ATMP-møteserie

CAR-T

Erfaringer fra pediatrien

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Disclosures

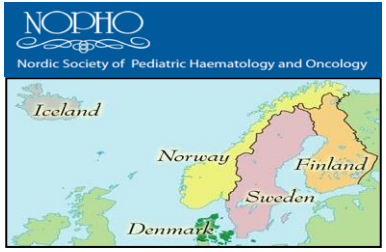
- Consultancy:
  - Novartis: Advisory boards/speakers bureau/non-financial support
  - Kite/Gilead: Advisory board
  - Janssen: Advisory board
  - Amgen: Advisory board

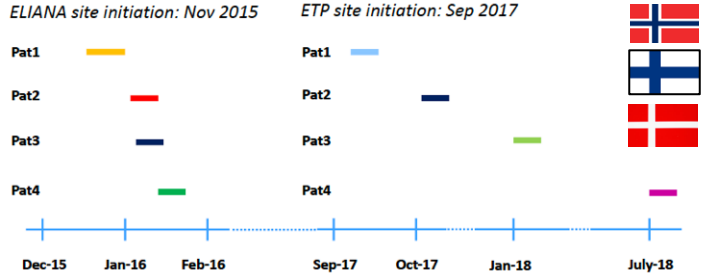
- CTL019 (now know as tisagenlecleucel, tisa-cel, Kymriah) is licensed by Novartis

Implementation of CAR T cell therapy in Norway – 2015

Pediatric r/r ALL: CTL019 study sites		
Country	Site	(Principal investigator)
US	13 sites	
Canada	2 sites	
Austria	Vienna	(C. Peters)
Norway	**Oslo**	**(J. Büchner)**
France	Paris	(A. Baruchel, N. Boissel)
Germany	Frankfurt	(P. Bader)
Italy	Monza	(A. Balduzzi)
Belgium	Ghent	(B. de Moerloose)
Spain	Barcelona	(S. Rives)
Australia	1 site	
Japan	1 site	

International recruitment





- ELIANA: B-ALL, age 1-21 y, ≥2nd relapse
  - EudraCT Number: 2013-003205-25

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

N Engl J Med 2018;378:439-48.

FDA APPROVED 2017

EMA APPROVED 2018

Ny genterapi til barn med leukemi innføres i Norge

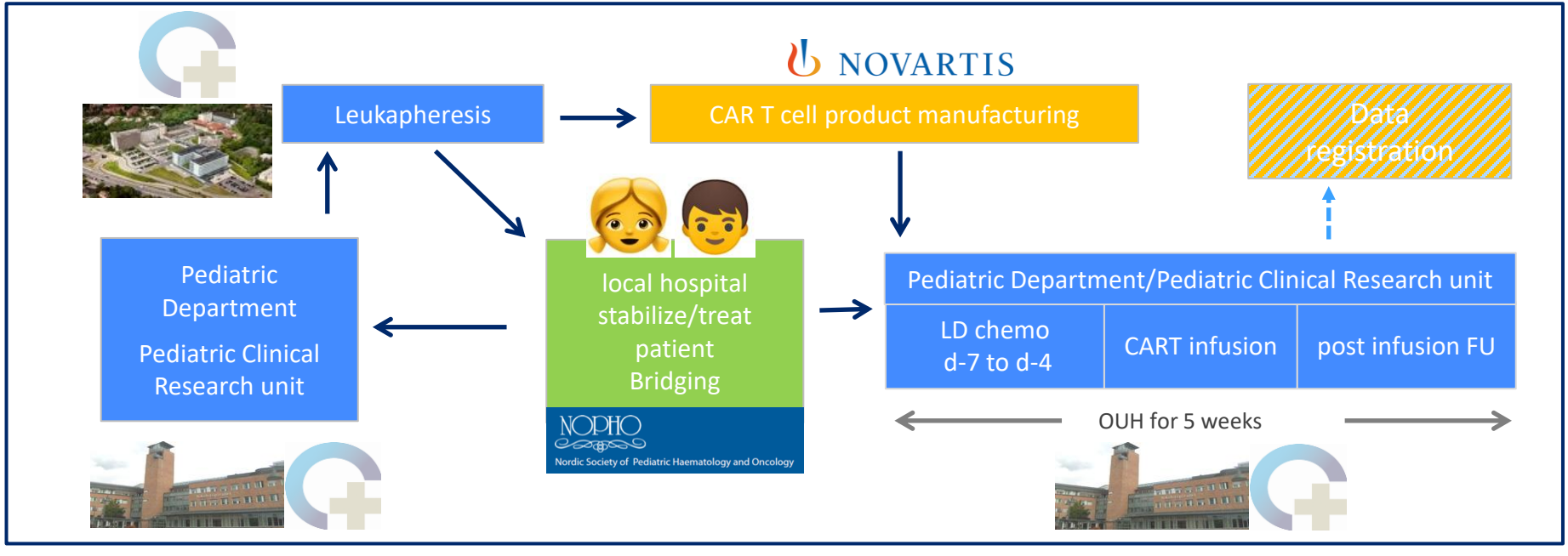
Beslutningsforum har sagt ja til å innføre CAR-T-behandlingen tisagenlecleucel (Kymriah) til behandling av akutt lymfoblastisk leukemi (ALL) for barn og unge.

https://www.dagensmedisin.no/artikler/2018/12/17/ny-genterapi-til-barn-med-leukemi-innfores-i-norge/

Publisert: 2018-12-17 13.00

ELIANA: Phase II registration trial with complex trial logistics

Global multi-center CAR-T cell trial in ALL with a centralized manufacturing



In parallell: «Pediatric Clinical Research Unit« formation

ELIANA
industry-sponsored trial

Dep. Clinical Cancer Research
Study nurse support (3 years)

2015

Pediatric Clinical Research Unit

Medical doctors, study PIs
Study coordinator
Study nurses
Bioengineers (biobank)

in 2020: total 6,2 positions

Trial support

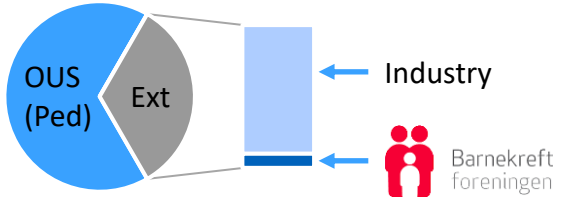
Pediatric
Phase I/II
studies

including
oncological
studies

90% (2020)

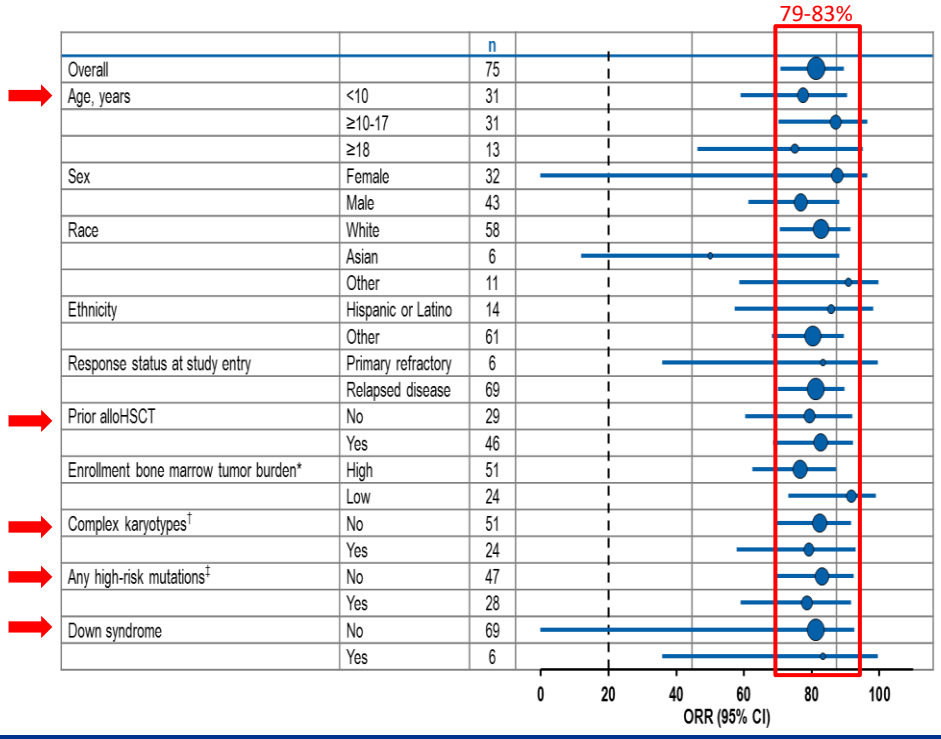
Pediatric Immunotherapy

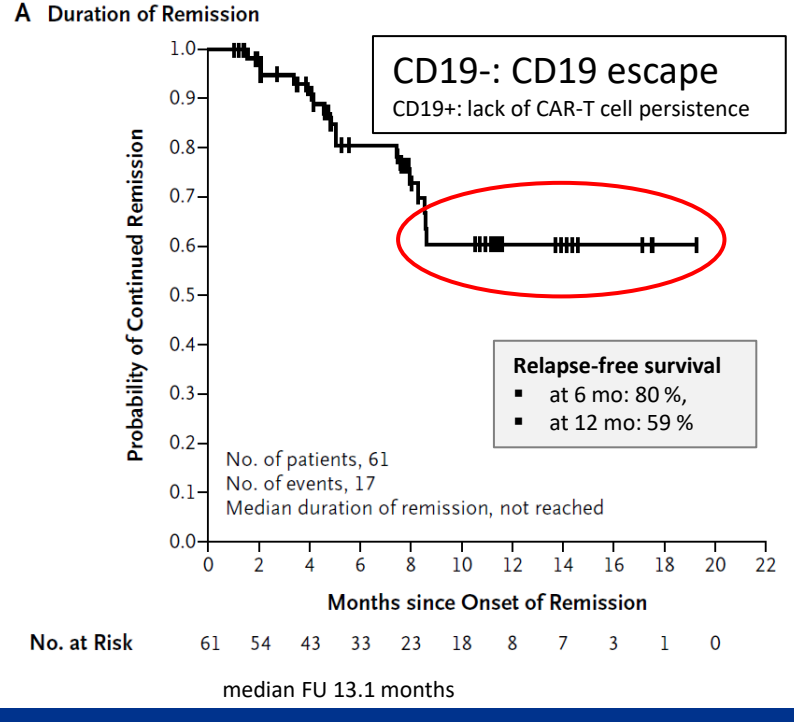
Funding



ELIANA – Key Efficacy Conclusions

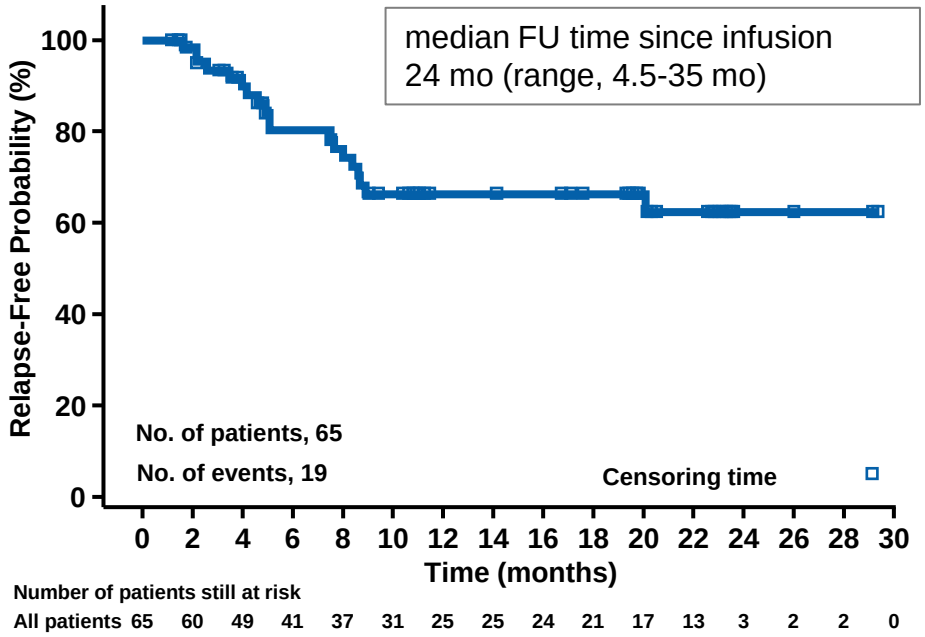
Primary endpoint ORR at 3 months: 81 % (61/75 pts); all CRs were MRD negative





median FU 13.1 months

ELIANA – longer follow-up



Relapse-free survival rate

- 12-month: 66% (95% CI, 52-77)
- 18-month: 66% (95% CI, 52-77)
- 24-month: 62% (95% CI, 47-75)

ELIANA data confirmed by

- ETP protocol (Baruchel, EHA 2020)
- «Real-world» cohorts
  - US: Pasquini, Blood Adv, 2021
  - EU: Dourthe, Leukemia, 2021

Grupp et al., Blood, 2018 (ASH 2018)

ELIANA – Key Safety Conclusions

Table 3. Adverse Events of Special Interest within 8 Weeks after Infusion, Regardless of Relationship to Tisagenlecleucel.*

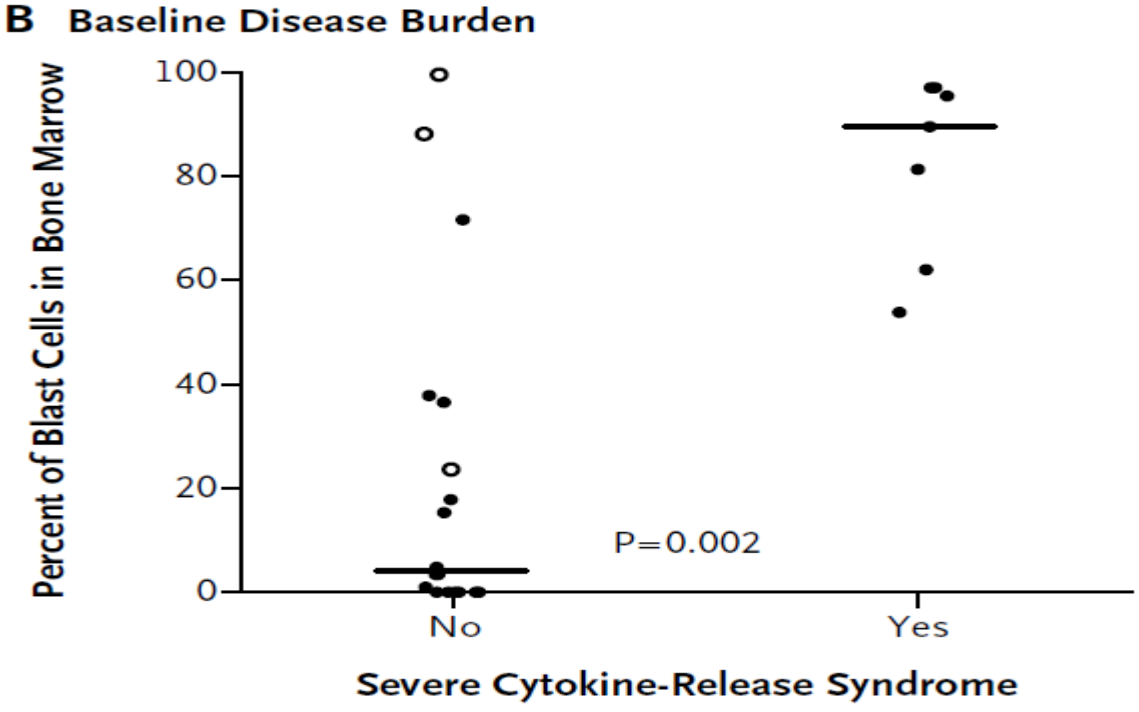
Type of Event	Any Grade (N=75)	Grade 3 (N=75)	Grade 4 (N=75)
	number of patients (percent)		
Any adverse event of special interest	67 (89)	26 (35)	30 (40)
Cytokine release syndrome	58 (77)	16 (21)	19 (25)
Neurologic event	30 (40)	10 (13)	0
Infection	32 (43)	16 (21)	2 (3)
Febrile neutropenia	26 (35)	24 (32)	2 (3)
Cytopenia not resolved by day 28	28 (37)	12 (16)	12 (16)
Tumor lysis syndrome	3 (4)	3 (4)	0

Maude et al. NEJM, 2018

Toxicity can be severe,
but is manageable if therapy is given in trained sites (key!)

Pooled safety analysis
ELIANA+ENSIGN:
Levine et al., J Immunother Cancer, 2021

CRS correlates with baseline disease burden



Maude et al. NEJM, 2014

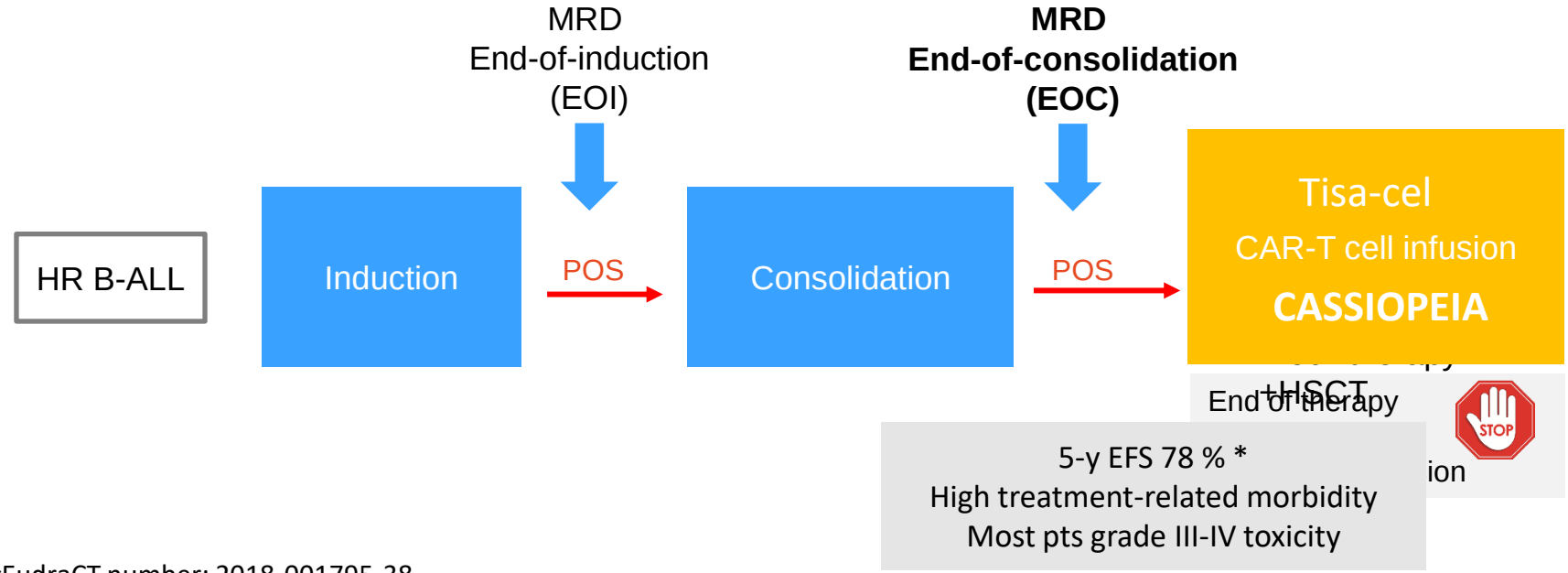
ELIANA – conclusions

- Effective therapy in very HR r/r ALL disease
  - long-term remissions in about 50% of patients
- Toxicity is manageable
  - on trained sites
- Logistics are possible
  - centralized manufacturing
  - product shipment across countries and continents
- Registered product but labelled for a small ALL population

- *“Can CD19CART substitute HSCT?”*
- *“Can CD19CART be moved further up the treatment line?”*

CAR-T cell option in ALLTogether for front-line HR B-ALL

- *"Can CD19CART substitute HSCT?"*
- *"Can CD19CART be moved further up the treatment line?"*



#EudraCT number: 2018-001795-38.

*Pieters, et al. *J Clin Oncol* 2016;34:2591–601.

CASSIOPEIA: A Phase 2 Study Evaluating Efficacy and Safety of Tisagenlecleucel as First-line Therapy for High-risk Pediatric and Young Adult Patients with B-cell Acute Lymphoblastic Leukemia who are MRD Positive at the End of Consolidation NCT03876769

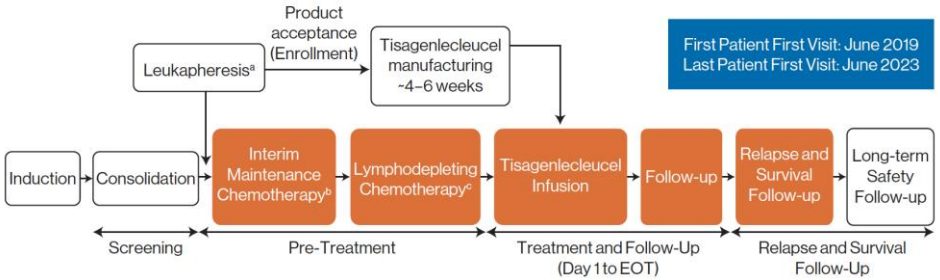
Patient cohort

Patients 1-25 years with de novo NCI-defined HR B-ALL (white blood count >50,000/µL or ≥ 10 years of age) who are in CR1 but remain MRD positive (≥0.01% by flow cytometry) at EOC

Collaboration between

- COG
- ALLTogether1
- other EU groups
- and Novartis

Single-arm design
w/historic COG control



Primary endpoint:	5-year DFS rate
Planned enrollment:	160 pts w/140 being infused.
Recruiting Nordic sites:	Oslo, Helsinki, Copenhagen, Stockholm

Poster, SITC 2019

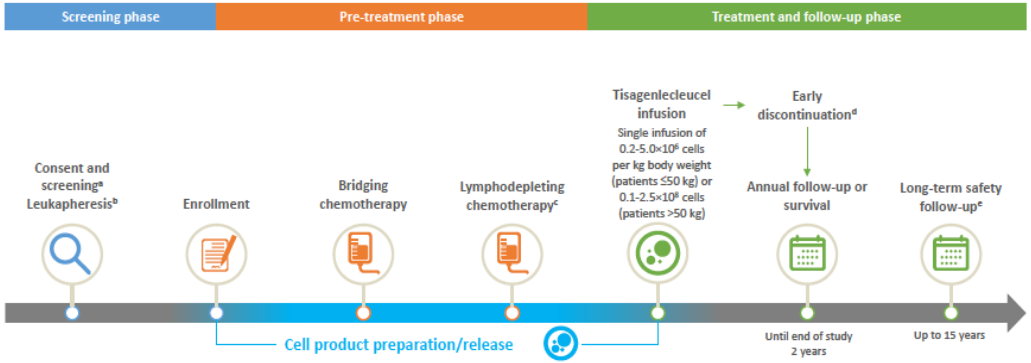
BIANCA: Phase 2, Single-Arm, Global Trial to Determine Efficacy and Safety of Tisagenlecleucel in Pediatric/Young Adult Patients With Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma

- *Given the efficacy of CD19CART in pediatric ALL and adult lymphoma:*
- *"Is CD19CART effective in CD19+ r/r pediatric B-cell lymphoma?"*

(Very rare) patient cohort
Histologically confirmed pediatric mature B-NHL

- Burkitt lymphoma/Burkitt leukemia
- DLBCL
- Primary mediastinal B-cell lymphoma
- Gray zone lymphoma
- Follicular lymphoma

who failed one or more prior therapies



Primary endpoint: Overall response rate
Planned enrollment: 35 pts w/26 infused and evaluable
Recruiting sites: 35 in total (in US, Canada, Europe, Japan, Australia)
Participating Nordic sites: Oslo, Helsinki, Copenhagen

Recruitment completed; primary analysis published in 2022

Poster, EHA 2020

Current CAR-T status in the Nordics (pediatric ALL)

CAR-T box

Commercial Kymriah product
- Patients <25 y, r/r B-ALL (≥ 2nd relapse or post-HSCT)

Ongoing Kymriah trials
- CASSIOPEIA
- BIANCA, recruitment completed

Candidates left outside

* 1st B-ALL relapse (very high-risk)

T-ALL

B-ALL
- not eligible for current trials or Kymriah
- relapsing after CD19CAR-T (CD19+/CD19-)

*academic trial, IntReALL BCP, start 2022/23
Industry-sponsor
Point-of-care manufacturing of CAR-T
Plan to open study site in Oslo

Bottlenecks – example adoptive T cell therapy (e.g., CAR T)

Trial preparation: protocol work; regulatory work (EC, NMA, contracts, budgets); site implementation; international dissemination etc.

Months

Funding, infrastructure (e.g., “clinician-scientists”)

Capacity, funding/investment into infrastructure for ATMP production

Leukapheresis (DNR)

CAR T cell product manufacturing

Scientific output

Pediatric Department

Pediatric Clinical Research unit

local hospital stabilize/treat patient

Pediatric Department/Pediatric Clinical Research unit

LD chemo d-7 to d-4	CAR infusion	post infusion FU

for 5 weeks

Schematic treatment course

Capacity

Acknowledgment

Department of Pediatric Hematology and Oncology

Department for Cellular Therapy

Department of Immunology

Department of Hematology

Department of Cancer Immunology

Intensive Care Units

Inven2

Pediatric Clinical Research Unit

Clinical Cancer Research Unit

NOPHO

Nordic Society of Pediatric Haematology and Oncology

All collaborative hospitals and contributing colleagues

NOVARTIS

Global and Nordic Team

Barnekreft foreningen

Families and patients

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