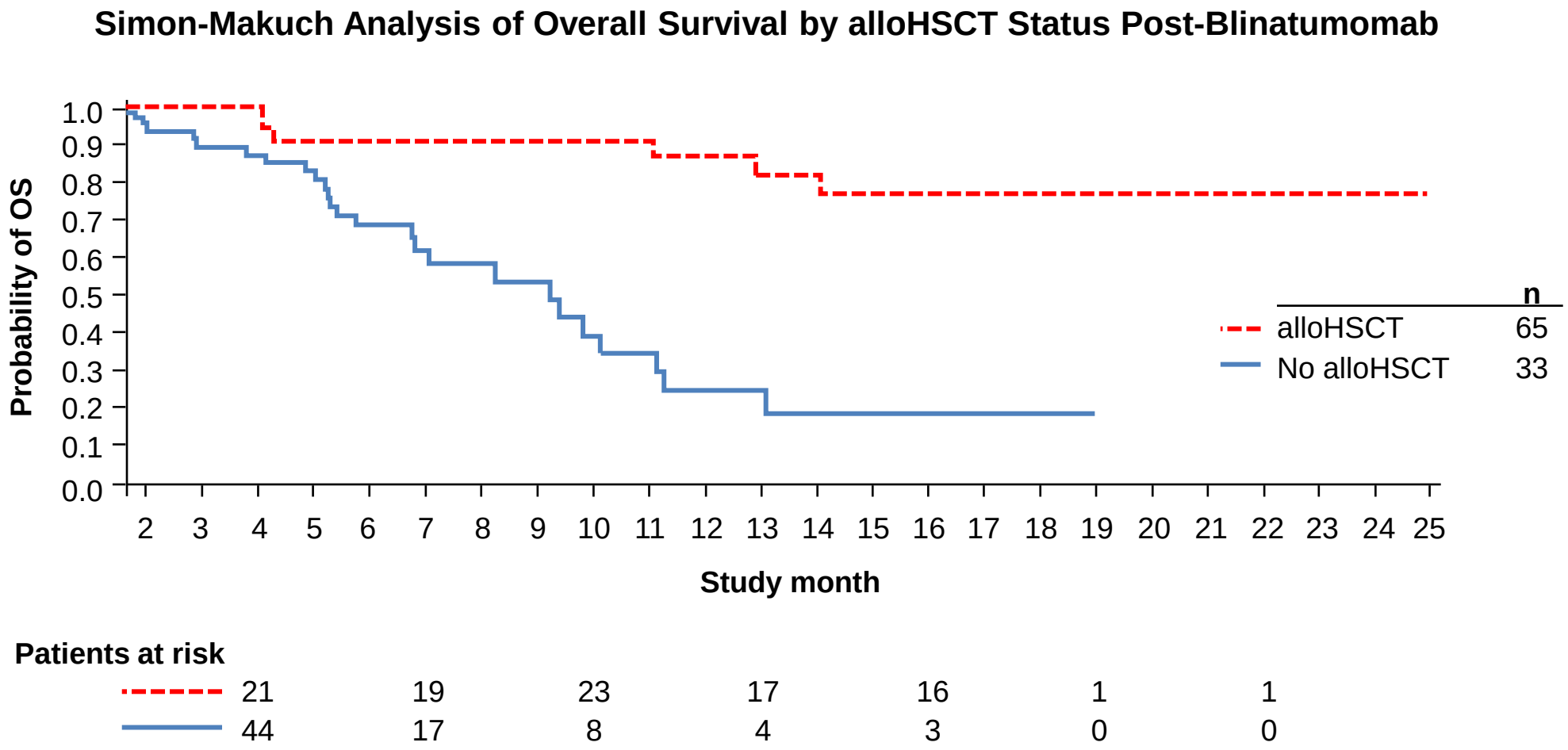


Simon-Makuch method using a 42-day landmark.
alloHSCT, allogeneic hematopoietic stem cell transplantation; OS, overall survival.
Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.

Best Response During the First Two Cycles of Blinatumomab

All patients (N = 98)	n (%)
CR during the first two cycles	59 (60)
CR with full recovery of peripheral blood counts	39 (40)
CR without full recovery of peripheral blood counts	20 (20)
Non-CR	
Hypoplastic or acellular bone marrow	1 (1)
Partial remission	1 (1)
Stable disease	4 (4)
Progressive disease	16 (16)
No response data or non-evaluable	17 (17)
Patients who achieved CR during first two cycles (n = 59)	**n (%)**
MRD response during the first two cycles[a]	47 (80)
Proceeded to alloHSCT	27 (46)

Of 59 patients who achieved CR during the first two cycles, 80% had a molecular response and 46% proceeded to alloHSCT

[a]MRD response was defined as < 10^{-4} leukemic blasts by PCR or flow cytometry.
alloHSCT, allogeneic hematopoietic stem cell transplantation; CI, confidence interval; CR, complete remission; MRD, minimal residual disease.
Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.

Conclusions

- In this expanded-access study, single-agent blinatumomab resulted in a CR rate of 58% in pediatric patients with R/R B-cell precursor ALL who had ≥ 5% blasts at baseline[1]
  - 77% of patients who achieved CR also had an MRD response during the first two cycles
  - Of the nine patients with CR at baseline (MRD ≥ 10^{-3}), seven achieved an MRD response during the first two cycles
  - 46% of responders subsequently received alloHSCT
  - A higher response rate was observed in patients with lower baseline tumor burden (< 50% blasts)
- The median relapse-free survival was 8.5 months; median overall survival was 13.0 months
  - Among responders, the overall survival probability was better if MRD response was achieved
- AEs in pediatric patients (including CRS and neurologic events) were consistent with those previously reported in blinatumomab-treated patients with R/R B-cell precursor ALL[1,2]
  - Discontinuation due to treatment-related AEs was infrequent
- These data further support the use of blinatumomab for children and adolescents with CD19-positive BCP-ALL

AE, adverse event; ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; CRS, cytokine release syndrome; MRD, minimal residual disease; R/R, relapsed/refractory.

1. Locatelli F, et al. Poster presented at: American Society of Hematology Annual Meeting; December 1-4, 2018; San Diego, CA.
2. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

Study 20120215

NCT02393859

Phase 3 Trial to Investigate the Efficacy, Safety, and Tolerability of Blinatumomab as Consolidation Therapy Versus Conventional Consolidation Chemotherapy in Pediatric Patients With High-Risk B-cell ALL at first relapse

Objectives

Primary

- To evaluate **event-free survival** after treatment with blinatumomab compared with standard of care consolidation chemotherapy in pediatric patients with R/R B-cell ALL

Secondary

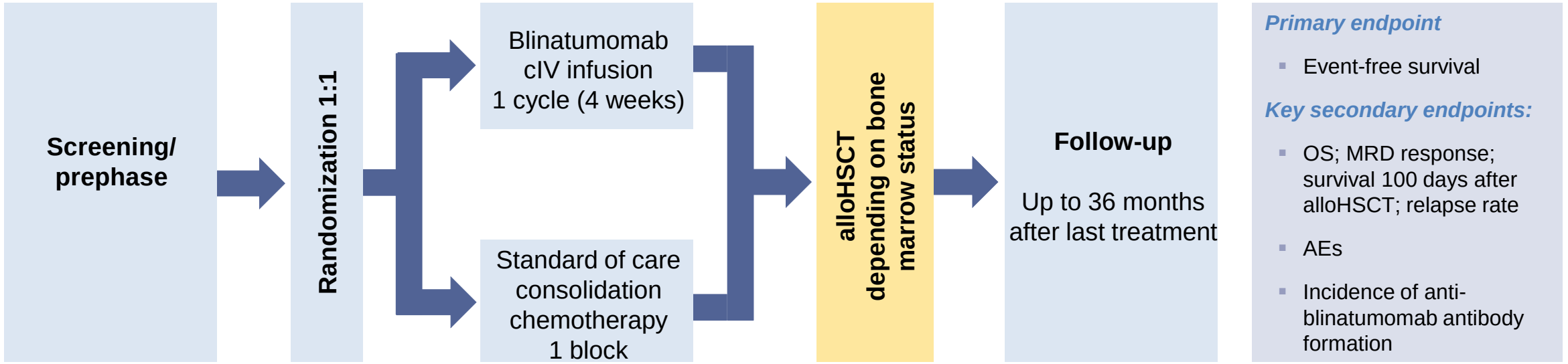
- To describe key **efficacy outcomes**, including incidence of overall survival and MRD response, AEs, 100-day mortality after alloHSCT, incidence of anti-blinatumomab antibody formation, cumulative incidence of relapse

AE, adverse event; ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; MRD, minimal residual disease; R/R, relapsed/refractory.

NCT02393859. Available at: https://clinicaltrials.gov/ct2/show/NCT02393859. Accessed July 18, 2018.

A Phase 3, Open-Label, Multicenter, Randomized Controlled Study in Pediatric Patients With R/R ALL

Pediatric Patients With High-Risk, First Relapse B-Cell Precursor ALL



Primary endpoint

- Event-free survival

Key secondary endpoints:

- OS; MRD response; survival 100 days after alloHSCT; relapse rate
- AEs
- Incidence of anti-blinatumomab antibody formation
- PK

AE, adverse event; ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; cIV, continuous intravenous; MRD, minimal residual disease; OS, overall survival; PK, pharmacokinetics; R/R, relapsed/refractory.

NCT02393859. Available at: https://clinicaltrials.gov/ct2/show/NCT02393859. Accessed November 27, 2018.

Key Eligibility Criteria for Enrolled Patients[1,2]

Inclusion criteria

- Philadelphia chromosome-negative (Ph-) high-risk, first relapse B-cell precursor ALL (as defined by I-BFM SG/IntReALL criteria)
- M1 or M2* marrow at the time of randomization
- Age > 28 days and < 18 years at the time of informed consent/assent

Exclusion criteria

- Clinically relevant CNS pathology requiring treatment (eg, unstable epilepsy)
- Evidence of current CNS (CNS 2, CNS 3)† involvement by ALL
- Abnormal renal or hepatic function prior to start of treatment (day 1)

*M1, < 5% leukemic blasts; M2, ≥ 5% and < 25% lymphoblasts.[2] †CNS 2, patients with blasts in the CSF but fewer than 5 WBC/µL, obtained at diagnosis; CNS 3, patients with 5 or more WBC/µL and blasts in the CSF, obtained at diagnosis.[3]

ALL, acute lymphoblastic leukemia; CNS, central nervous system, CSF, cerebrospinal fluid; WBC, white blood cell.

1. NCT02393859. Available at: https://clinicaltrials.gov/ct2/show/NCT02393859. Accessed November 27, 2018. 2. Data on file, Amgen; [Protocol 20120215]; December 2017.
3. Childhood Acute Lymphoblastic Leukemia Treatment (PDQ®): Health Professional Version. 2018.

Next Steps and Timelines

- Estimated enrollment: 202 patients

Actual Study Start Date:	Estimated Primary Completion Date:	Estimated Study Completion Date:
10 November 2015	22 September 2022	25 July 2023

NCT02393859. Available at: https://clinicaltrials.gov/ct2/show/NCT02393859. November 27, 2018.

Children’s Oncology Group (COG) Study AALL1331

NCT02101853

Risk-Stratified Randomized Phase 3 Testing of Blinatumomab in First Relapse of Childhood B-Lymphoblastic Leukemia

Objectives

Primary

- To estimate **disease-free survival** of high-risk, intermediate-risk, and low-risk relapse in patients with B-cell precursor ALL

Secondary

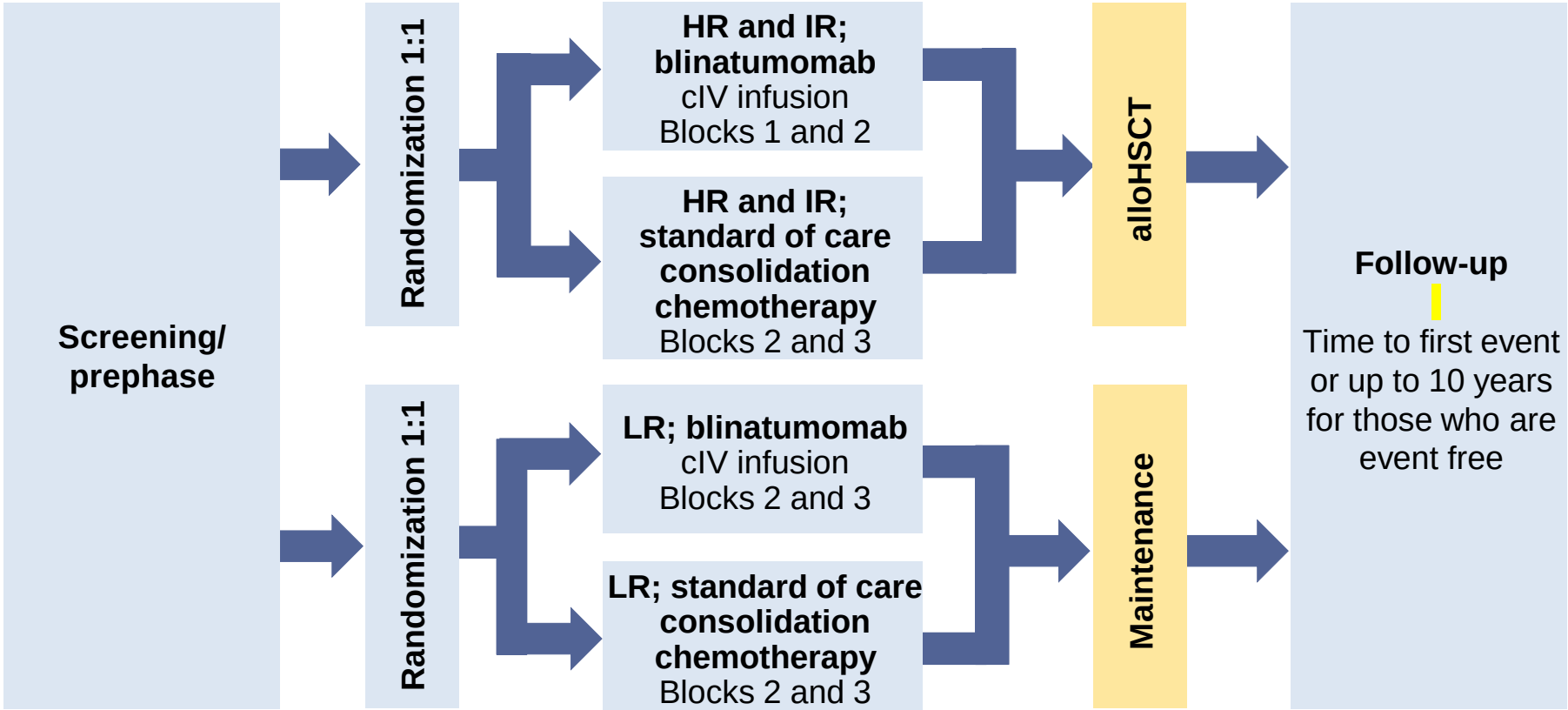
- To evaluate incidence of **overall survival** in patients with B-cell precursor ALL with high-risk, intermediate-risk, or low-risk relapse
- To assess other efficacy outcomes including:
  - Rate of CR, MRD positivity, and MRD negativity
  - Proportion of patients proceeding to HSCT following treatment
  - Feasibility and safety of rapid taper of immune suppression for subset of HSCT patients
  - PK of blinatumomab

ALL, acute lymphoblastic leukemia; CR, complete remission; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; PK, pharmacokinetics.

NCT02101853. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02101853. November 27, 2018.

A Phase 3, Open-Label, Multicenter, Randomized Controlled Study in Patients With R/R ALL

Pediatric Patients With First Relapse B-Cell Precursor ALL



Primary endpoint

- Disease-free survival

Secondary endpoint

- Overall survival

Other endpoints:

- MRD positivity
- CR
- MRD negativity
- Number of patients proceeding to alloHSCT
- PK

ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; cIV, continuous intravenous; CR, complete remission; HR, high-risk; IR, intermediate-risk; LR, low-risk; MRD, minimal residual disease; PK, pharmacokinetics; R/R, relapsed/refractory.

NCT02101853. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02101853. Accessed November 27, 2018.

Key Eligibility Criteria for Enrolled Patients

Inclusion criteria

- First relapse B-cell precursor ALL without prior stem cell transplant or rescue
- Patients who relapsed on frontline therapy and have recovered from acute toxic effects
- No prior treatment with blinatumomab
- GFR ≥ 70 mL/min/1.73 m^2
- Age > 1 year and < 30 years at the time of informed consent/assent

Exclusion criteria

- Philadelphia chromosome/BCR-ABL1 positive ALL
- Burkitt leukemia/lymphoma or mature B-cell leukemia
- Patients with T-lymphoblastic leukemia/lymphoma and B-lymphoblastic lymphoma
- Patients with pre-existing significant CNS pathology

ALL, acute lymphoblastic leukemia; *BCR-ABL*, breakpoint cluster region–Abelson murine leukemia viral oncogene homolog fusion gene; CNS, central nervous system; GFR, glomerular filtration rate.

NCT02101853. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02101853. Accessed November 27, 2018.

Next Steps and Timelines

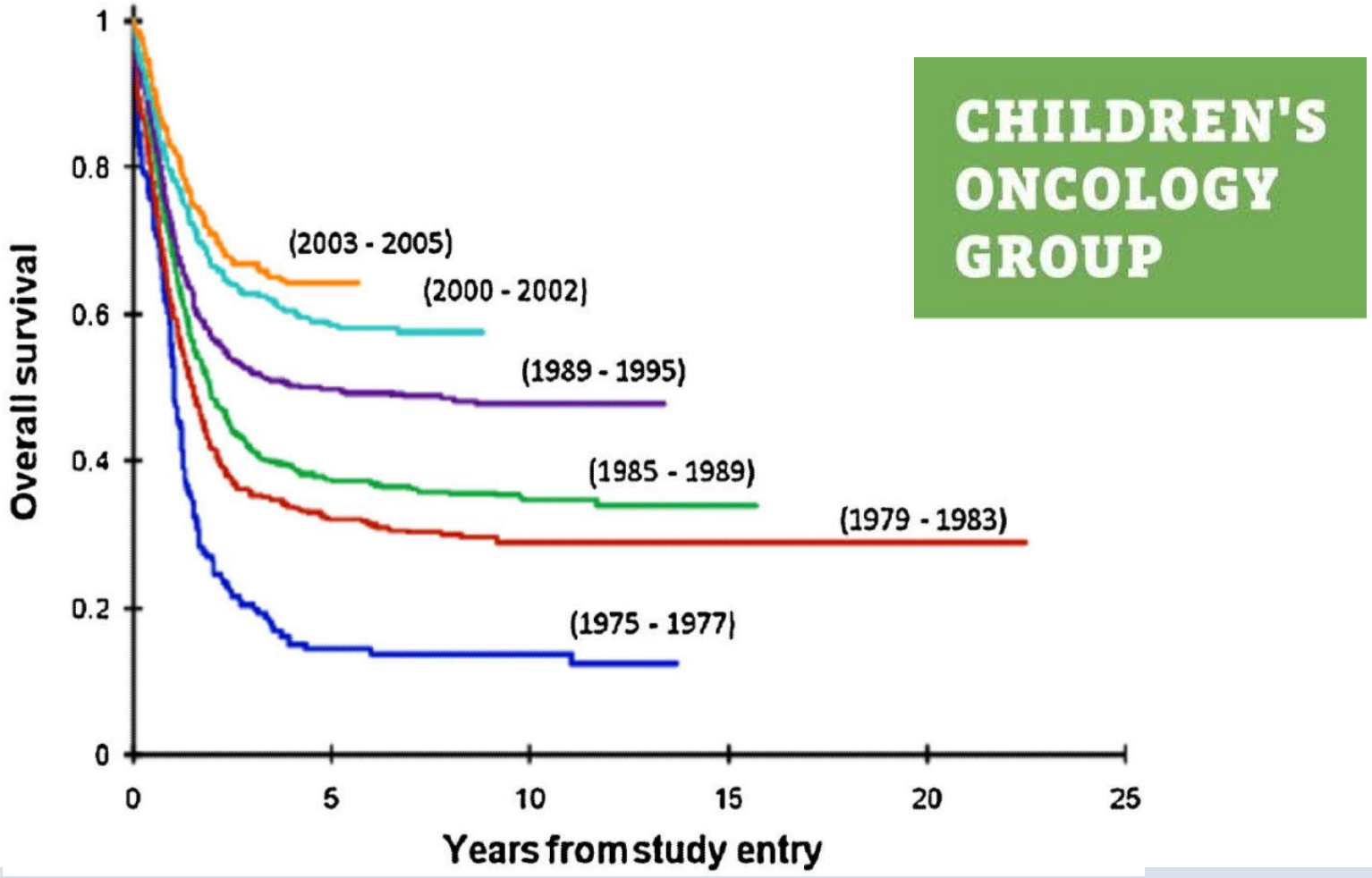
- Estimated enrollment: 598 patients

Actual Study Start Date:	Estimated Primary Completion Date:
8 December 2014	31 March 2022

NCT02101853. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02101853. Accessed November 27, 2018.

Acute myeloid leukemia

Overall Survival in Childhood AML has improved over the last 40 years



Gamis AS et al, Pediatr Blood Cancer, 2013.

Cytogenetic Study

- Cytogenetic abnormalities found in 70-80% of children with AML

- The most frequent chromosomal abnormalities
  - t(8;21)(q22;q22)
  - inv(16)(p13.1q22)

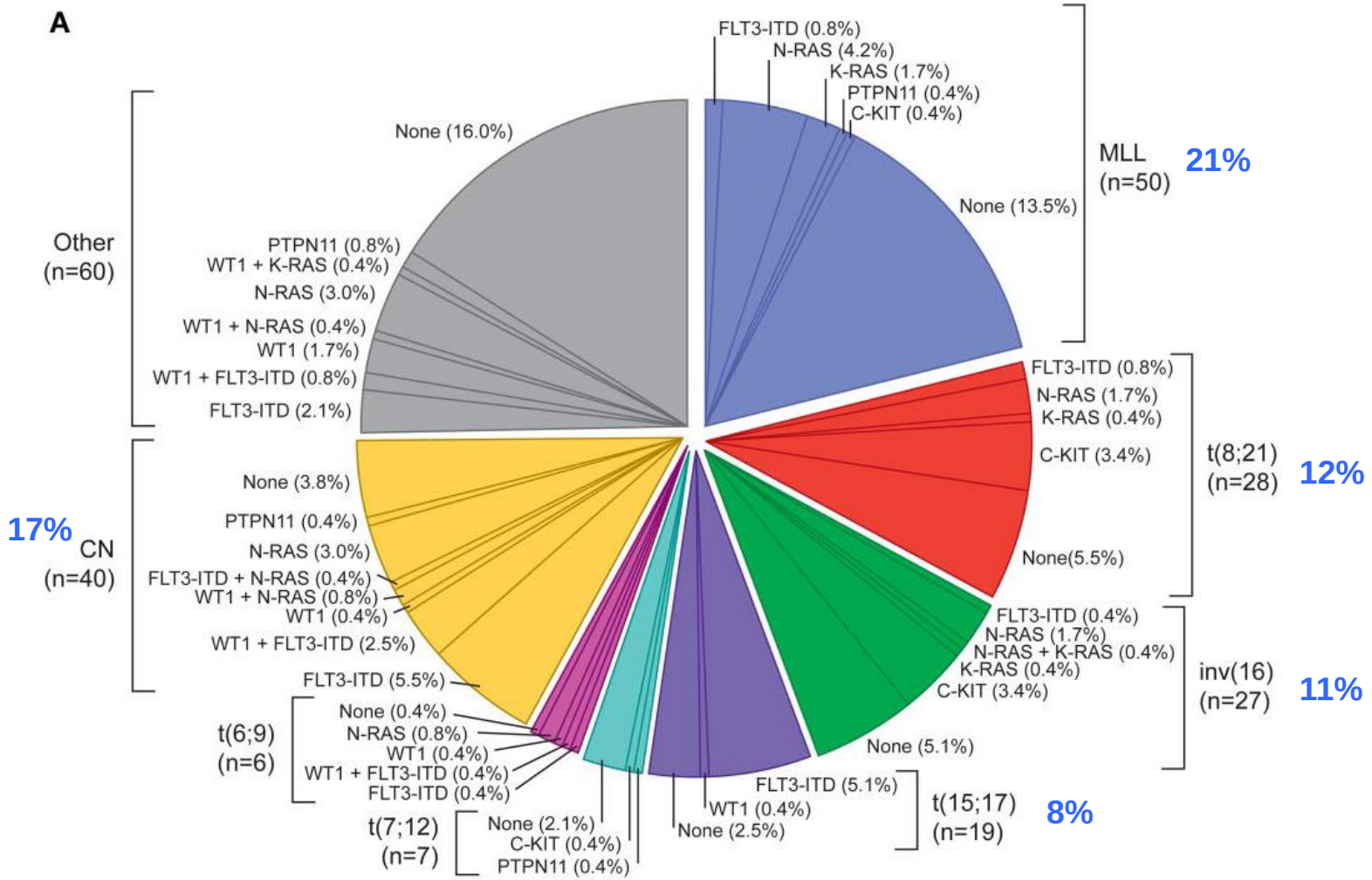
  CBF-AML

  - t(15;17)(q22;q21)/*PML-RARA*
  - 11q23/MLL-rearranged abnormalities

  50% of pediatric AML

- Cytogenetic abnormalities strongly correlate with age
  - *MLL*-rearranged AML : ***infants***
  - CBF-AML : ***older children***

Molecular and Cytogenetic Aberrations in Pediatric AML



Creutzig U et al, Blood, 2012

AML and risk classification

Favorable risk

- Core binding factor AML
- Nucleophosmin (*NPM1*) mutations
- *CEBPα* mutations

Unfavorable risk

- Chromosome 3 (inv(3)(q21;q26), t(3;3)(q21;q26)), 5 (monosomy 5 and del(5q)) or 7(monosomy 7) abnormalities
- FMS-like tyrosine kinase 3 receptor–internal tandem duplication (*FLT3-ITD*)
- *MLL* gene rearrangements
- t(8;16) (*MYST3-CREBBP*)

Risk-based strategy in AML treatment

Study	Low/standard risk	High risk
AIEOP	CBF leukemia and CR after induction 1 course	otherwise
AML BFM 2004	AML FAB M1/2 and Auer rods, M3, M4eo, t(15;17), t(8;21) inv(16) and CR at day 15 **No *FLT3/ITD*+**	*FLT3/ITD*+ **OR** otherwise
COG AAML 1031	inv(16)/t(16;16) or t(8;21) cytogenetic features or *NPM* or *CEBPα* mutation regardless of monosomy 7, monosomy 5, or del5q and regardless of MRD at end of induction I **OR** negative MRD (< 0.1%) at end of induction I and no high risk disease features **No *FLT3/ITD*+ with high allelic ratio > 0.4**	*FLT3/ITD*+ with high allelic ratio > 0.4 (HR *FLT3/ITD*+) regardless of low risk features **OR** presence of monosomy 7, monosomy 5, or del5q, without inv(16)/t(16;16) or t(8;21) cytogenetics or *NPM* or *CEBPα* mutations **OR** AML without inv(16)/t(16;16), t(8;21), *NPM*, *CEBPα* mutations, monosomy 7, monosomy 5, del5q, or HR *FLT3/ITD*+, but with evidence of residual AML (MRD ≥ 0.1%) at end of Induction I.

Role of MRD in AML

- Contrary to ALL, role of MRD is still controversial
- Not refine the prognosis Karol SE et al. Br J Haematol. 2015 Jan;168(1):94-101

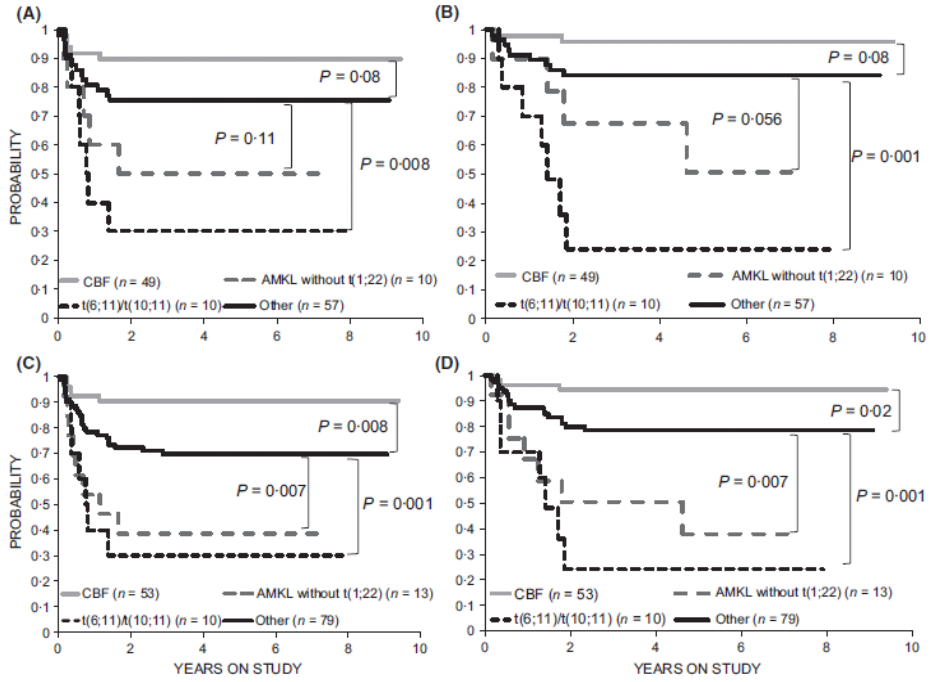


Fig 1. Kaplan-Meyer curves for minimal residual disease–negative patients. (A) Disease-free survival and (B) overall survival after induction I. (C) Disease-free survival and (D) overall survival after induction II. AMKL, acute megakaryoblastic leukaemia; CBF, core-binding factor. Other, patients not in the other 3 groups.

Karol SE et al. ibid

Acute Myeloid Leukemia (AML): arising from clonal proliferation of haematopoietic stem or progenitor *cells*[1]

➔ Most common acute leukaemia in adults - estimated **20,830** new diagnoses and > **10,000** deaths in 2015[1]

Biomarkers associated with AML[1]

- KIT
- FLT3-ITD
- NPM1
- CEBPA

Value of FoundationOne Heme in AML:

- Interrogates **diverse classes of genomic alterations** in a **broad set of clinically-relevant genes,** including **gene fusions**[2]
- Detects gene alterations which may **indicate treatment options** (i.e. midostaurin targeting *FLT3*)[2,3]
- Results may suggest eligibility for **enrolment in open clinical trials**[2]
- Genomic sequencing partner for the Leukaemia and Lymphoma Society's Beat AML Master Protocol Trial[4]

1. De Kouchkovsky, I. and Abdul-Hay, M. (2016) *Blood Cancer J* 6:e441; 2. Foundation Medicine, Inc. (2017) FoundationOne®Heme technical information and test overview. Information accessed April 2017 from https://www.foundationmedicine.com/genomic-testing/foundation-one-heme; 3. Stone, R.M. et al. (2017) N Engl J Med 377:454-64; 4. Leukemia and Lymphoma Society. (2016) Press release accessed March 2018 from https://www.lls.org/lls-us-hq/news/the-leukemia-lymphoma-society-launches-groundbreaking-precision-medicine-approach-to-treat-acute-myeloid-leukemia-one-of-the-deadliest-blood-cancers.

FMS-like tyrosine kinase 3 receptor–internal tandem duplication (*FLT3-ITD*) mutation

- Poor prognosis
- More common in adult
- Associate with specific translocation:

  t(6;9) (*DEK-NUP214*) and t(5;11)(*NUP98/NSD1*).
- BFM and COG classify as a high risk regardless of favorable features
- Multi-kinase inhibitor might be beneficial

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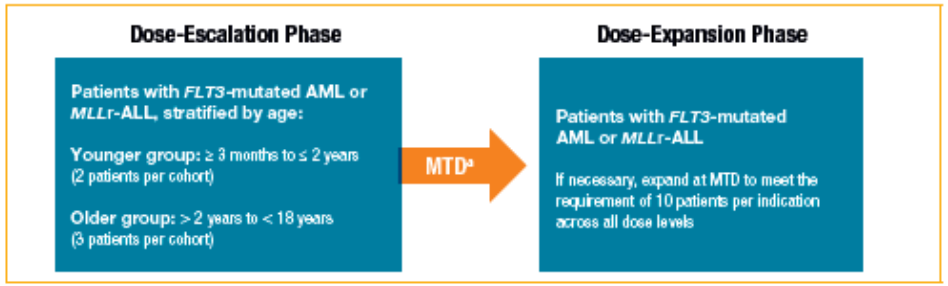
A Phase 1/2, Open-Label, Dose-Escalation Study of Midostaurin in Pediatric Patients With Relapsed or Refractory Acute Leukemia: Final Results of Study ITCC-024 (CPKC412A2114)

C. Michel Zwaan,[1] Stefan Söderhäll,[2] Benoit Brethon,[3] Matteo Luciani,[4] Carmelo Rizzari,[5] David Sternberg,[6] Emmanuelle Besse,[7] Catherine Dutreix,[8] Franca Fagioli,[9] Phoenix Ho,[10] Carlo Dufour,[11] Rob Pieters[1,12]

[1]Erasmus MC/Sophia Children's Hospital, Rotterdam, the Netherlands; [2]Karolinska Institutet, Stockholm, Sweden; [3]Hôpital Robert-Debré, Paris, France; [4]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy; [5]Fondazione MBBM, Azienda Ospedaliera San Gerardo, Monza, Italy; [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [7]Novartis France, Paris, France; [8]Novartis Oncology, Basel, Switzerland; [9]Pediatric Onco-Hematology, Stem Cell Transplantation and Cellular Therapy Division, A.O.U. Città della Salute e della Scienza di Torino, Ospedale Infantile Regina Margherita, Torino, Italy; [10]Children's Hospital, Seattle, WA; [11]Hematology Unit, IRCCS Instituto Giannina Gaslini, Genova, Italy; [12]Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

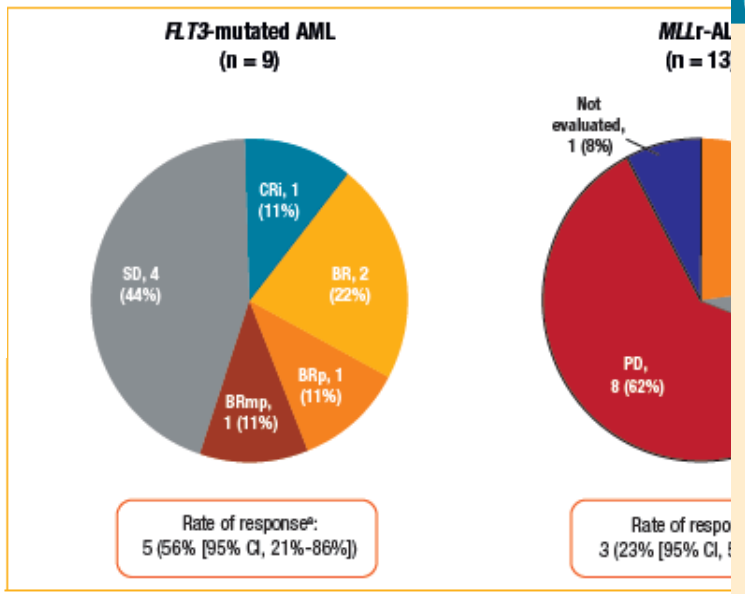
Figure 1. Study Design



[a] If an MTD could not be established within an age group because escalation to a dose > 60 mg/m² was required, then the MTD was not reached, and the

Doses were escalated sequentially to the maximum dose or until stopping rules were met due to dose-limiting toxicity (DLT; starting dose, 30 mg/m² BID; maximum dose, 60 mg/m² BID)

Figure 4. Best Overall Response



BR, bone marrow blast response; BRm, minor blast response; BRmp, minor peripheral blood blast response; CR, complete remis
leukemia-free state; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Best clinical response includes LFS, CR, CRi, PR, BR, BRm, BRp, and BRmp.

CONCLUSIONS

- This study was the first to evaluate the efficacy, safety, and PK of oral midostaurin solution in children
- According to the BLRM, the 60 mg/m² BID dose satisfied the criteria for a tolerable dose in each age group
  - The study design (and patient recruitment), however, did not allow dosing beyond this dose; hence, a true MTD beyond 60 mg/m² BID could not be determined
- The RDE of midostaurin for future studies using combination chemotherapy in the pediatric acute leukemia setting is 30 mg/m² BID due to a higher frequency of grade 3/4 AEs in the 60 mg/m² BID dose group and known toxicities of existing standard pediatric AML regimens
- Single-agent midostaurin showed only limited clinical activity in pediatric patients with *FLT3*-mutated AML or *MLL*r-ALL, indicating that further clinical evaluation in children should be in combination with established chemotherapeutic regimens
- In general, the safety profile of single-agent midostaurin in this indication was consistent with that observed in previous studies of this drug in adult patients with AML[6,7] and with the overall safety profile in pediatric patients with relapsed or refractory acute leukemia

Management of chronic myeloid leukemia in children and adolescents: Recommendations from the Children's Oncology Group CML Working Group

Pediatr Blood Cancer. 2019;66:e27827.
https://doi.org/10.1002/pbc.27827

Uma Athale[1] | Nobuko Hijiya[2] | Briana C. Patterson[3,4] | John Bergsagel[4] | Jeffrey R. Andolina[5] | Henrique Bittencourt[6] | Kirk R. Schultz[7] | Michael J. Burke[8] | Michele S. Redell[9] | E. Anders Kolb[10] | Donna L. Johnston[11]

blood® 30 MAY 2019 | VOLUME 133, NUMBER 22

How I treat chronic myeloid leukemia in children and adolescents

Nobuko Hijiya[1] and Meinolf Suttorp[2]

[1]Department of Pediatrics, Columbia University Medical Center, New York, NY; and [2]Medical Faculty, Pediatric Hematology and Oncology, Technical University Dresden, Dresden, Germany

Table 1. Recommended TKI doses approved for children and proportion of patients achieving MMR

Recommended TKI dose for CML-CP treatment	Proportion of pediatric patients with CML-CP treated with first-line TKI who achieved MMR				
	Patients, no.	12 mo	18 mo	24 mo	References
Imatinib					
340 mg/m²/dose, once daily	51	NR	NR	NR	16
300 mg/m²/dose, once daily	140	42%*	59%*	69%*	14
260 mg/m²/dose, once daily	44	31%†	55%*	60%*	15
Nilotinib					
230 mg/m²/dose, twice daily	25	64%*	68%§	NR	18
Dasatinib					
60 mg/m²/dose, once daily	84	52%*	65%*	70%*	17

NR, not reported.

*Results are reported as a cumulative rate at the indicated time point.

†Results are reported as a response rate at the indicated time point.

§Cumulative response rate by data cutoff at 16.6 mo.

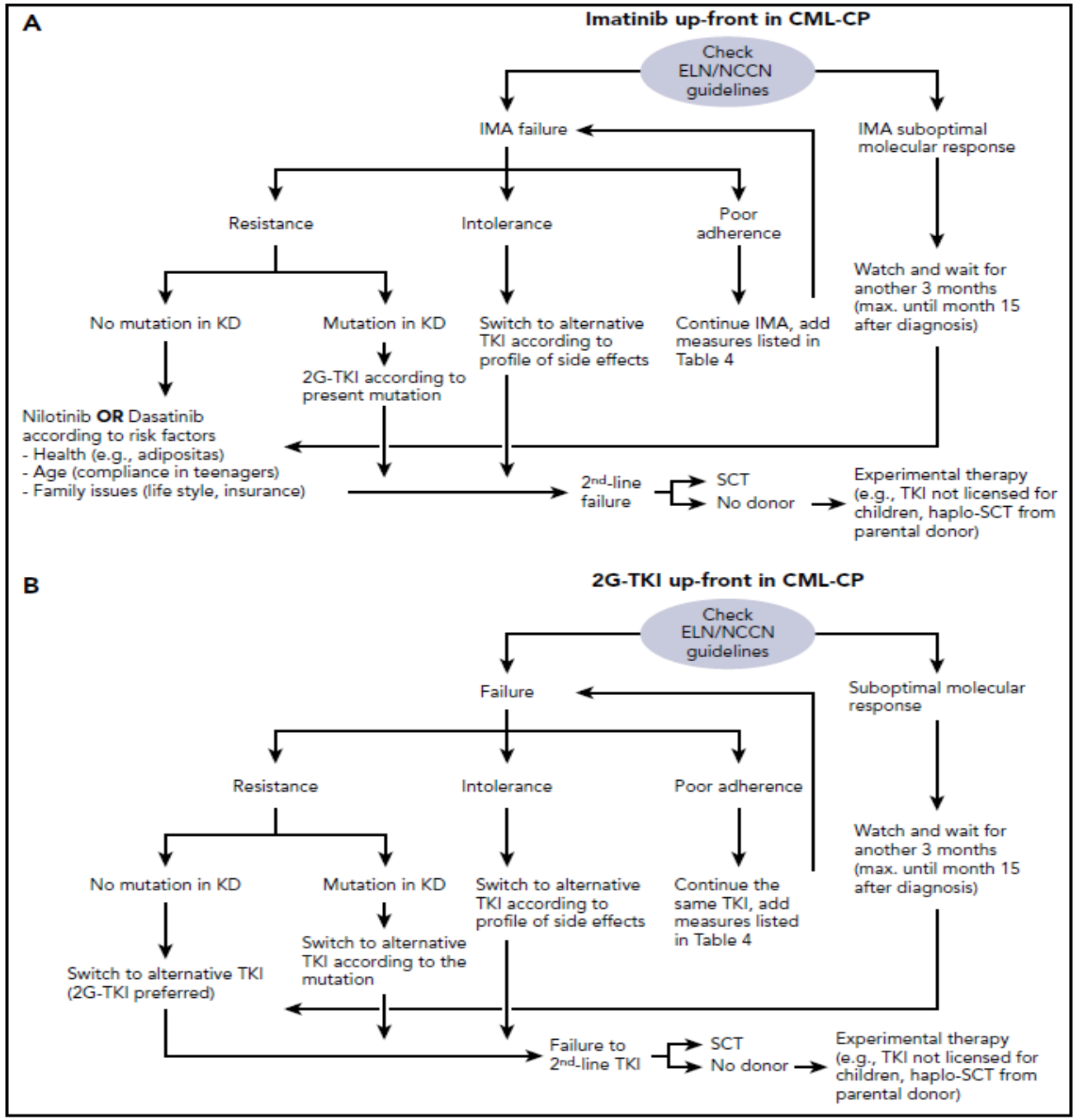


Table 5. Recommended monitoring for endocrine toxicities in children and adolescents with CML on TKI

Parameter	Potential changes	Recommended monitoring	Management
Growth	Growth attenuation	Accurate height and weight at each visit	Referral to endocrinologist for possible GH stimulation testing
		Close monitoring of growth velocity	
		Calculate prospective height from mid parental height	
Bone	Dysregulation of bone remodeling	DEXA scan if radiograph indicates low bone mineral density or unprovoked fractures occur	Referral to endocrinologist
	Altered calcium, phosphate, and vitamin D metabolism		
Thyroid	Hypothyroidism	TSH and free T4 levels every 4-6 wk after initiation of therapy; every 6-12 mo thereafter or with symptoms suggestive of hypo- or hyperthyroidism	Referral to endocrinologist and consider thyroid hormone replacement therapy
	Hyperthyroidism		
Gonadal function	Delayed puberty	Accurate Tanner staging at reasonable intervals	Referral to endocrinologist for delayed puberty
	Gonadal dysfunction	Check gonadotropins and sex steroids for delayed puberty or gonadal dysfunction	Offer sperm cryopreservation to pubertal males
	Potentially decreased fertility		Fertility preservation before therapy may be discussed
Pregnancy outcome	Fetal abnormalities	Pregnancy test at initiation of therapy for female patients of childbearing age	Recommend counseling on contraceptives for female patients of childbearing age. Efforts should be made to increase the chance of TKI discontinuation to facilitate safe pregnancies in adult life.

GH, growth hormone; DEXA, dual-energy x-ray absorptiometry; T4, thyroxine TSH, thyroid-stimulating hormone.

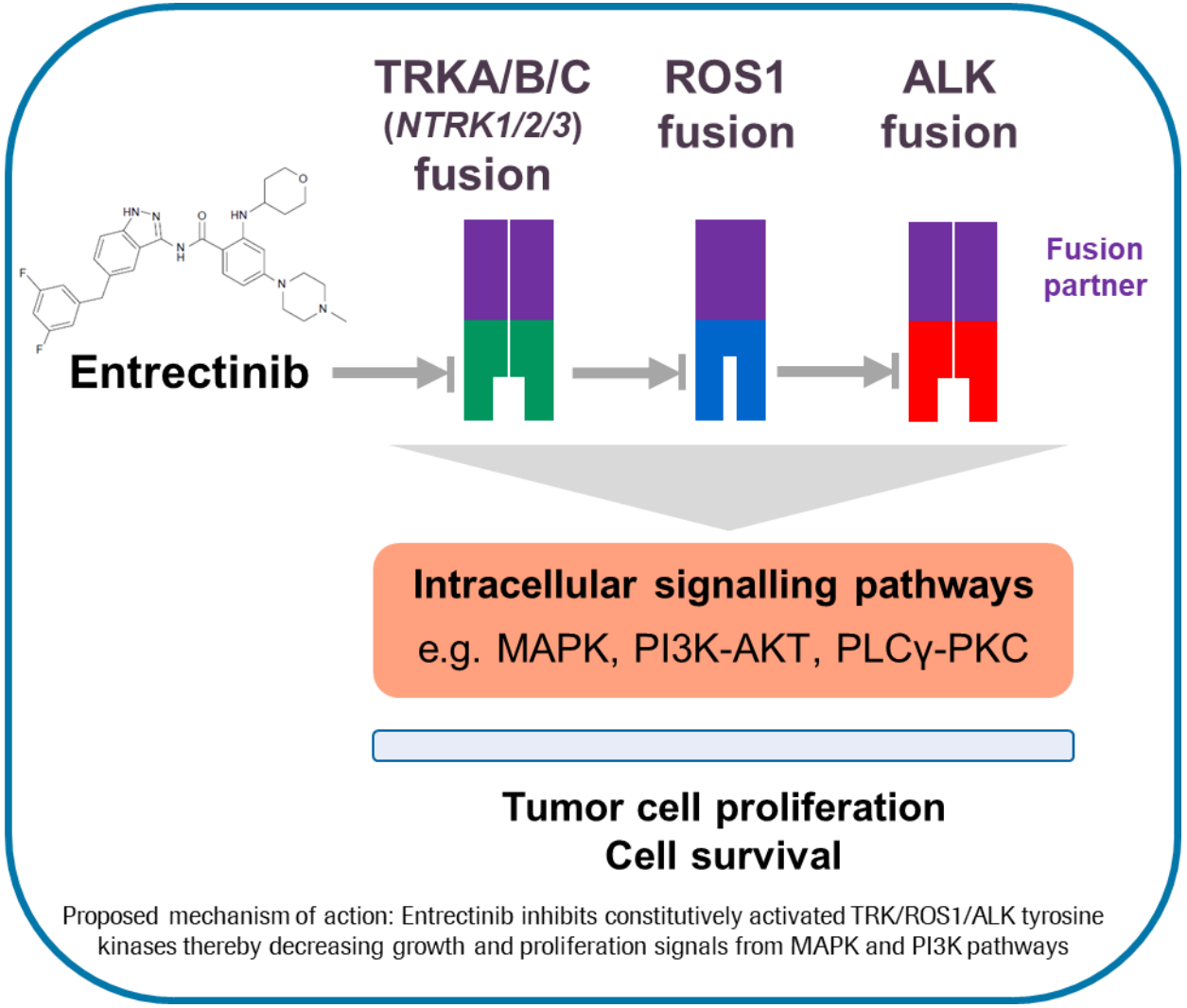
Phase 1/1B trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumors including central nervous system (CNS) tumors

Authors: Giles W. Robinson[1], Amar Gajjar[1], Karen Gauvain[2], Ellen M. Basu[3], Margaret E. Macy[4], Luke Maese[5], Amit J. Sabnis[6], Jennifer Foster[7], Suzanne Shusterman[8], Janet Yoon[9], Brian Weiss[10], Mohamed S. Abdelbaki[11], Mufiza Farid-Kapadia[12], Georgina Meneses-Lorente[13], Alison Cardenas[14], Katherine E. Hutchinson[14], Guillaume Bergthold[15], Edna Chow Maneval[16], Elizabeth Fox[17], Ami V. Desai[18]

1. St. Jude Children's Research Hospital, Memphis, TN; 2. Washington University School of Medicine, St. Louis, MO; 3. Memorial Sloan Kettering Cancer Center, New York, NY; 4. Children's Hospital Colorado, Aurora, CO; 5. University of Utah/Huntsman Cancer Institute, Primary Children's Hospital, Salt Lake City, UT 6. University of California San Francisco, Benioff Children's Hospital, San Francisco, CA; 7. Texas Children's Hospital, Houston, TX; 8. Dana Farber Cancer Institute, Boston Children's Cancer and Blood Disorders Center, Boston, MA; 9. Rady Children's Hospital, San Diego, CA; 10. Cincinnati Children's Hospital Medical Center, Cincinnati, OH; 11. Nationwide Children's Hospital, Columbus, OH; 12. F. Hoffmann-La Roche Limited, Mississauga, ON, Canada; 13. Roche Products Limited, Welwyn Garden City, UK; 14. Genentech, South San Francisco, CA; 15. F. Hoffmann-La Roche, Basel, Switzerland; 16. Ignyta, Inc, San Diego, CA; 17. Children's Hospital of Philadelphia, Philadelphia, PA; 18. University of Chicago Medical Center, Chicago, IL, USA

Background

- Fusions and alterations in the ***NTRK1/2/3***, ***ROS1*** and ***ALK*** genes act as drivers of certain cancers[1–3]
- Entrectinib is an oral, potent inhibitor of **TRKA/B/C, ROS1**, and **ALK** proteins that also **penetrates into the CNS** to reach tumors in the brain and spine[4,5]
- Clinical activity was seen in adult solid tumor patients with target gene rearrangements[6,7] even with **brain metastases** or when the tumor was **primarily located in the brain**[8]
- A variety of pediatric cancers harbor mutations and fusions in *NTRK1/2/3, ROS1* and *ALK*:[9]
  - **infantile fibrosarcomas** (*NTRK*), **pediatric high grade gliomas** (*NTRK, ROS1, ALK*), **neuroblastoma** (*ALK*), **inflammatory myofibroblastic tumor** (*ALK, ROS1*)
  - while rare, this list is growing as mutations and fusions are detectable with next-generation sequencing
- Here, we report on the activity of **entrectinib in children** with recurrent or refractory solid tumors including primary CNS tumors



Proposed mechanism of action: Entrectinib inhibits constitutively activated TRK/ROS1/ALK tyrosine kinases thereby decreasing growth and proliferation signals from MAPK and PI3K pathways

ALK, anaplastic lymphoma kinase; CNS, central nervous system; *NTRK*, neurotrophic tropomyosin receptor kinase; TRKA, tropomyosin receptor kinase A

1. Vaishnavi, et al. Cancer Discov 2014; 2. Lin, et al. J Thorac Oncol 2017; 3. Hofman. Cancers 2017; 4. Menichincheri, et al. J Med Chem 2016
5. Ardini, et al. Mol Cancer Ther 2016; 6. Doebele, et al. J Thorac Oncl 2018; 7. Demetri, et al. Ann Oncol 2018;
8. Drilon, et al. Cancer Discov 2017; 9. Okaruma, et al. JCO Precis Oncol. 2018

STARTRK-NG (RXDX-101-03) study design

Pediatric and adolescent patients
Total enrolled (n=29); data cut-off October 31, 2018

Eligibility criteria
- Birth–21 years
- Relapsed or refractory solid tumors (including primary CNS tumors)
- Karnofsky or Lansky score ≥60%, minimum life expectancy ≥4 weeks
- Measurable or evaluable disease (dose escalation), measurable disease (dose expansion)
- With or without target molecular aberrations in *NTRK1/2/3*, *ROS1* or *ALK*

Treatment
- Oral administration
- QD, 28-day cycles

Primary endpoints*
- MTD, RP2D

Key secondary endpoints
- Safety and tolerability
- Plasma PK: C_{max}, CSS, $T_{1/2}$, AUC
- Anti-tumor activity: ORR, PFS

Dose-finding phase 1 (N=16) in patients with relapsed or refractory solid tumors
Dose level 250–750mg/m²

Sequential assignment to escalating doses of entrectinib (3+3 design), initially dosed by BSA

- 250mg/m² (n=3)
- 400mg/m² (n=3)
- 550mg/m² (n=7)
- 750mg/m² (n=3)

Basket trial phase 1b (N=13)
Dose level 550mg/m² (n=7) OR 400mg/m² in patients unable to swallow intact capsules (n=6)

- Primary CNS tumors (n=6)
- Neuroblastoma (n=3)
- Extracranial solid tumors (n=4)

*Investigator assessed. AUC, area under curve; BSA, body surface area; CSS, concentration at steady state; MTD, maximum tolerated dose; NG, next generation; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; RP2D, recommended phase II dose; STARTRK-NG, **S**tudies of **T**umour **A**lterations **R**esponsive to **T**argeting **R**eceptor **K**inases – **N**ext **G**eneration

STARTRK-NG baseline patient characteristics

Characteristic		Phase 1 dose-escalation (n=16)				Phase 1b (n=13)	All patients (n=29)
		250 mg/m² (n=3)	400 mg/m² (n=3)	550 mg/m² (n=7)	750 mg/m² (n=3)		
Median age	**Years (range)**	9 (7–13)	15 (6–20)	7 (6–17)	10 (4–16)	5 (0–19)	**7 (0–20)**
Sex, n (%)	**Male**	2 (66.7)	1 (33.3)	5 (71.4)	2 (66.7)	5 (38.5)	**15 (51.7)**
	Female	1 (33.3)	2 (66.7)	2 (28.6)	1 (33.3)	8 (61.5)	**14 (48.3)**
Race, n (%)	**White**	2 (66.7)	2 (66.7)	6 (85.7)	3 (100.0)	13 (100.0)	**26 (89.7)**
	Black/African American	1 (33.3)	1 (33.3)	1 (14.3)	0	0	**3 (10.3)**
Karnofsky/Lansky score, n (%)*	**100**	3 (100.0)	1 (33.3)	1 (16.7)	0	6 (46.2)	**11 (39.3)**
	90	0	1 (33.3)	4 (66.7)	2 (66.7)	3 (23.1)	**10 (35.7)**
	80	0	1 (33.3)	0	1 (33.3)	3 (23.1)	**5 (17.9)**
	70	0	0	1 (16.7)	0	1 (7.7)	**2 (7.1)**
Prior systemic therapies, n (%)	**Chemotherapy**	3 (100.0)	3 (100.0)	5 (71.4)	3 (100.0)	10 (76.9)	**24 (82.8)**
	Immunotherapy	0	2 (66.7)	4 (57.1)	1 (33.3)	4 (30.8)	**11 (37.9)**
	Targeted therapy**	0	2 (66.7)	1 (14.3)	0	0	**3 (10.3)**
	Monoclonal antibody	0	3 (100.0)	2 (28.6)	3 (100.0)	3 (23.1)	**11 (37.9)**
	Radiation	3 (100.0)	3 (100.0)	5 (71.4)	2 (66.7)	9 (69.2)	**22 (75.9)**

Data cut-off: October 31, 2018 *n=28; one patient excluded from 550 mg/m² phase 1 dose level due to incorrect performance score scale for age; **prior treatment with approved or investigational TRK, ROS1, or ALK inhibitors were excluded

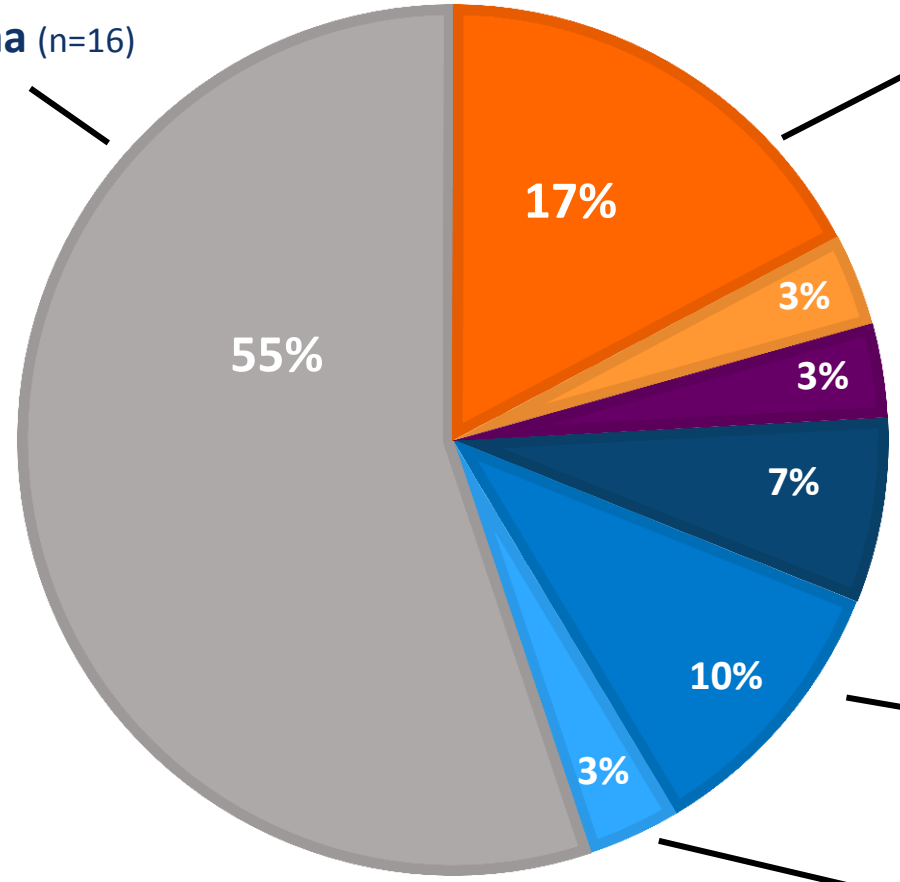
STARTRK-NG overall safety

- Most treatment-related AEs were Grade 1/2 (mild cytopenias and GI disturbances)
- Three dose-limiting toxicities (green) in the phase 1 study led to 550mg/m2 as the MTD/RP2D for phase 1b
  - were reversible upon dose interruption and/or reduction
- The treatment-related AE that continued to accumulate and result in dose reductions in the phase 1b study portion was weight gain
- There were no grade 5 treatment-related AEs

Most common (>10% Total) + any Grade 3/4 TRAE, n (%)	Phase 1 dose-escalation, mg/m² (n=16)								Phase 1b (n=13)		Total (n=29)		
	250 (n=3)		400 (n=3)		550 (n=7)		750 (n=3)						
	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	Any G
Any TRAE	3 (100)	0	2 (67)	1 (33)	7 (100)	0	1 (33)	2 (67)	11 (85)	0	**24 (83)**	**3 (10)**	**27 (93)**
Anemia	1 (33)	0	0	0	2 (29)	0	2 (67)	0	7 (54)	0	**12 (41)**	**0**	**12 (41)**
Blood creatinine increased	2 (67)	0	2 (67)	0	2 (29)*†	0	2 (67)†	0	4 (31)	0	**12 (41)†**	**0**	**12 (41)**
ALT increased	0	0	1 (33)	0	3 (43)	0	2 (67)	0	4 (31)	0	**10 (35)**	**0**	**10 (35)**
AST increased	2 (67)	0	2 (67)	0	1 (14)	0	2 (67)	0	3 (23)	0	**10 (35)**	**0**	**10 (35)**
Nausea	3 (100)	0	1 (33)	0	2 (29)	0	1 (33)	0	3 (23)	0	**10 (35)**	**0**	**10 (35)**
Neutrophil count decreased	0	0	0	1 (33)	1 (14)	0	0	1 (33)	2 (15)	3 (23)	**3 (10)**	**5 (17)**	**8 (28)**
White blood cell decreased	0	0	0	0	0	0	2 (67)	0	6 (46)	0	**8 (28)**	**0**	**8 (28)**
Weight increased	0	0	0	0	3 (43)†	0	1 (33)	0	4 (31)†	0	**8 (28)†**	**0**	**8 (28)**
Constipation	1 (33)	0	0	0	3 (43)	0	1 (33)	0	1 (8)	0	**6 (21)**	**0**	**6 (21)**
Dysgeusia	0	0	1 (33)	0	2 (29)	0	2 (67)*†	0	1 (8)	0	**6 (21)†**	**0**	**6 (21)**
Flatulence	0	0	0	0	2 (29)	0	2 (67)	0	1 (8)	0	**5 (17)**	**0**	**5 (17)**
Diarrhea	0	0	1 (33)	0	2 (29)	0	0	0	1 (8)	0	**4 (14)**	**0**	**4 (14)**
Somnolence	0	0	0	0	0	0	1 (33)	0	3 (23)	0	**4 (14)**	**0**	**4 (14)**
Hypernatremia	1 (33)	0	0	0	0	0	1 (33)	0	2 (15)	0	**4 (14)**	**0**	**4 (14)**
Muscular weakness	1 (33)	0	0	0	1 (14)	0	0	0	2 (15)	0	**4 (14)**	**0**	**4 (14)**
Platelet count decreased	0	0	0	0	0	0	1 (33)	1 (33)	1 (8)	0	**2 (7)**	**1 (3)**	**3 (10)**
Dyspnea	0	0	0	0	0	0	0	1 (33)	0	0	**0**	**1 (3)**	**1 (3)**
Pulmonary edema	0	0	0	0	0	0	0	1 (33)*†	0	0	**0**	**1 (3)**	**1 (3)**

*DLTs: 1 patient phase 1 550mg/m² Grade 2 increased creatinine > 7 days; 1 patient phase 1 750mg/m² Grade 2 dysgeusia + fatigue >7 days; 1 patient 750mg/m² Grade 3 pulmonary edema; †TRAEs leading to dose reduction
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event. Data relate to those AEs >10% population

Baseline characteristics by tumor type and target gene fusion



Neuroblastoma (n=16)
1 x ***ALK*** **F1174L**
15 x no *ALK/ROS1/NTRK* aberrations or unknown

High-grade glioma (n=5)
1 x ***EEF1G-ROS1***
1 x ***GOPC-ROS1***
1 x ***TPR-NTRK1***
1 x ***EML1-NTRK2***
1 x ***ETV6-NTRK3***

CNS embryonal tumor (n=1)
1 x ***KANK1-NTRK2***

Melanoma (n=1)
1 x ***ETV6-NTRK3***

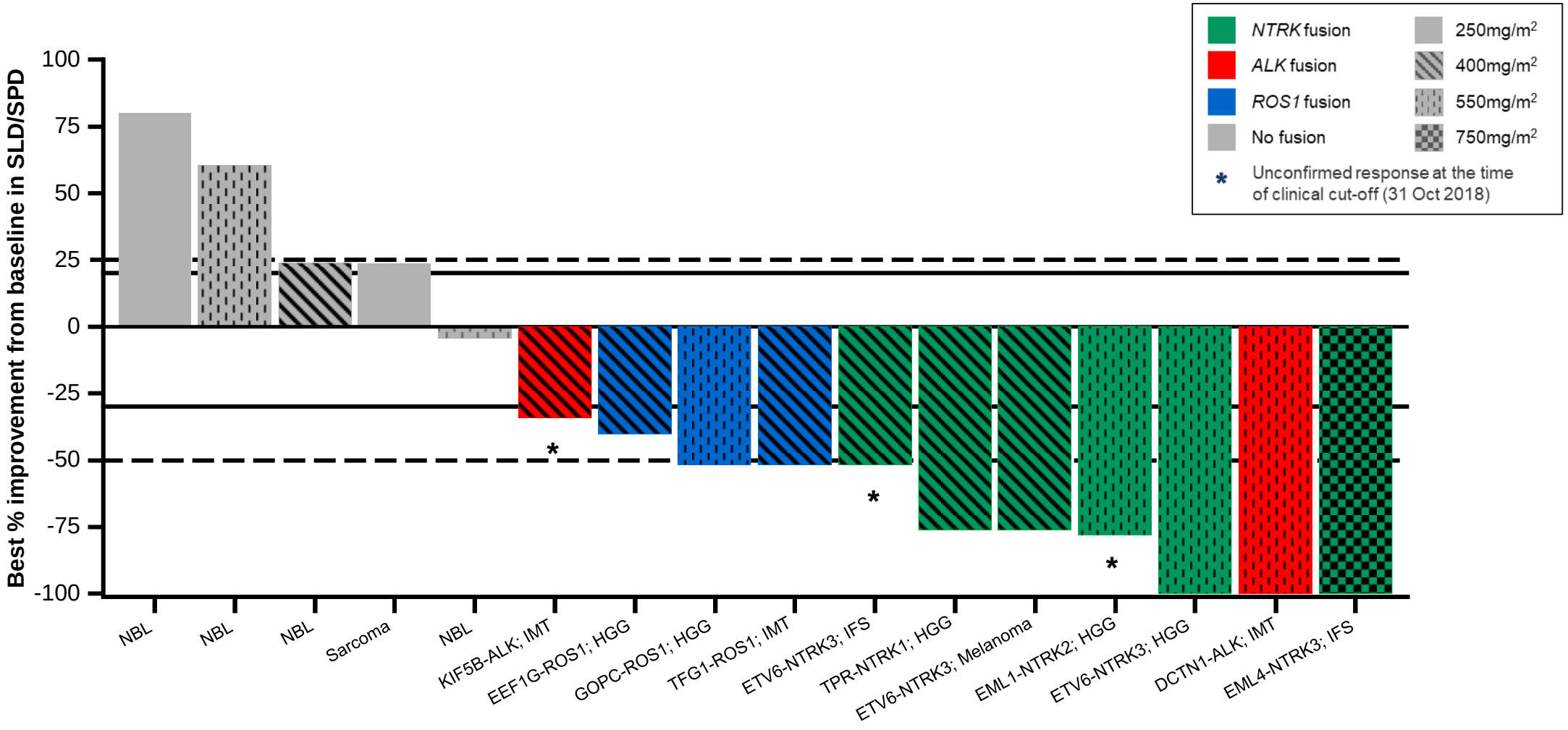
Sarcoma: IFS (n=2)
1 x ***ETV6-NTRK3***
1 x ***EML4-NTRK3***

Sarcoma: IMT (n=3)
1 x ***DCTN1-ALK***
1 x ***KIF5B-ALK***
1 x ***TFG1-ROS1***

Sarcoma: synovial (n=1)
None

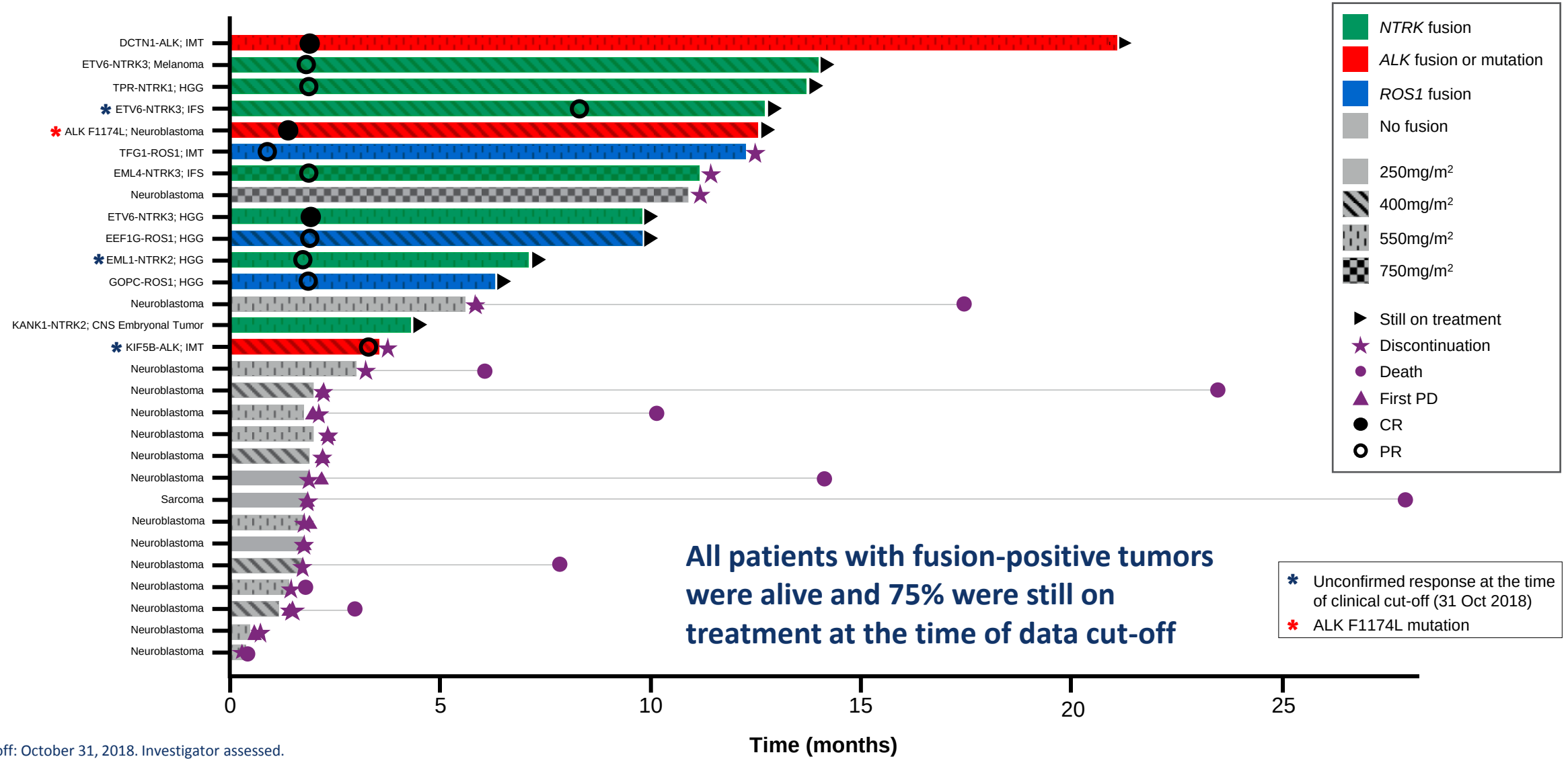
Data cut-off: October 31, 2018
IFS, infantile fibrosarcoma; IMT, inflammatory myofibroblastic tumor

Entrectinib in pediatric solid tumors: individual patient responses



Data cut-off: October 31, 2018. Investigator assessed
Includes only patients with measureable disease at baseline and tumor assessment

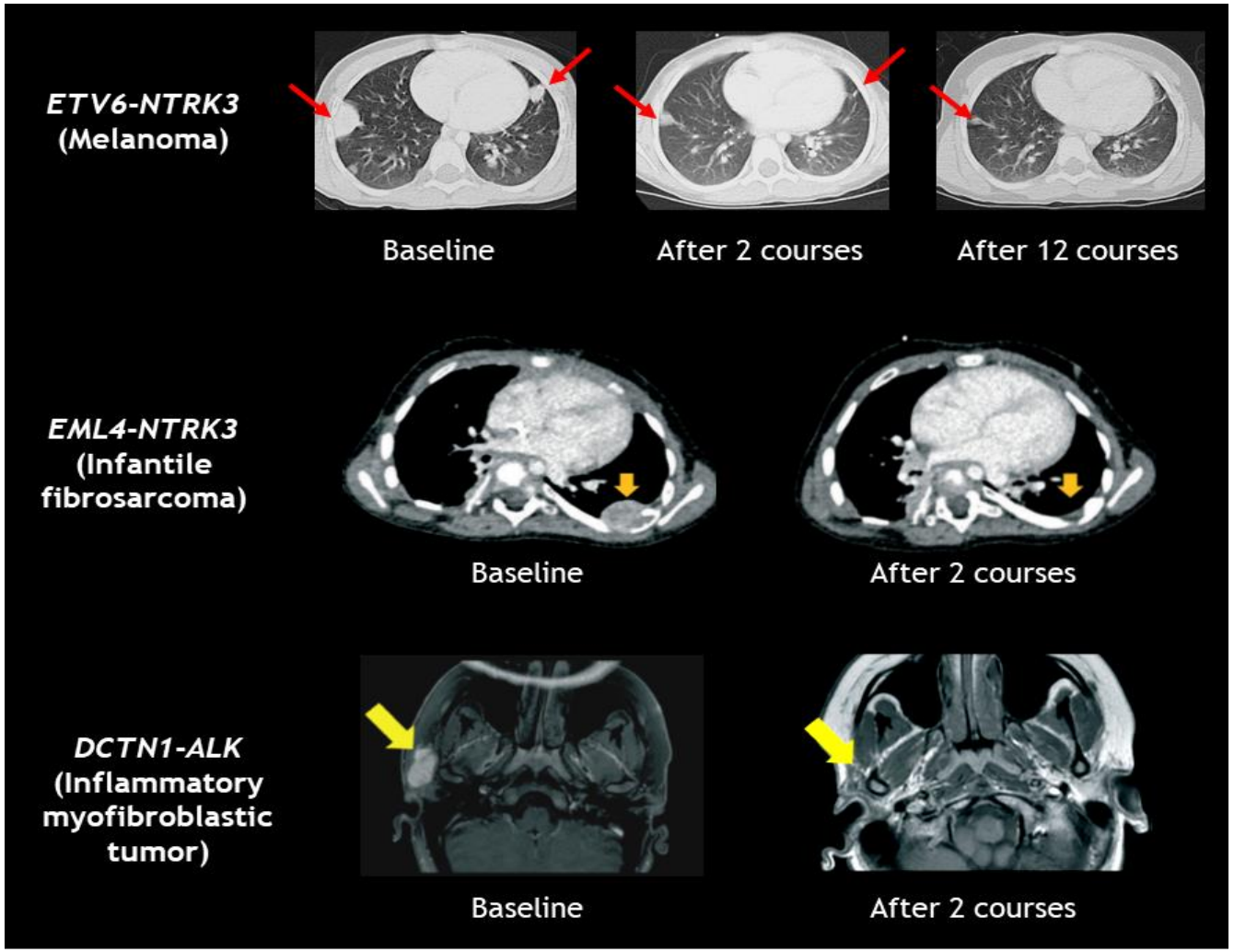
Entrectinib in pediatric solid tumors: duration of response



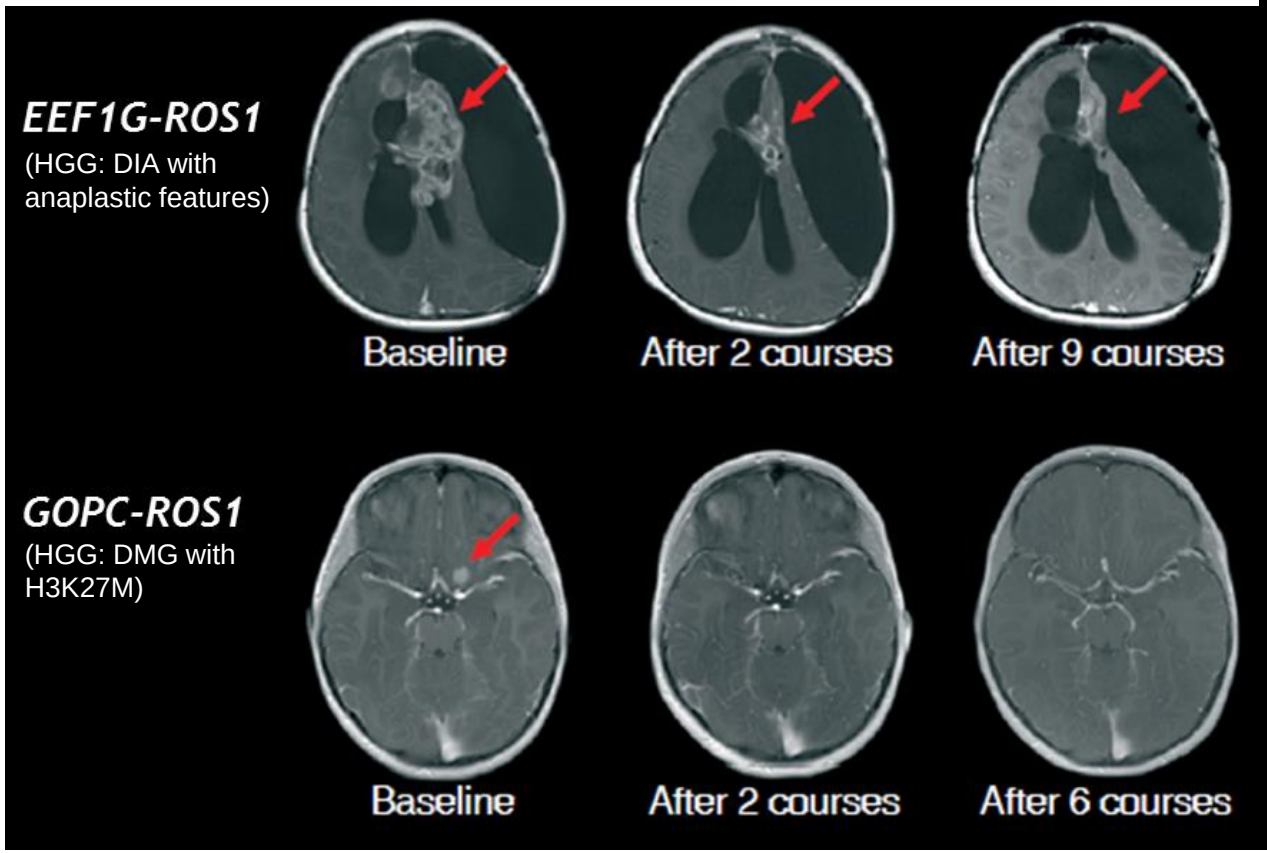
Data cut-off: October 31, 2018. Investigator assessed.
Overall duration of response: median not estimable (95% CI: NE; range 1.8 to 15.7 months). Median time to response was 57d (30–58d)
Median duration of therapy was 85 days (6–592 days) for all patients; 56 days (6–338 days) for non-responders; and 281 days (56–592 days) for responders

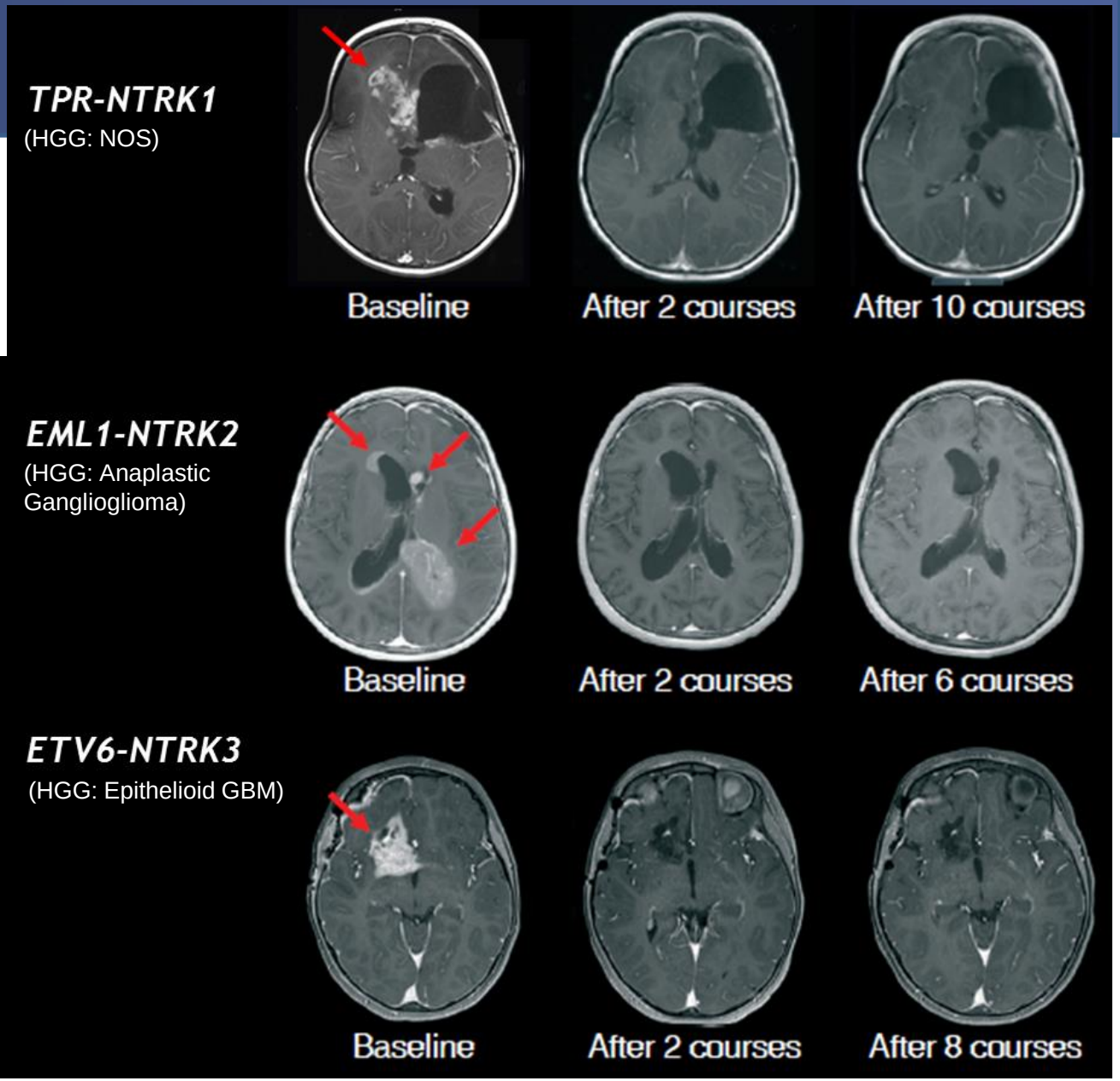
All patients (N=29)

solid tumors

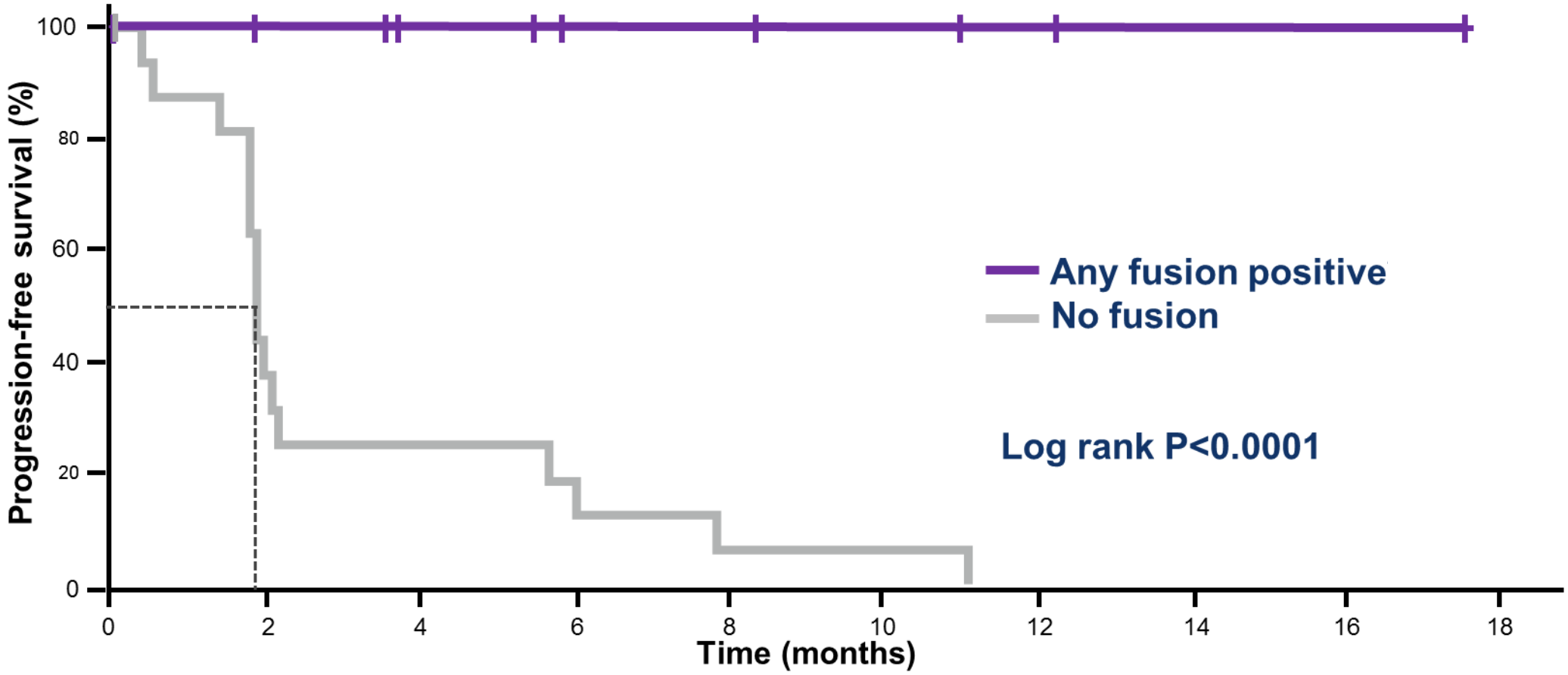


Measureable and durable responses in CNS tumors





PFS: patients with and without gene fusions



No. at Risk								
Any fusion positive	12	10	8	6	6	3	2	1	1
No fusion	17	6	4	3	1	1			

Data cut-off: October 31, 2018. Investigator assessed

A NBL patient with ALK F1174L point mutation was censored from day 1 as no further tumor assessment as per RECIST/RANO has been recorded. Patient has been assessed as per Curie criteria

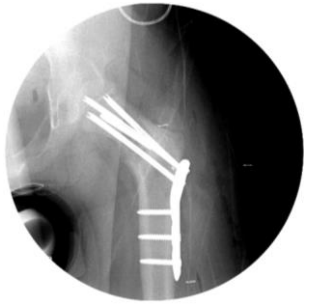
STARTRK-NG summary of safety: Dose discontinuations, reductions, and adverse events

- Discontinuations:
  - 2 patients (6.9%) discontinued drug
    - One treatment-related AE (pulmonary edema)
    - One event not related to treatment (dyspnea)

- Reductions:
  - 11 patients (39.7%) were dose reduced for treatment-related AE – see table

AE leading to dose reductions by patient	
Phase 1 dose escalation (n=5/16)	**Phase 1b (n=6/13)**
Increased blood creatinine	Weight gain
Weight gain (2 episodes)	Ataxia
Dysgeusia	Intermittent falling episodes
Pulmonary edema (3 episodes)	Weight gain
Increased blood creatinine	Headache
	Prolonged QT interval

- Notable adverse events:
  - **Elevated Creatinine**
    - 41% of all patients – all G1/G2
    - May not reflect true renal clearance since Entrectinib inhibits the MATE1 transporter which is involved in creatinine excretion.[1]
  - **Weight gain**
    - Possible **on-target effect** (hyperphagia, obesity) [1-4]
    - Most common reason for dose reduction
    - More common in patients on the drug for prolonged period (i.e. responders)
    - 2 patients have experienced **bilateral femoral neck fractures** possibly related to study drug, rapid weight gain, and steroid use.
  - **Dysgeusia/Ataxia/Falling**
    - Also possible on-target effects [1-4]
    - Sensory impairments from TRK protein inhibition?
    - Dysgeusia 21% total - G1/G2
    - Ataxia and falling < 10% total



Data cut-off: October 31, 2018. AE, adverse event; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

1. Entrectinib – Investigator Brochure v8; 2. Drilon, et al. Cancer Discov 2017
3. Drilon, et al. NEJM 2018; 4. Cocco, et al. Nat Rev Clin Oncol. 2018

Conclusions

- Entrectinib was generally well tolerated; the recommended dose of the clinical trial formulation in children is 550 mg/m^2 daily
  - dose-limiting toxicities were elevated creatinine, dysgeusia, fatigue and pulmonary edema
  - other adverse events that resulted in dose reductions included weight gain and sensory impairments (dysgeusia, ataxia) and these still need to be followed closely (on-target effects)
- Entrectinib produced striking, rapid and durable objective responses in children with refractory CNS and solid tumors harboring *NTRK1/2/3*, *ROS1* or *ALK* fusions (11/11) as well as in a patient with *ALK* mutation-positive neuroblastoma
- No responses were seen in tumors lacking aberrations in target kinases
- Entrectinib has very promising anti-tumor activity and PFS in patients with target gene fusions, especially malignant CNS tumors
  - as a result the study remains open to accrual for patients with target gene fusions

Thank you for your attention

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