Loncastuximab Tesirine

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Disclosures

Research funding	Genentech, ADC Therapeutics
Advisory Board / Honoraria	ADC Therapeutics, Kite pharmaceuticals, BMS, Novartis, Genentech, Genmab, MEI Pharma, Lilly Oncology, Seattle Genetics, Takeda.

Preclinical

- Variability in B cell surface antigen properties
  - *Differences in number of binding sites*

Table 2 ***Characterization of murine mAbs recognizing human B cell antigens***

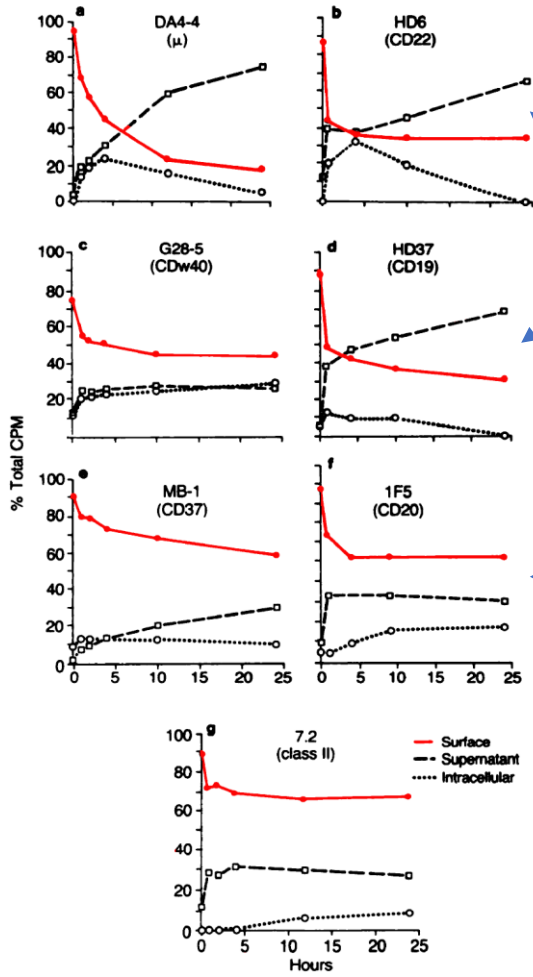
Antibody	Antigen[a]	Isotype	Binding sites/cell[b]	Avidity[c] (L/M)	Immunoreactivity (%)[d]
DA4-4	μ	IgG1	330,772	4.34×10^9	92
HD6	CD22	IgG1	86,683	2.88×10^9	69
G28-5	CDw40	IgG2a	86,835	4.50×10^9	86
HD37	CD19	IgG1	91,131	0.30×10^9	76
MB-1	CD37	IgG1	234,311	2.99×10^9	92
1F5	CD20	IgG2a	306,097	0.37×10^9	59
7.2	Class II	IgG2b	393,163	1.71×10^9	74

[a] CD, cluster designation as assigned by the Third International Workshop on Monoclonal Antibodies (8).

Press OW, et al. Cancer Res, 1989 (colorized)

Preclinical

Radioimmunoassays



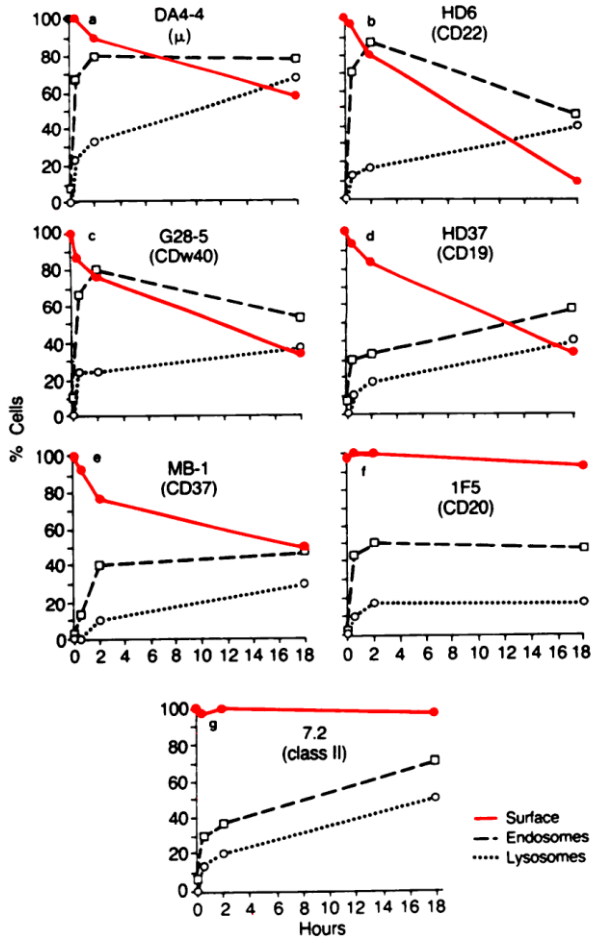
antiCD22 and antiCD19 are rapidly internalized

antiCD20 is retained on the surface longer

Press OW, et al. Cancer Res, 1989 (colorized)

Preclinical

- *Endocytosis rates* (immuno-electron microscopy)



antiCD22 and antiCD19 removed rapidly from surface

antiCD20 is retained on the surface longer

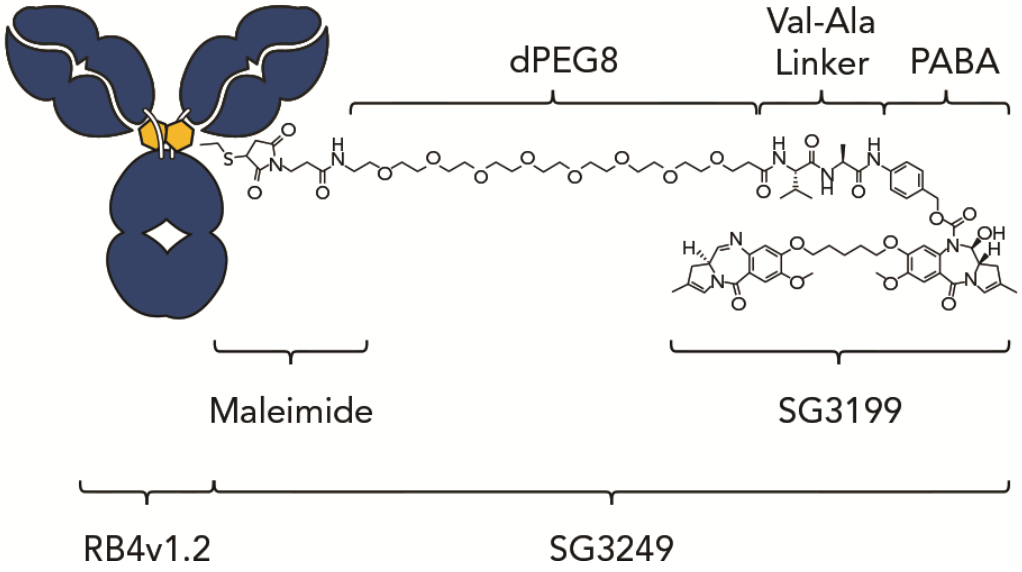
Press OW, et al. Cancer Res, 1989 (colorized)

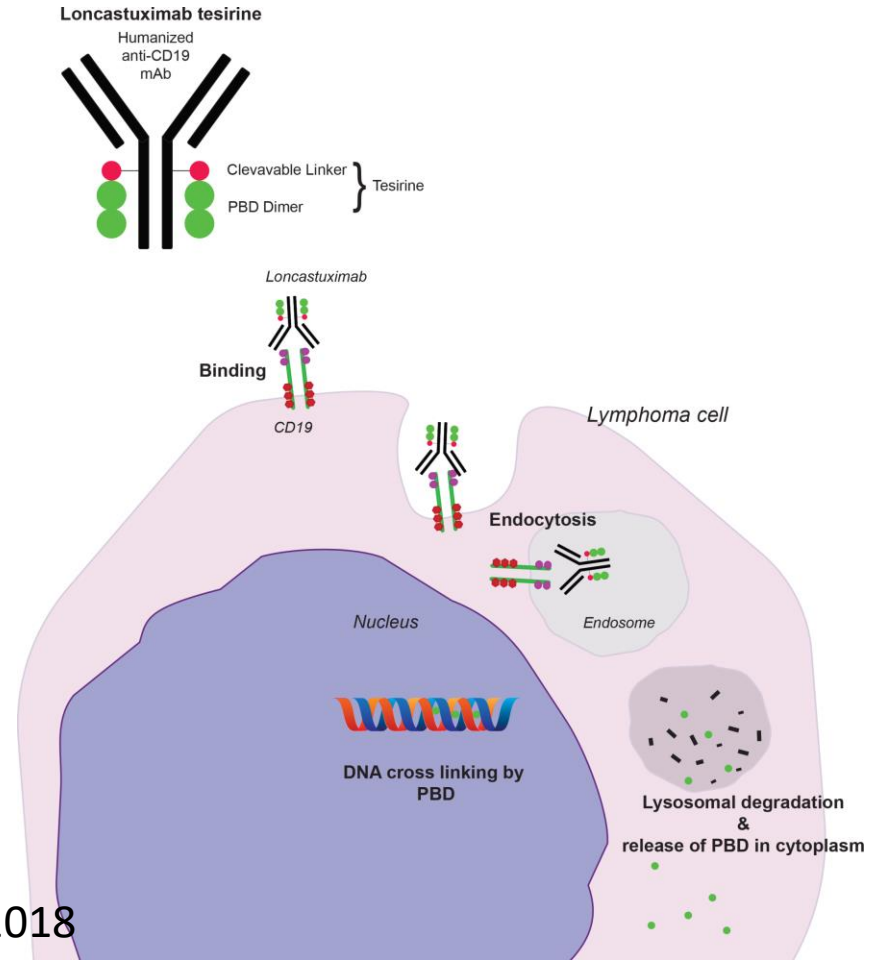
Preclinical

- CD19

Loncastuximab tesirine

- AntiCD19 (B4) conjugated to pyrrolobenzodiazepine dimer
  - PBD causes DNA minor groove interstrand crosslinking



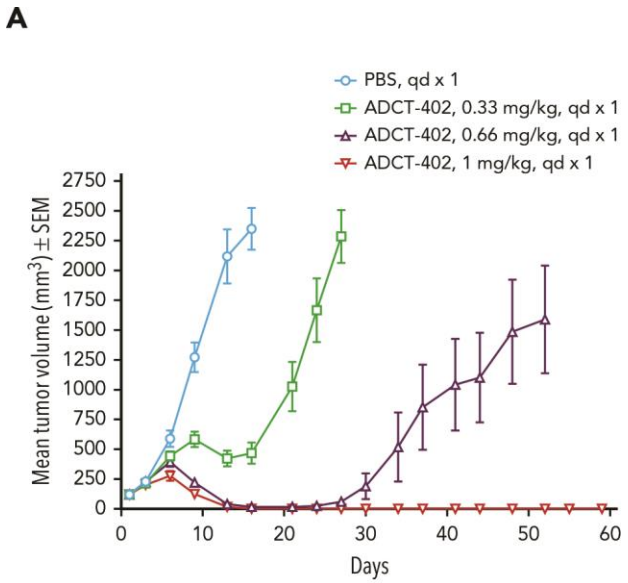


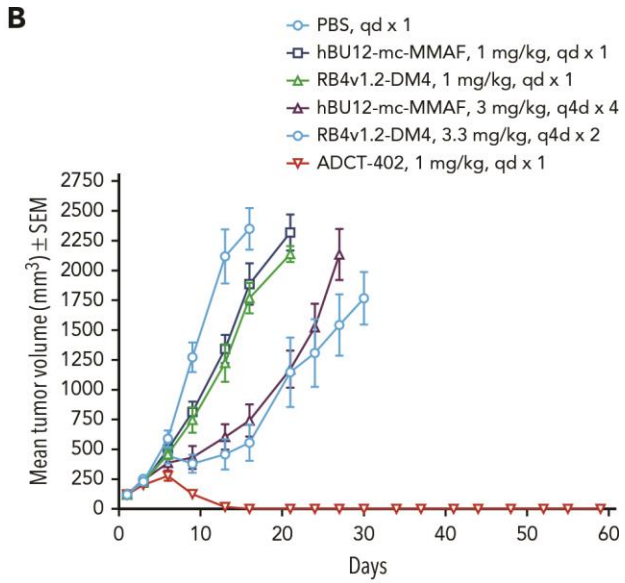
Zammarchi F, et al. Blood, 2018

Loncastuximab tesirine

- Mouse xenograft studies

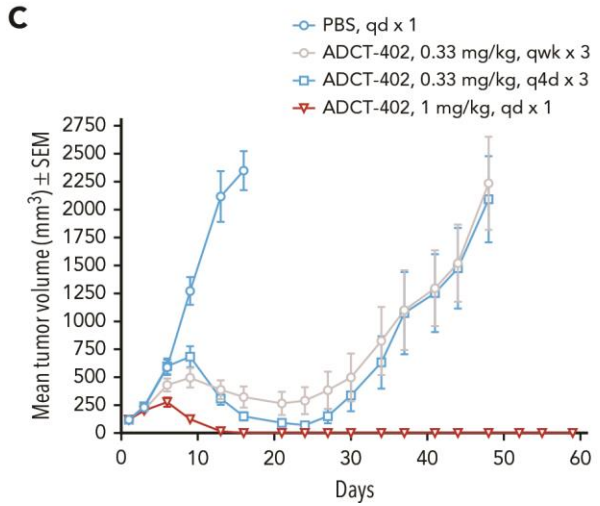
Dose escalation

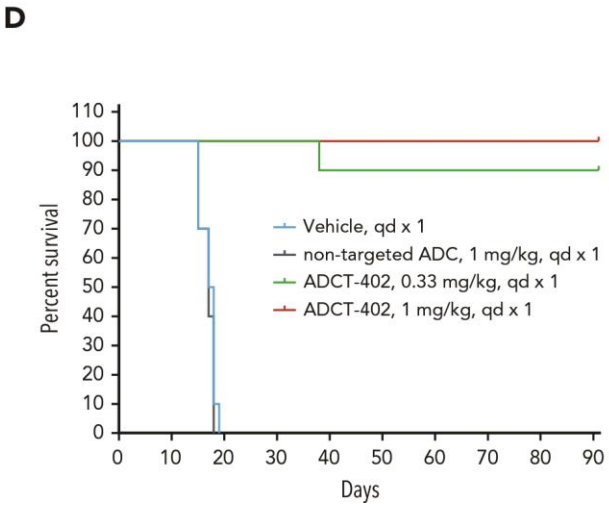




Vs. other payloads

Single dose vs. fractions





Disseminated model

Zammarchi F, et al. Blood, 2018

Phase I trial

- 183 patients
  - Relapsed refractory NHL
  - DLBCL (n = 139)
  - Median lines of therapy = 3 (1-13)

- Dose escalation (15-200) = 88 patients
- Dose expansion (120-150) = 95 patients

- 98.9 % of patients had TEAE
- No DLTs
- 77% had grade 3 or higher AE →

Grade ≥ 3 TEAEs in > 5% of patients, n (%)	
TEAE	Total (n = 183)
Any	141 (77
Neutrophil count decreased	71 (39.7)
Platelet count decreased	48 (26.7)
GGT increased	39 (21.3)
Anemia	28 (15.3)
Alkaline phosphatase increased	12 (6.6)
Lymphocyte count decreased	12 (6.6)
Febrile neutropenia	10 (5.5)
Hypokalemia	10 (5.5)

Other relevant AEs: Edema (31.7%), rash (24.6%)

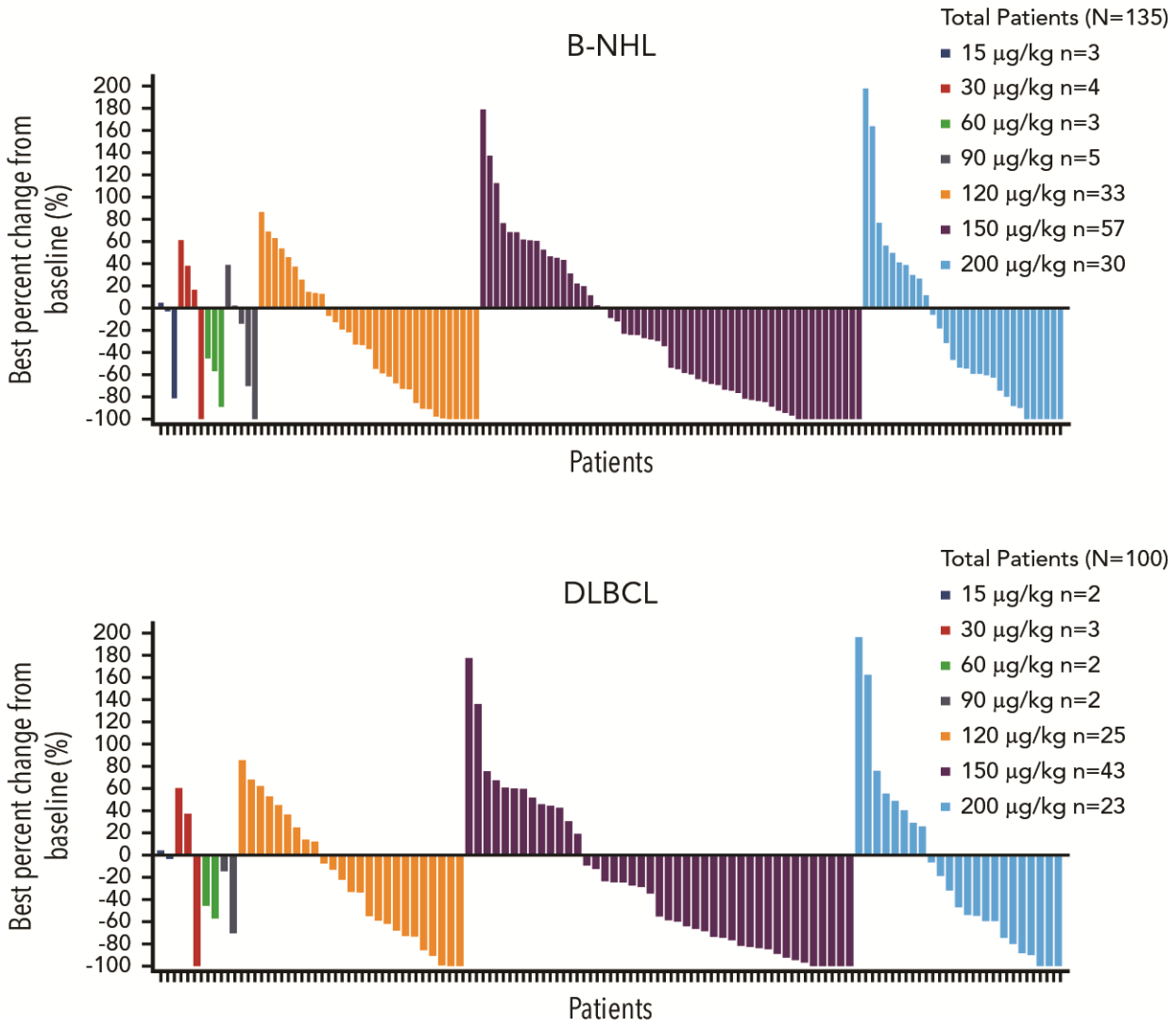
Kahl B, et al. Clin Cancer Res, 2019 | Hamadani M, et al. Blood, 2021

Phase I trial

Overall response rate = 45.6%
Complete response rate = 26.7%

	n (%)		
	DLBCL (n = 137)	MCL (n = 15)	FL (n = 14)
ORR 95% CI	58 (42.3) 33.9-51.1	7 (46.7) 21.3-73.4	11 (78.6) 49.2-95.3
CR	32 (23.4)	5 (33.3)	9 (64.3)
PR	26 (19.0)	2 (13.3)	2 (14.3)

Median PFS = 3.1 months
Median OS = 8.3 months



Kahl B, et al. Clin Cancer Res, 2019 | Hamadani M, et al. Blood, 2021

Toxicities and Management

- Elevated GGT
  - Usually isolated.
  - No identified hepatic toxicity markers.
  - Trial mandated discontinuation if delay more than approximately 6 weeks.
  - Premedication with steroids decreases incidence

Toxicities and Management

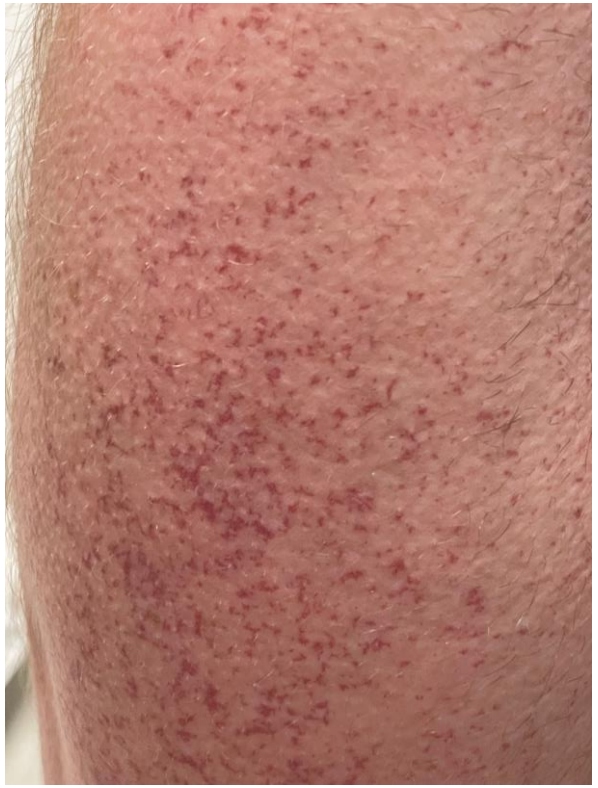
- Edema
  - Variable presentation

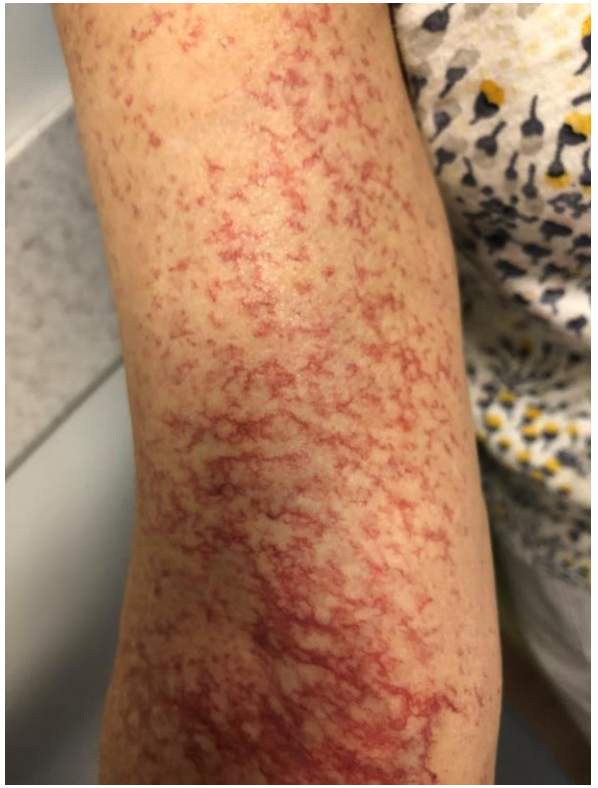
  (central, peripheral, effusions)
  - Discontinue / delay treatment
  - Diuretics
    - Spironolactone
    - I personally add loop diuretics

Toxicities and Management

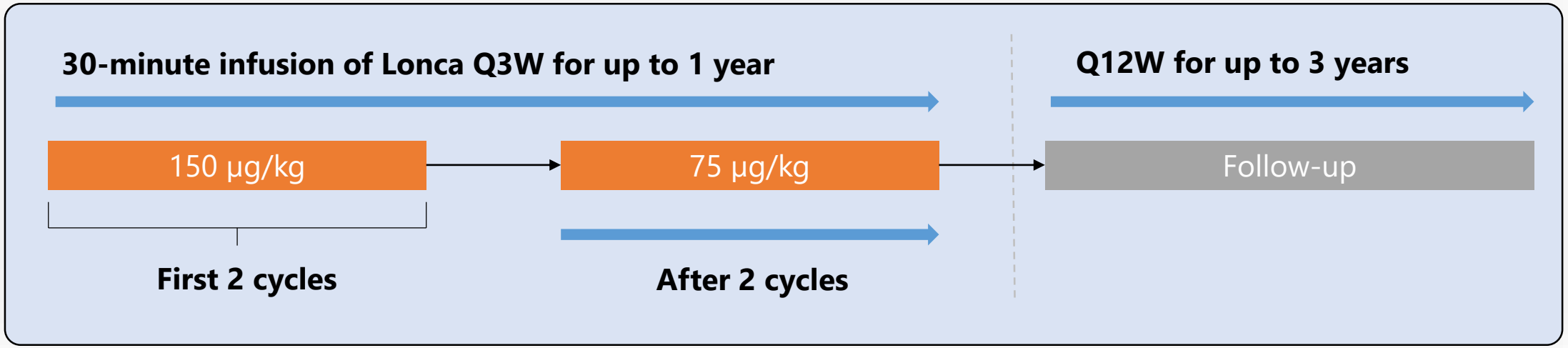
- Rash
  - More than one type
  - Photosensitivity
  - Telangiectasia

  - Both are probably result of SG3199 effect





Phase II trial (LOTIS-2)



Eligibility

DLBCL

- Including transformed indolent
- Including double/triple hit
- Including primary refractory

Relapsed/refractory to ≥ 2 lines of therapy

If prior CAR-T cell therapy, repeat biopsy with CD19+ required

Excluded:

- Bulky disease (> 10 cm)
- ASCT within 30 days, AlloHCT within 60 days
- CNS disease

Caimi PF, et al. Lancet Oncol, 2021

Phase II Results

	Patients n = 145
Median age	66 years (56 – 71)
Median previous therapyes	3 (2 – 7)
Lymphoma	
DLBCL, NOS	88%
HGBCL	8%
PMBCL	5%
Double hit	10%
Transformed	20%
Primary refractory	20%
Refractory to last therapy	58%

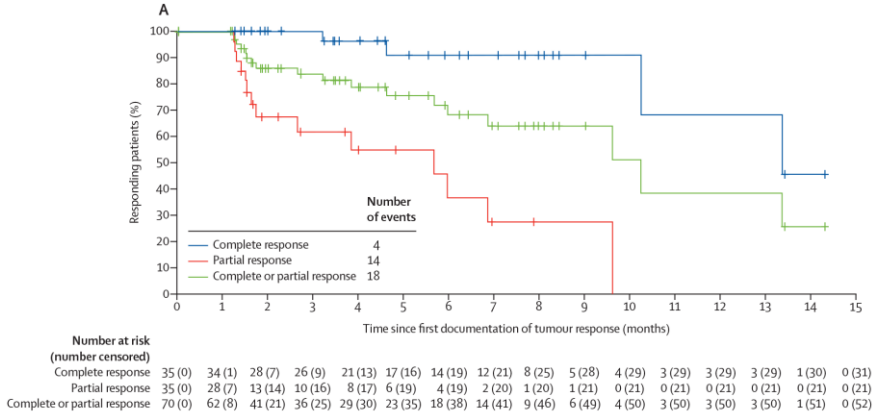
Caimi PF, et al. Lancet Oncol, 2021

Phase II Results

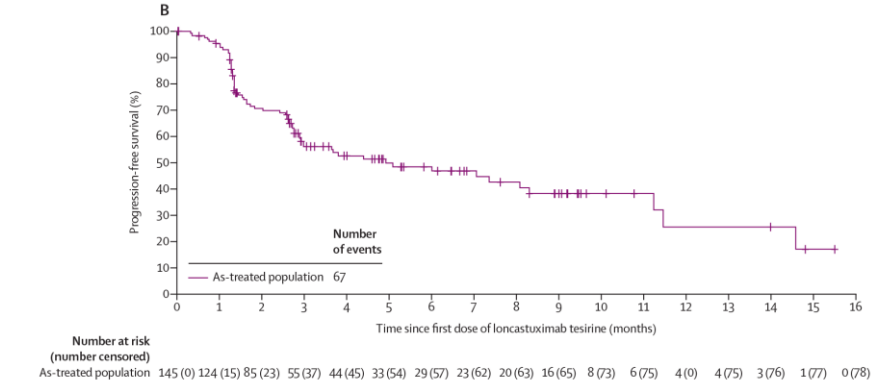
	As-treated population (n=145)
Overall response rate (complete or partial response)	70 (48·3% [39·9–56·7])
Complete response rate	35 (24·1% [17·4–31·9])
Complete response	35 (24%)
Partial response	35 (24%)
Stable disease	22 (15%)
Progressive disease	30 (21%)
Not evaluable*	23 (16%)

Data are n (% [95% CI]) or n (%). Response was assessed by central independent review. A best overall response of stable disease could only be achieved after the patient was on the study for a minimum of 35 days following the first dose of loncastuximab tesirine. Any disease assessment indicating stable disease before this timepoint was considered not evaluable for response if no assessment after this timepoint was available. *Patients without any scan available to the independent reviewer or patients whose scan was determined to be not evaluable by the independent reviewer.

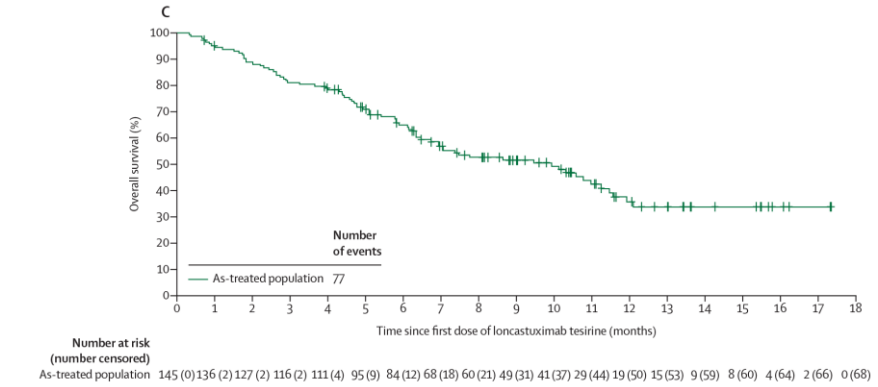
Table 2: **Best overall responses and overall response rate**



DoR:
10.3 months
(13.4 for CR)



PFS:
4.9 months



OS:
9.9 months

Caimi PF, et al. Lancet Oncol, 2021

Phase II Subgroup analysis

High-risk subgroup analysis of ORR

Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
Age			
<65 years	32/65		49.2 (36.6, 61.9)
≥65 years	38/80		47.5 (36.2, 59.0)
Double/triple hit			
No	65/130		50.0 (41.1, 58.9)
Yes	5/15		33.3 (11.8, 61.6)
Transformed disease			
Transformed	13/29		44.8 (26.4, 64.3)
De novo	57/116		49.1 (39.7, 58.6)
Cell-of-origin			
GCB	26/48		54.2 (39.2, 68.6)
ABC	11/23		47.8 (26.8, 69.4)
Double/triple expressor			
No	60/125		48.0 (39.0, 57.1)
Yes	10/20		50.0 (27.2, 72.8)
WHO classification			
DLBCL NOS	64/127		50.4 (41.4, 59.4)
PMBCL	1/7		14.3 (0.4, 57.9)
HGBCL	5/11		45.5 (16.7, 76.6)

Subgroup	Patients (n/N)	ORR	ORR (95% CI)
All	70/145		48.3 (39.9, 56.7)
First-line response*			
Relapse	53/99		53.5 (43.2, 63.6)
Refractory†	11/29		37.9 (20.7, 57.7)
Last-line response*			
Relapse	29/43		67.4 (51.5, 80.9)
Refractory†	31/84		36.9 (26.6, 48.1)
Response to any prior line*			
Relapse	60/115		52.2 (42.7, 61.6)
Refractory†	9/25		36.0 (18.0, 57.5)
Prior stem cell transplant			
Yes	14/24		58.3 (36.6, 77.9)
No	56/121		46.3 (37.2, 55.6)
Prior CAR-T therapy			
Yes	6/13		46.2 (19.2, 74.9)
No	64/132		48.5 (39.7, 57.3)
Prior systemic therapies			
2 prior lines	30/63		47.6 (34.9, 60.6)
3 prior lines	17/35		48.6 (31.4, 66.0)
>3 prior lines	23/47		48.9 (34.1, 63.9)

Phase II Safety

TEAEs in ≥20% of the all-treated population

PREFERRED TERM	PATIENTS N (%)		
	<65 YEARS (N=65)	≥65 (N=80)	TOTAL (N=145)
Patients with any TEAE	65 (100)	78 (97.5)	143 (98.6)
GGT increased	33 (50.8)	27 (33.8)	60 (41.4)
Neutropenia	34 (52.3)	24 (30.0)	58 (40.0)
Thrombocytopenia	28 (43.1)	20 (25.0)	48 (33.1)
Fatigue	21 (32.3)	19 (23.8)	40 (27.6)
Anemia	23 (35.4)	15 (18.8)	38 (26.2)
Nausea	17 (26.2)	17 (21.3)	34 (23.4)
Cough	19 (29.2)	13 (16.3)	32 (22.1)
Alkaline phosphatase increased	18 (27.7)	11 (13.8)	29 (20.0)
Peripheral edema	11 (16.9)	18 (22.5)	29 (20.0)

Most common (≥10%) grade ≥3 TEAEs were:

- Neutropenia (38 patients; 26.2%)
- Thrombocytopenia (26 patients; 17.9%)
- GGT increased (25 patients; 17.2%)
- Anemia (15 patients; 10.3%)

Treatment-related TEAEs leading to treatment discontinuation occurred in 26 (17.9%) patients, most commonly (≥2%):

- GGT increased (16 patients; 11.0%)
- Peripheral edema (4 patients; 2.8%)
- Localized edema (3 patients; 2.1%)

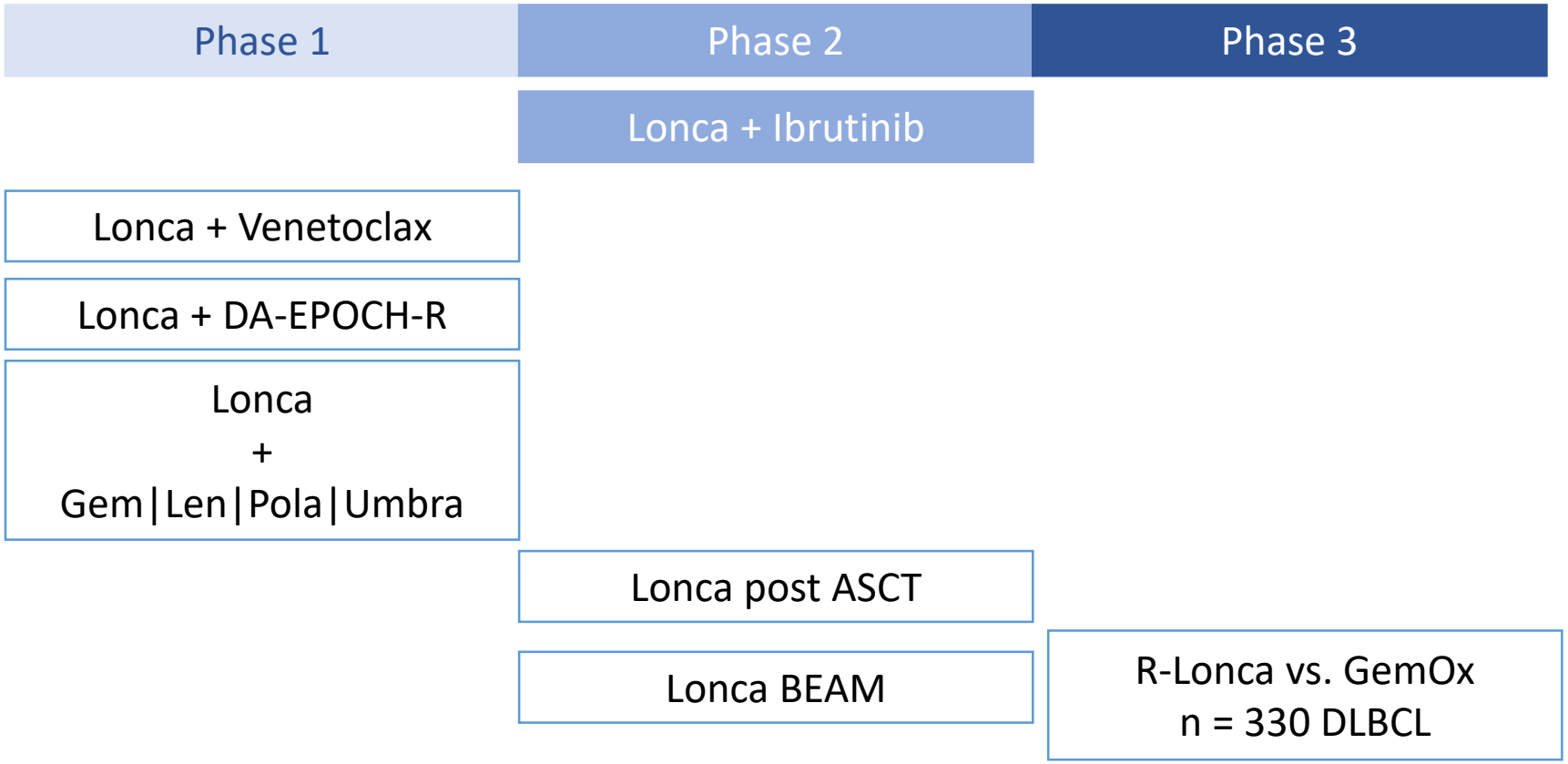
Caimi PF, et al. Lancet Oncol, 2021

CAR-T post lonca

- 14 patients
  - CD19 expression
    - Positive = 10 (71%)
    - Not checked 4 (29%)
  - Response to CAR-T
    - CR = 6 (43%)
    - PR = 1 (7%)
    - PD = 7 (50%)

Thapa B, et al. Blood Adv, 2020

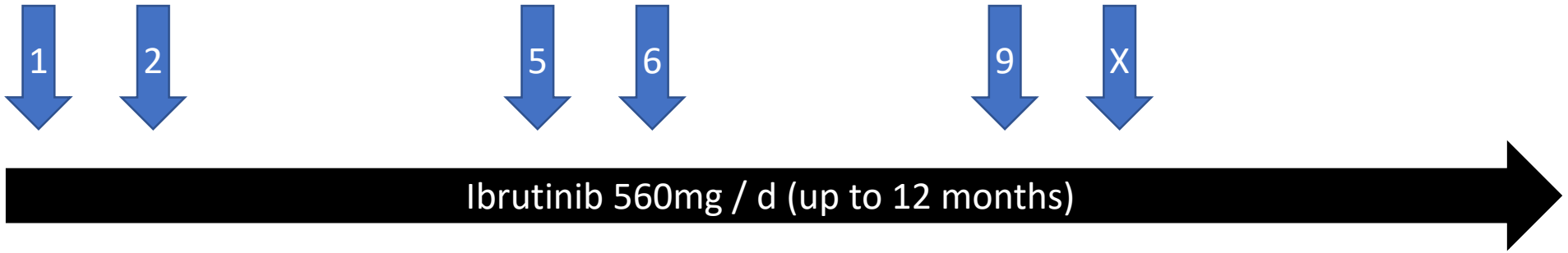
Other trials



https://ClinicalTrials.gov, accessed March 21, 2022

Loncastuximab + Ibrutinib

- Relapsed refractory DLBCL and MCL



Carlo Stella C, et al. Blood (2021);138:54

Loncastuximab + Ibrutinib

- 35 patients enrolled
  - DLBCL
    - Non GCB = 13
    - GCB = 22
  - Median age = 72 years
  - Previous therapies = 3 (1-6)

  - Median treatments
    - Ibrutinib = 10 cycles
    - Lonca = 4 cycles

Carlo Stella C, et al. Blood (2021);138:54

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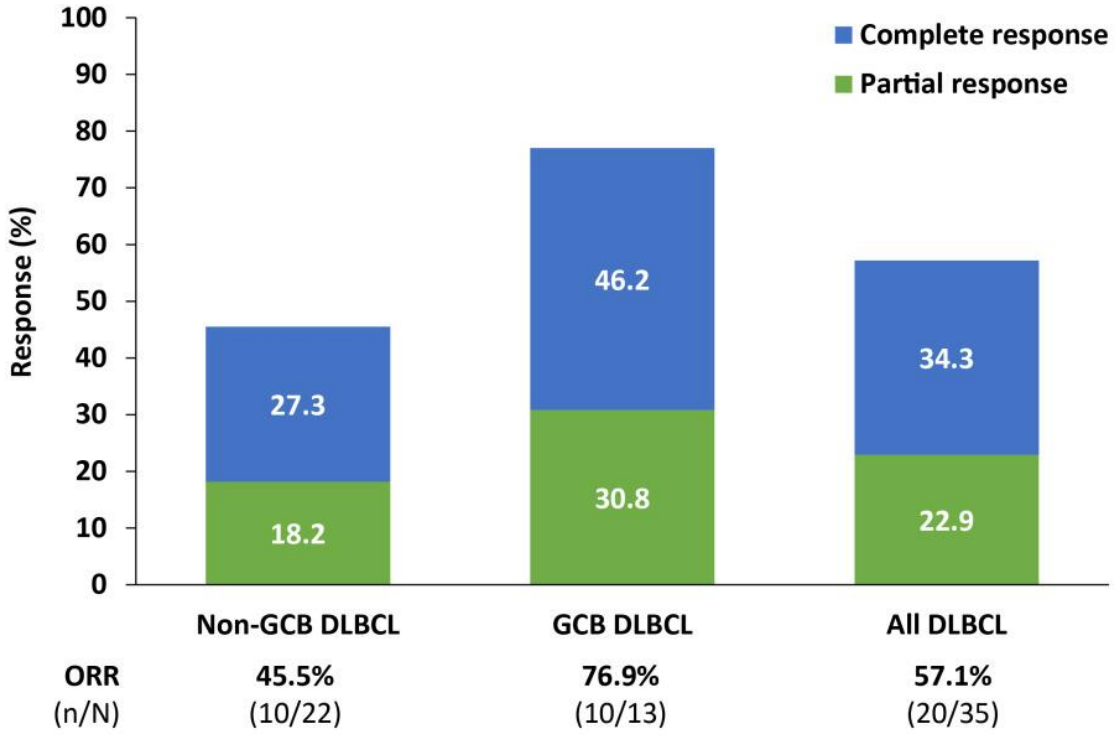
Figure 1. ORR in the overall DLBCL cohort and by cell of origin (planned interim analysis set)



DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell like; ORR, overall response rate

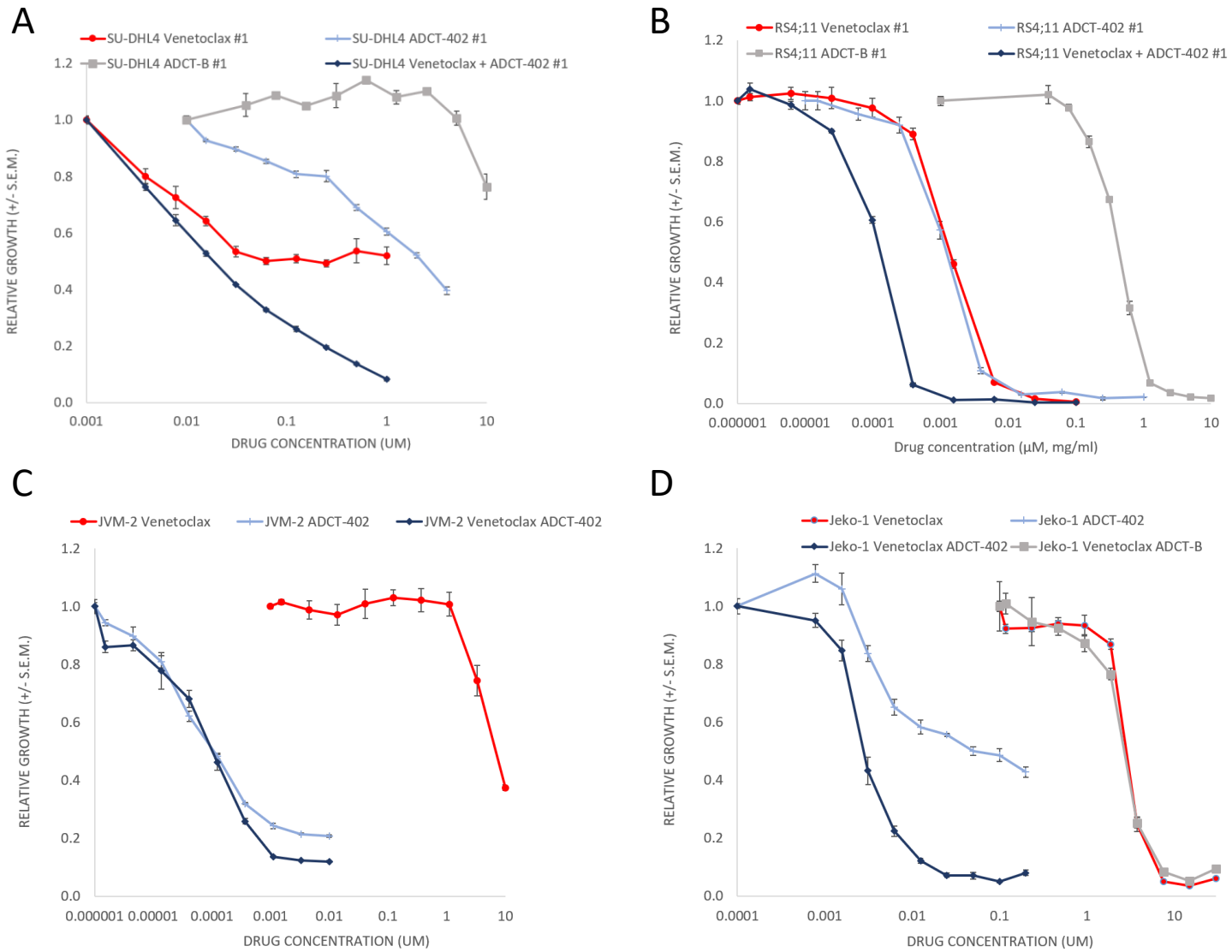
Carlo Stella C, et al. Blood (2021);138:54

Loncastuximab + Ibrutinib

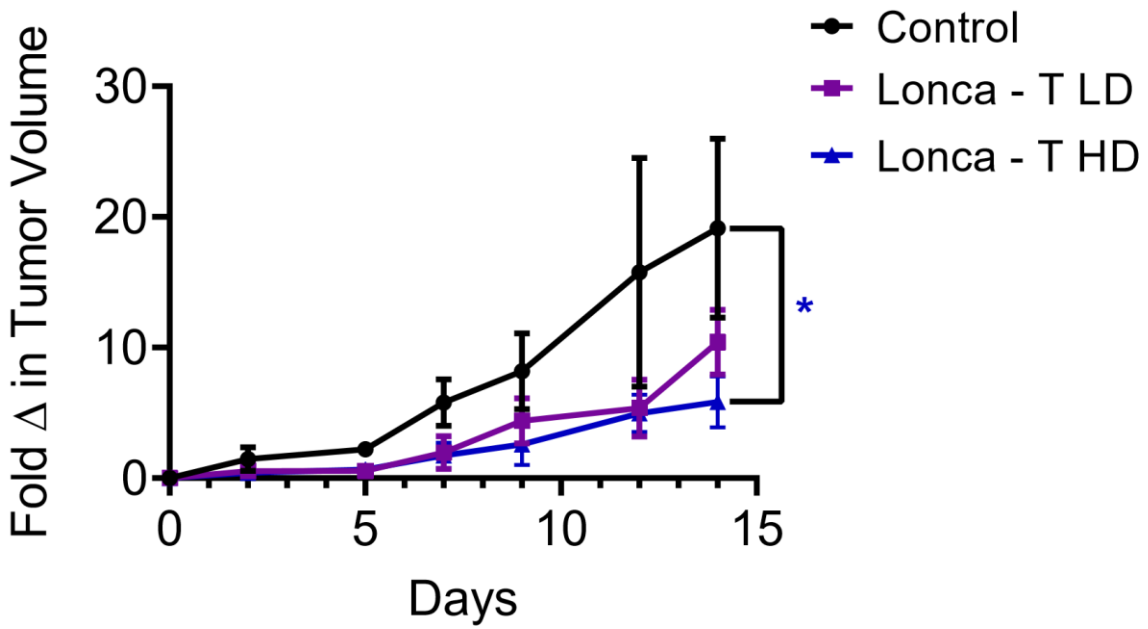
- 32 patients experienced an adverse event
- 16 patients had an adverse event of grade ≥ 3
  - Neutropenia (20%)
  - Thrombocytopenia (11%)
- 17 patients had dose delays / reductions due to TEAEs
- 8 patients had discontinuation due to TEAEs

Carlo Stella C, et al. Blood (2021);138:54

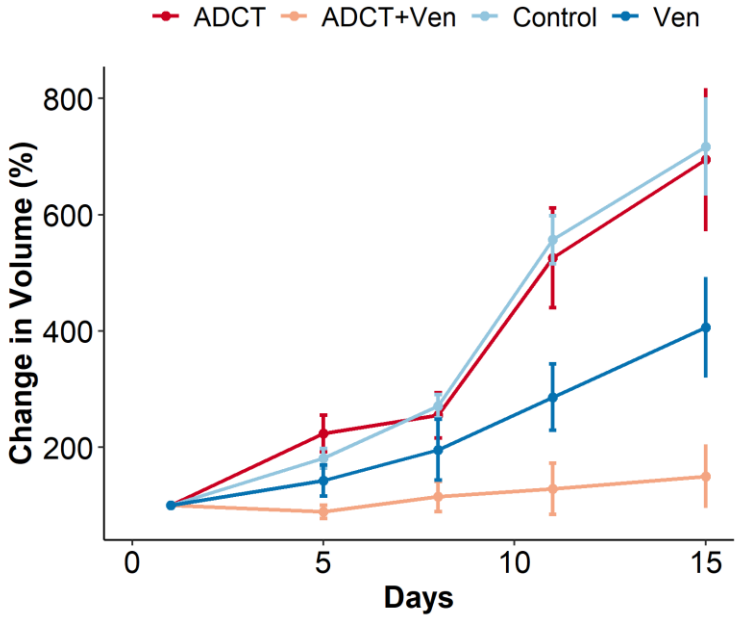
Loncastuximab + Venetoclax



Loncastuximab + Venetoclax



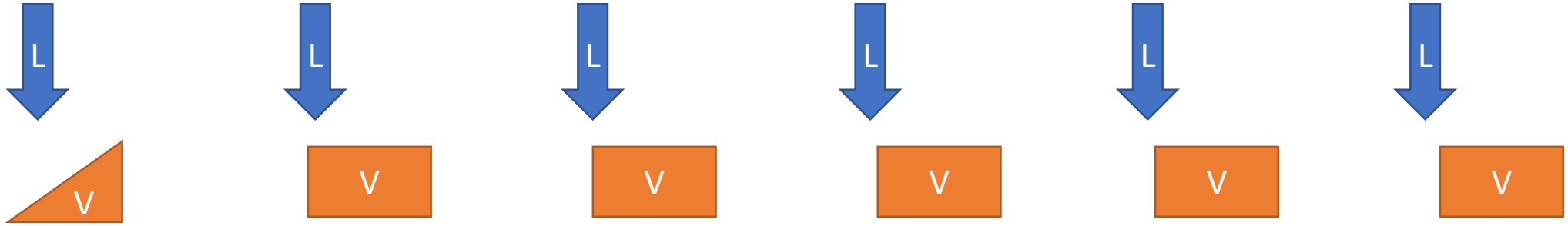
JEKO1 Xenografts
Low dose lonca 0.2mg/kg
High dose lonca 0..5mg/kg



NSG Mice
JEKO Subcutaneous tumors
Venetoclax gavage daily
ADCT 1mg/kg dose x 1

Loncastuximab + Venetoclax

- Phase I trial



- Dose levels
  - Lonca 50, 100 and 150mg dose level
  - Venetoclax 400, 600 and 800mg

Carlo Stella C, et al. Blood (2021);138:54

Conclusions

- Loncastuximab
  - First approved ADC with PBD payload
  - AntiCD19 with single agent activity
    - Consistent throughout risk groups
  - Specific safety profile
    - Discontinuation rates comparable to other approved agents in R/R setting
  - Combination studies ongoing
  - Questions remaining
    - Role in antiCD19 sequence: preliminary data
    - Clinical performance of combinations