STARLYTE
Phase II Study of Coltuximab Ravtansine (SAR3419) single agent:
Clinical Activity and Safety in Patients with Relapsed/Refractory Diffuse Large B-cell Lymphoma (NCT01472887)

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PRESENTED AT THE 2014 ASCO ANNUAL MEETING. PRESENTED DATA IS THE PROPERTY OF THE AUTHOR.

Presenter disclosure information

- **Employment or leadership position :** No
- **Consultant / Advisory role :** No
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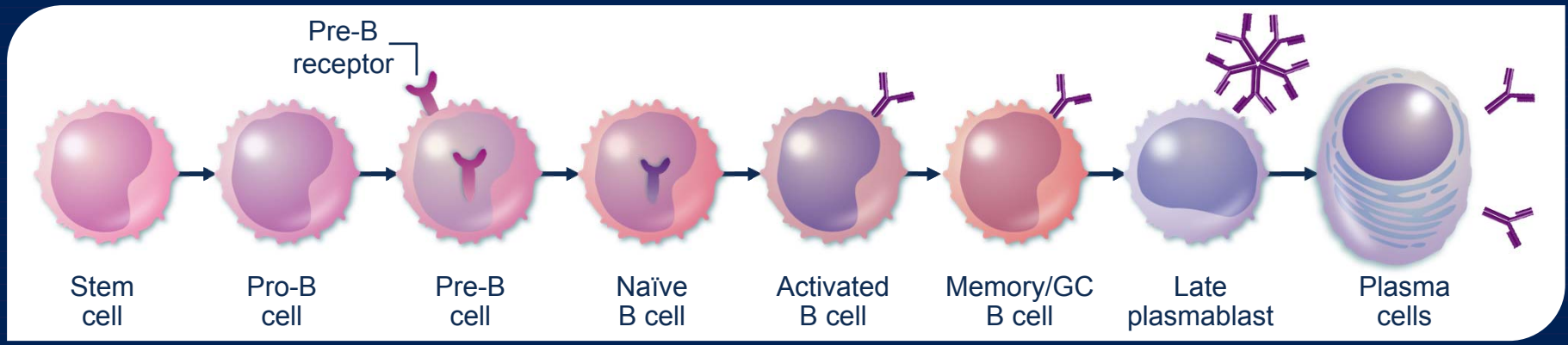
CD19 is expressed on a Broad Range of B-Cell Malignancies



Bone Marrow	Periphery	Bone Marrow

Associated B cell malignancies	ALL	MCL	DLBCL	WM	MM
		MZL	CLL	FL	

CD19

CD20

ALL: Acute Lymphoblastic Leukemia, **MCL:** Mantle Cell Lymphoma; **DLBCL:** Diffuse Large B Cell Lymphoma; **CLL:** Chronic Lymphocytic Leukemia; **FL:** Follicular Lymphoma; **WM:** Waldenstrom Macroglobulinemia; **MM:** Multiple Myeloma **MZL:** Marginal Zone Lymphoma;

Peter Park, adapted from Janeway, Immunobiology, 6th ed. & Uckun, Blood 76:1908 (1990)

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SAR3419 structure
Key attributes

POTENT TOXIN

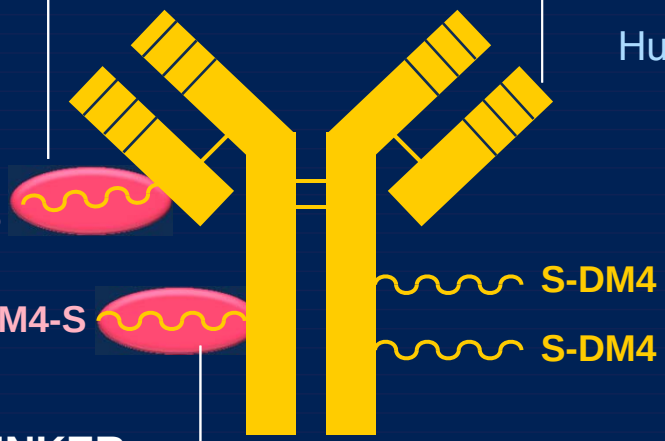
DM4: Maytansinoid derivative

Highly potent tubulin binder
-vinca-alkaloid site-
MoA active in B-cell Lymphoma
3-4 molecules/ antibody

SELECTIVE TARGET

Selectively expressed on B-cells

Humanized IgG1 mAb

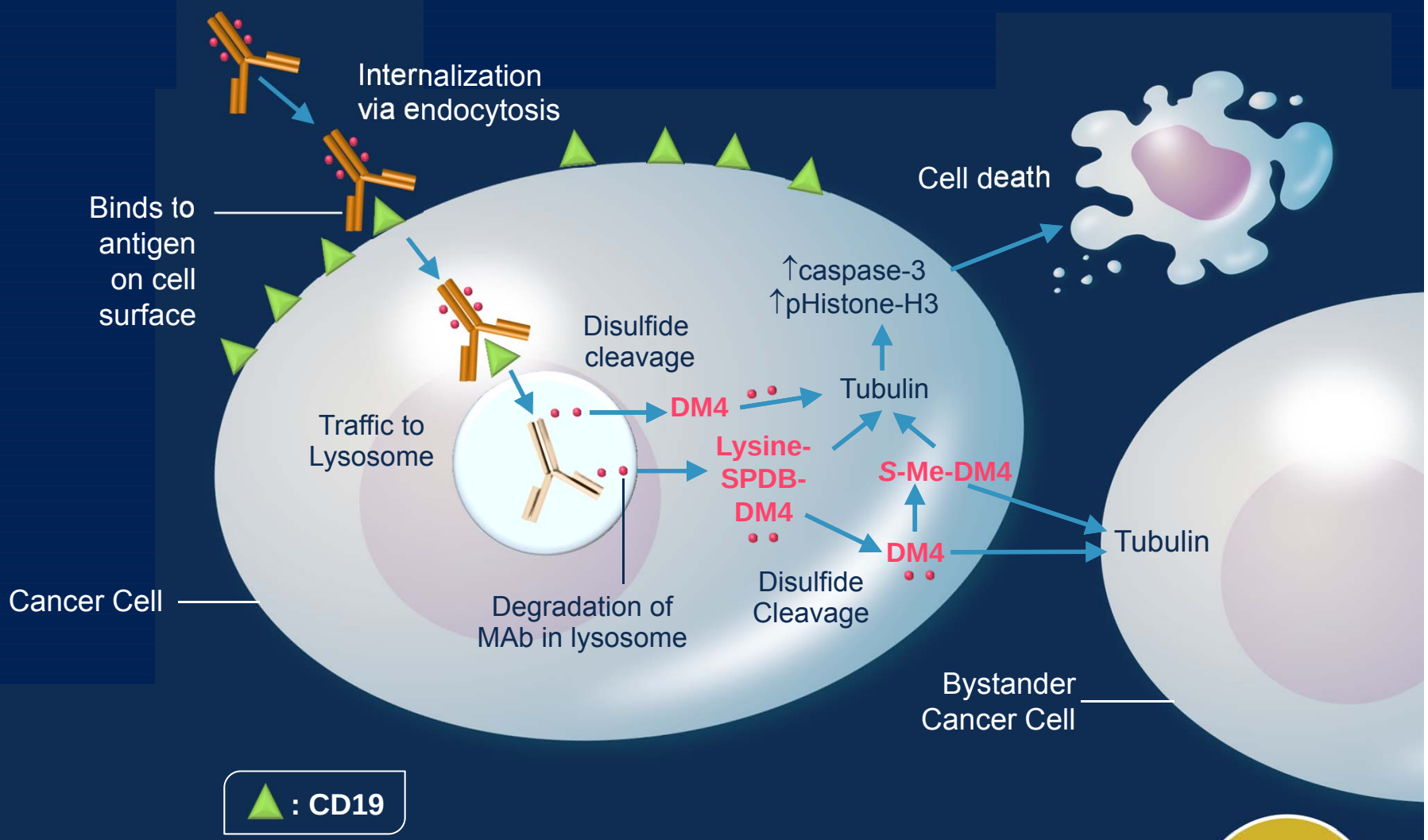


STABLE LINKER

SPDB: optimized **cleavable** linker
[N-Succinimidyl-4-(2-Pyridyldithio)butanoic acid]

Hindered disulfide bond stable in bloodstream

How does SAR3419 work?



Based on Erickson *et al. Cancer Res.* – April 15, 2006.

Background

- **Data from phase I** (relapse/refractory NHL)
  - → TED 6828: SAR3419 administered every 21 days up to 6 cycles
    - 39 patients treated at dose levels 10 to 270 mg/m²
    - DLTs: **reversible ocular toxicity and peripheral neuropathy**
    - MTD: **160 mg/m²**
    - ORR at the MTD: **22%**
  - → TED 6829: SAR3419 weekly dose for 8-12 doses:
    - 44 patients treated at dose levels 5 to 70 mg/m²
      - 1 DLT at 70 mg/m² (grade 3 neutropenia requiring dose delay)
      - Grade 2 ocular late events at 70 mg/m²
      - MTD: **55 mg/m²/week**
      - ORR: **33%**
    - 25 patients treated at MTD with modified schedule: **4 weekly administrations, followed by 1 dose every 2 weeks** (optimized schedule)**:**
      - Safety improvement; efficacy preserved in DLBCL patients
- **Data from phase II SAR3419 + rituximab R/R DLBCL**
  - → 55 mg/m² optimized schedule
    - **ORR**: 58.3% relapsed patients, 42.9% patients refractory to last Tx, 15.4% patients primary refractory

Younes A et al, JCO 2012 - Ribrag et al ,Clin Canc Res , 2014 - Coiffier B et al, ASH 2013 abst 4395

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STARLYTE Study Objectives (1)

- **Primary objective:**
  - → To determine the overall response rate (ORR) in CD19+ DLBCL patients
    - Relapsed/refractory
    - After failure of at least 1 prior line of standard therapy
    - Primary refractory patients - not eligible

STARLYTE Study Objectives (2)

- **Secondary:**
  - → Duration of response (DoR), Progression Free Survival (PFS) and Overall Survival (OS)
  - → Global safety profile
  - → Pharmacokinetics (PK) of SAR3419 and its metabolites DM4 and Me-DM4
  - → Immunogenicity of SAR3419
- **Exploratory:**
  - → characterize patient's tumor tissue for expression of biomarkers
  - → correlate antitumor and biological activity of SAR3419 with biomarker status

STARLYTE Study Design

- **Drug administration**
  - → SAR 3419 (55 mg/m²), 4 weekly administrations followed by bi-weekly administrations until progression
  - → One cycle defined as a 4-week period except for cycle 1 which should last 5 weeks
  - → Premedication:
    - ▶ Histamine blocker (diphenhydramine 50 mg i.v.),
    - ▶ Antipyretic/analgesic (acetaminophen 650 mg p.o. 30-45 min before)
- **Response assessment:**

  Cheson criteria 2007 (tumor assessment every 3 months)
- **Statistical hypothesis:**
  - → Primary endpoint: ORR
    - ▶ H0 ORR: < 20%
    - ▶ H1 ORR: ≥ 40%
  - → 44 patients evaluable for response; 90% statistical power to reject a null RR of 20% with a one-sided α level of 5%

STARLYTE Main eligibility criteria

- **Histological diagnosis of DLBCL** (de novo or transformed) **based on recent biopsy/FNA**
- **CD19 positive disease** (> 30% for CD19 positive cells)
- **Relapse or refractory after at least one standard treatment including rituximab for aggressive setting, not eligible for ASCT or in relapse after ASCT**
  - → Primary refractory patients (progressed during or within 6 m from the end of 1st line Tx) were not eligible
- **No corneal abnormalities, recent history of eye surgery, keratitis or optic neuropathy**
  - → Ophtalmological exam at baseline and EOT

Demography - SAFETY population

Characteristics	N=61 (%)
Histology type as per investigator • **De novo / Transformed**	**50 (82) / 11 (18)**
Age median (years) [range]	**69 [30:88]**
Age group (years) N (%) • **> 60**	**52 (85.2)**
Sex: N (%) • **Male / Female**	**31 (50.8) / 30 (49.2)**
ECOG PS: (N=60) N (%) • **0 / 1 / 2**	**27 (45) / 26 (43.3) / 7 (11.7)**
Ann Arbor stage • **III / IV**	**15 (24.6) / 31 (50.8)**
LDH baseline > ULN (N=60)	**41 (68.3)**
Extranodal involvement • **> 1 site**	**36 (59)** **16 (26.2)**
Bone marrow involvement	**13 (21.3)**

Disease characteristics (2) - SAFETY population

Characteristics	N=61 (%)
Bulky disease (at least one lesion ≥5 cm)	28 (45.9)
Secondary IPI • Low risk (0-1 factor) / Low intermediate risk (2 factors) • High intermediate risk (3 factors) / High risk (4/5 factors)	 12 (19.7) / 11 (18) 25 (41) / 13 (21.3)
Number of prior regimens • 0 / 1 / 2 • 3 • > 3 Median [range]	 1 (1.6) / 25 (41) / 17 (27.9) 9 (14.8) 9 (14.8) 2 [0:9]
Prior transplant for DLBCL	12* (19.7)
Status at study entry (N=60) • Relapsed • Refractory to last regimen • Primary refractory	 28 (46.7) 16 (26.7) 16 (26.7)
Time to progression for Primary Refractory patients (N=16) • [0; 3 months] • [3; 6 months]	 9 (56.3) 7 (43.8)

STARLYTE Study status on May 2014

Characteristics	N=61 (%)
Total number of cycles per patient: • **Median [range]**	**3 [1:10]**
Duration of study treatment (weeks): • **Median [range]**	**13.3 [5:41]**
Treatment status • **On treatment** • **Discontinuation**	**5 (8.2)** **56 (91.8)**
Reason for treatment discontinuation • **Progressive Disease** • **Adverse Event** • **Other reason****	**44 (72.1)** **4 (6.6)*** **2 (3.3)**
Status at last study contact • **Alive** • **Dead** - deaths within 42 days from last dose SAR3419 - deaths more than 42 days from last dose SAR3419	**21 (34.4)** **40 (65.6)** 7 (11.5) 33 (54.1)

*** 2 pts with gr 2 thrombocytopenia (cy 1),**
1 pt gr 3 thrombocytopenia (cy 5) and 1 pt gr 4 pyrexia and acute pulmonary oedema cy 1

**** investigator's decision**

STARLYTE - Overall Response Rate

55 patients were evaluated for the response

	PP	Refr. to last regimen	Relapse	MPP	Primary refractory
N (%)	**41**	15	26	55	14
ORR *(90%CI)*	**18 (43.9%)**[#] (30.6-57.9%)	4 (**26.7%**) (9.7-51.1%)	14 (**53.8%**) (36.2-70.8%)	21 (**38.2%**) (27.2-50.2%)	3 (**21.4%**) (6.1-46.6%)
CR	**4 (9.8%)**	1 (6.7%)	3 (11.5%)	5 (9.1%)	1 (7.1%)
PR	**14 (34.1%)**	3 (20.0%)	11 (42.3%)	16 (29.1%)	2 (14.3%)
SD	7 (17.1%)	3 (20.0%)	4 (15.4%)	9 (16.4%)	2 (14.3%)
PD	16 (39.0%)	8 (53.3%)	8 (30.8%)	25 (45.5%)	9 (64.3%)

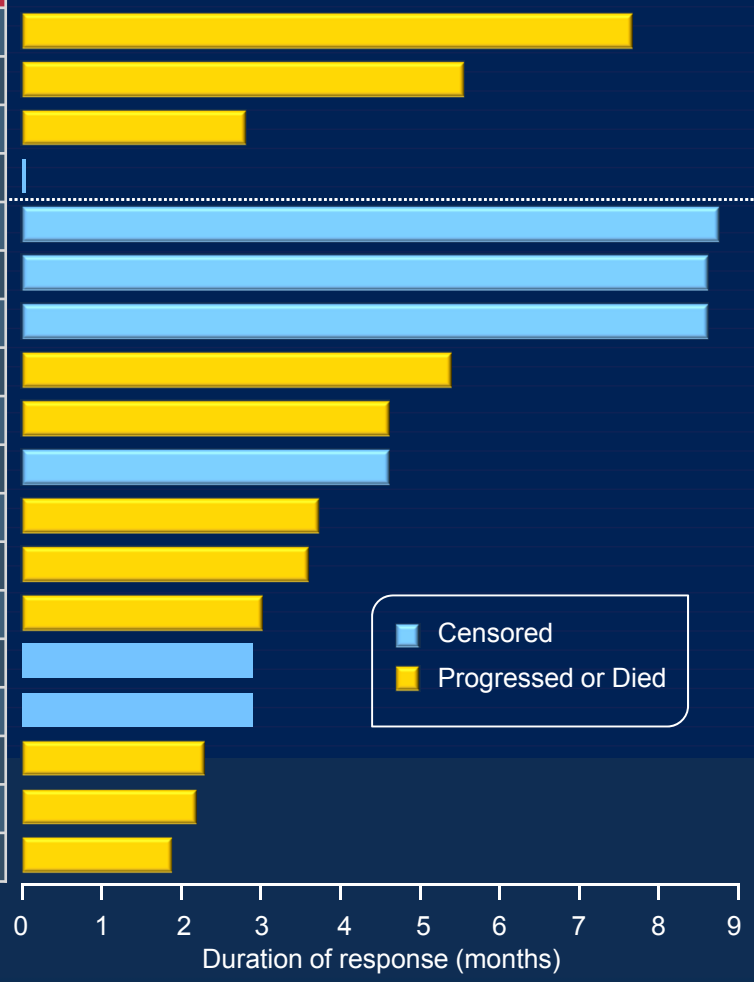
Per protocol (PP): all patients without any important protocol deviation impacting efficacy at study entry and who had a post-baseline evaluation of response

Modified PP (MPP): PP population and primary refractory pts without any other major deviation at study entry

[#] $p < 0.0001$ *(vs null hypothesis)*- estimated by Clopper-Perason exact method

STARLYTE - Duration of Response - PP population (median FUP 12.8 months)

DLBCL status	Patient Id	BOR	Nb cycles	Duration
Refractory	203001002	PR	10	7.75
	616003002	PR	10	5.55
	380003002	PR	9	2.79
	724004001	CR	1	0.03
Relapse	724004002	CR	14	8.80
	724002001	CR	12	8.74
	724001004	CR	12	8.71
	84005001	CR	8	5.49
	826002003	PR	9	5.8
	380007001	CR	6	4.67
	724004003	PR	11	4.63
	792001002	PR	6	3.81
	826001005	PR	6	3.68
	56001002	PR	6	3.02
	792003001	PR	7	2.92
	203001008	PR	7	2.30
	840005003	PR	4	2.20
	724003002	PR	5	1.91



Median DoR 5.49 m (0-8.8

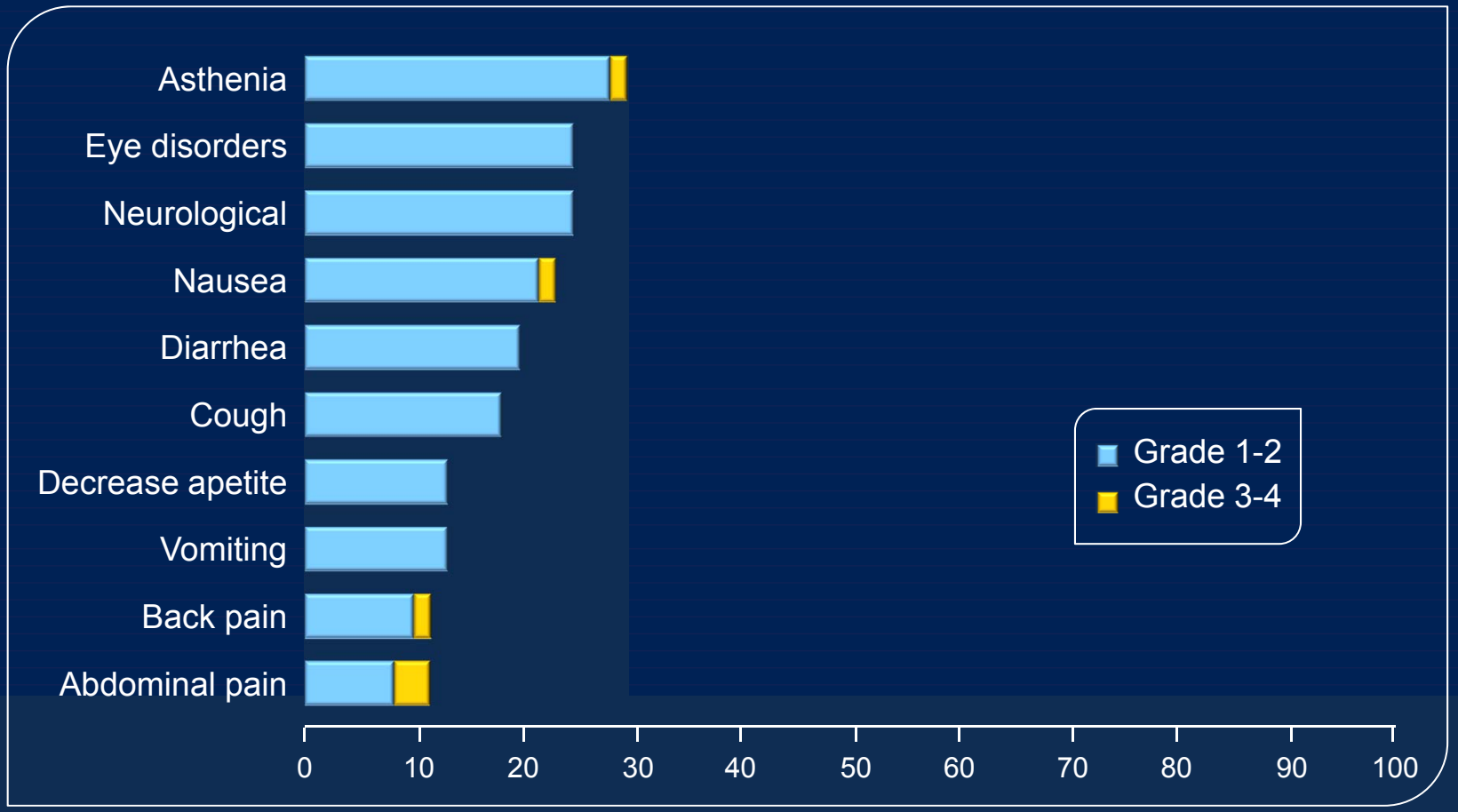
Treatment Emergent Adverse Events
Safety population (Overview)

	N=61 (%)
Pts with any TEAE	61 (100)
Pts with any gr 3-4 TEAE	23 (37.7)
Pts with any gr 5 TEAE*	8 (13.1)
Pts with any treatment emergent SAE**	24 (39.3)
Pts with any study drug related TEAE	33 (54.1)
Pts with any TEAE leading to dose modification • TEAEs leading to dose delay • TEAEs leading to dose omission • TEAEs leading to dose interruption	17 (27.9) 13 (21.3) 4 (6.6) 1 (1.6)
Pts with any TEAE leading to treatment discontinuation	**4 (6.6)**

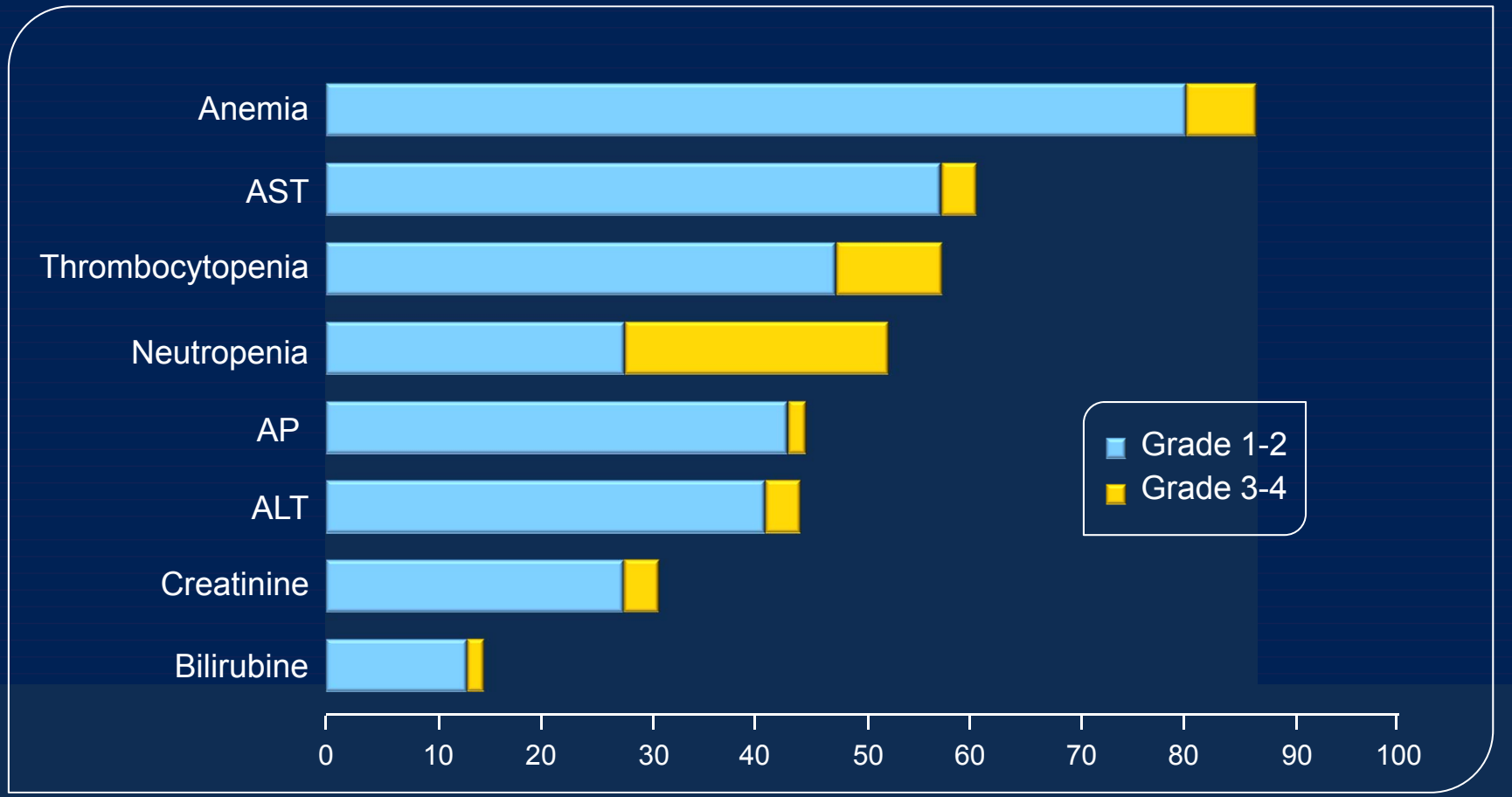
*All in the context of PD, except one febrile neutropenia that occured under further therapy post-PD to SAR3419;

** only 6 SAEs (5 pts) were considered related to SAR3419: pneumonia, hepatotoxicity (2), abdominal pain, nausea, febrile neutropenia

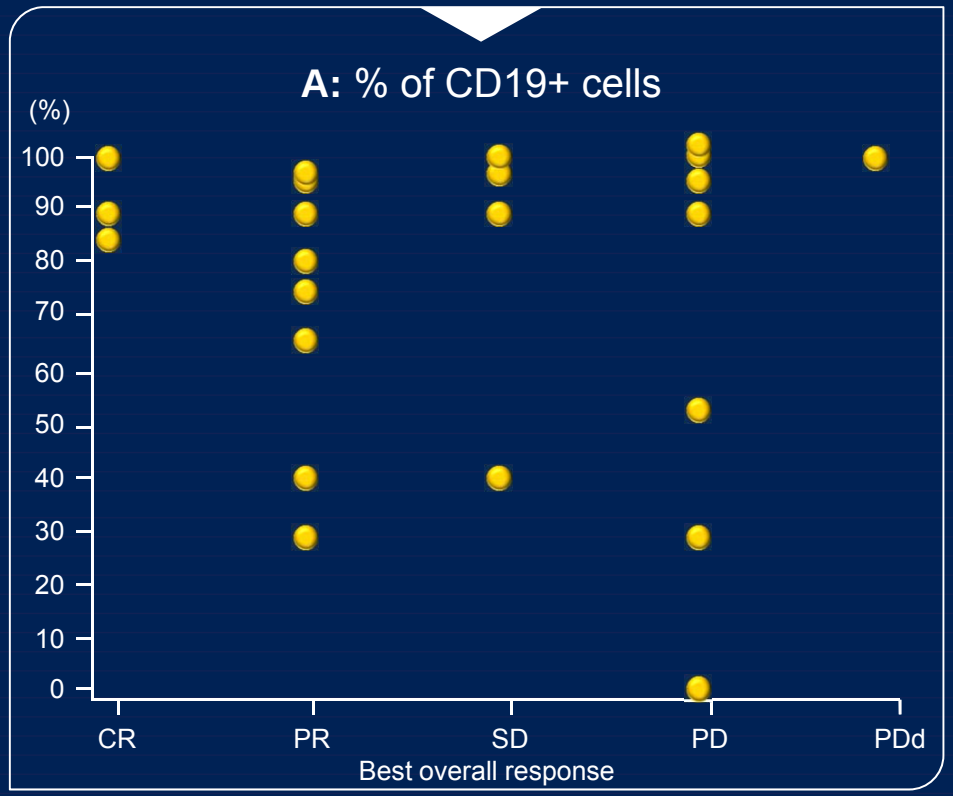
Most Frequent TEAEs > 10% (except lab TEAEs) (N=61)



Laboratory Abnormalities (N=61)



Biomarker Analysis - Response according to:



	Per Protocol	% CD19+ Cells (n=37)	
	(n=41)	<98 * (n=27)	≥98 (n=10)
Responders	**18 (43.9%)**	**15 (55.6%)**	**2 (20.0%)**
Non responders	**23 (56.1%)**	**12 (44.4%)**	**8 (80.0%)**

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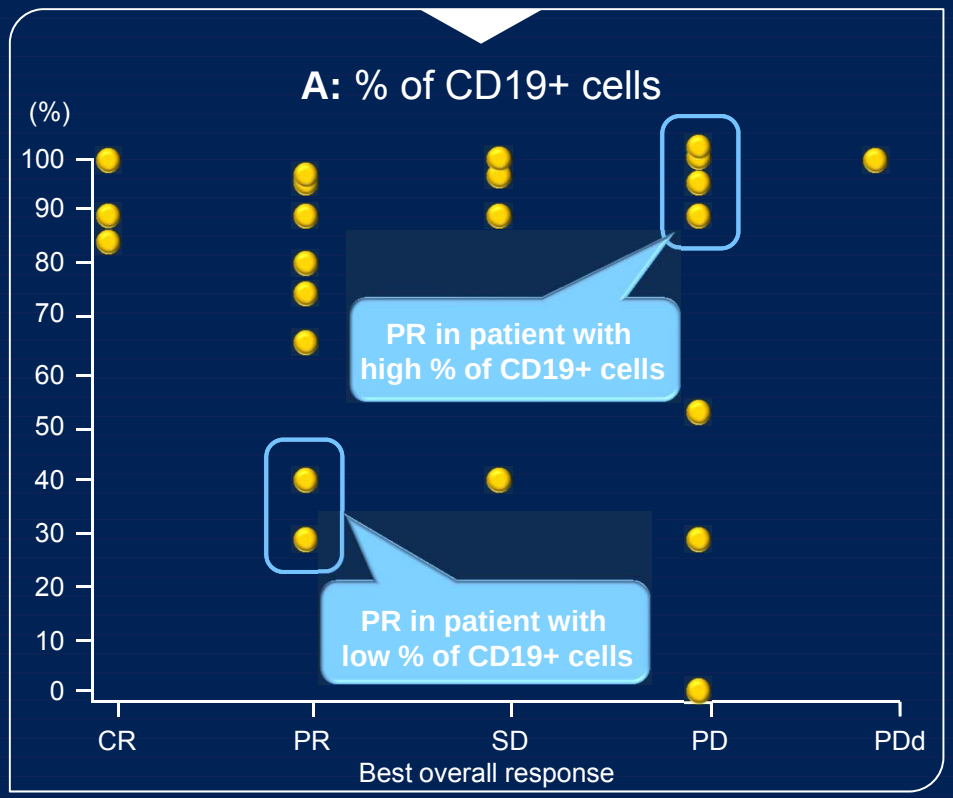

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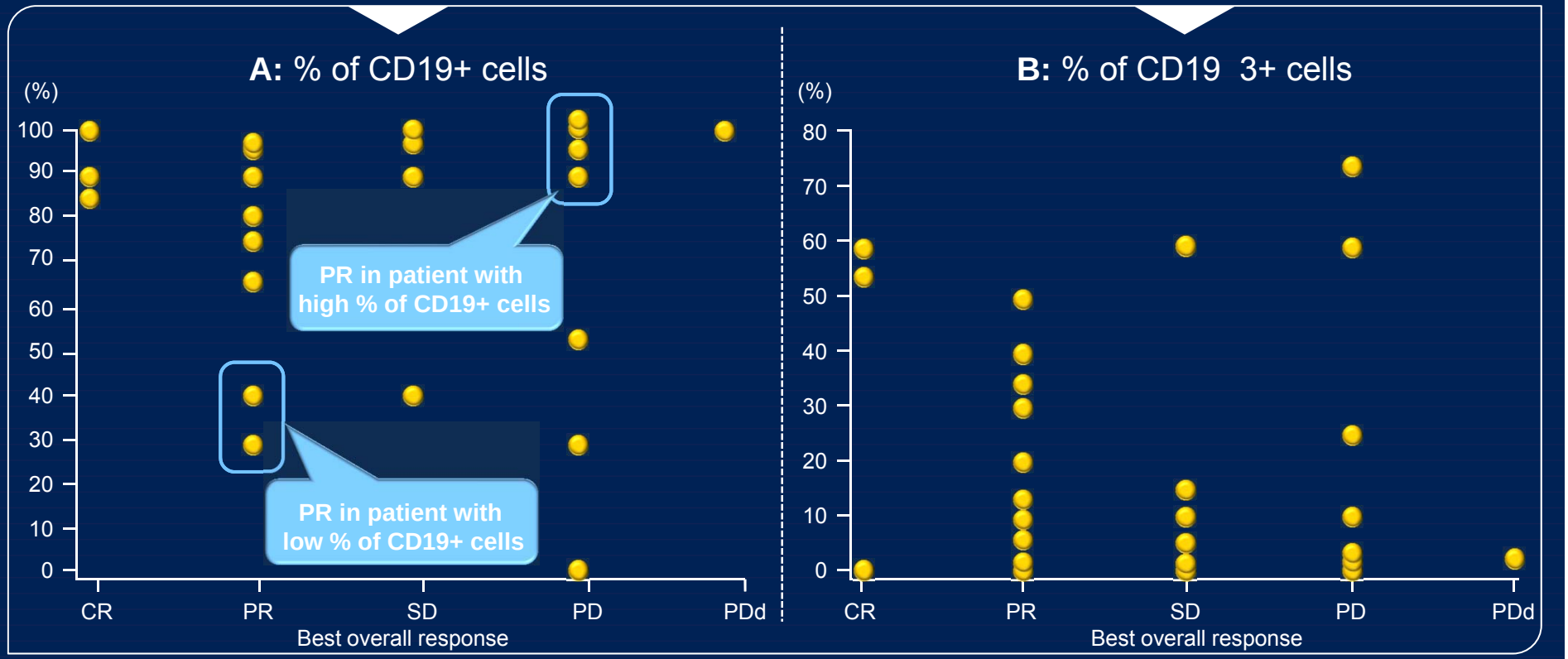

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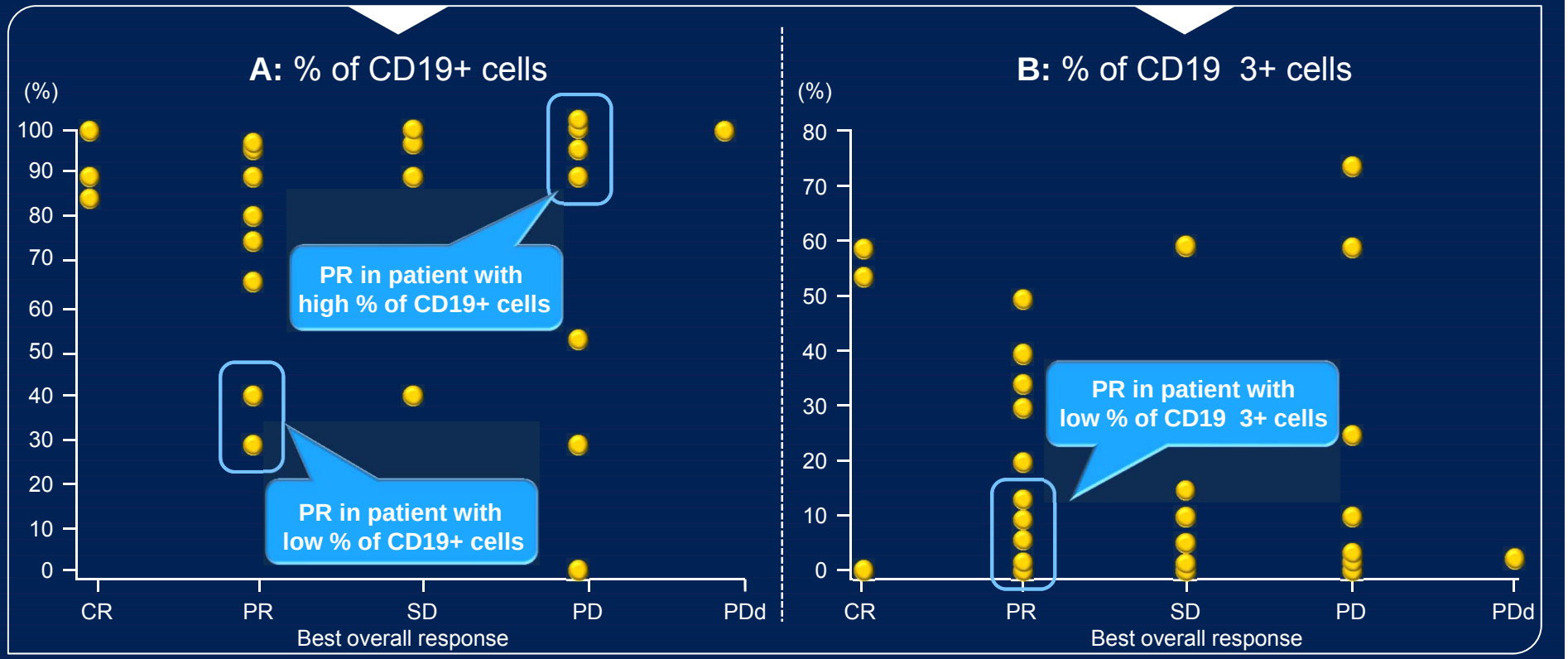

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23 (56.1%)	**17 (65.4%)**	**3 (27.3%)**

* The optimal cut-off point for each measure of CD19 expression was identified using the minimal p-value from the two-sided Fisher exact test for difference in response rate between BM+ and BM- subgroups; no significant optimal cut-off point for each measure of CD19 expression was found

Biomarker Analysis
Response according to COO

	Cells of Origin (n=37)		
	ABC	GCB	Unclass,
N	**16**	**17**	**4**
Responders	**8 (50.0%)**	**7 (41.2%)**	**2 (50.0%)**
Non responders	**8 (50.0%)**	**10 (58.8%)**	**2 (50.0%)**

➔ **No significant difference in terms of ORR based on COO classification**

Biomarker Analysis
Response according to MYC/BCL2 expression

	Double MYC/BCL2 expression (n=23)	
	Yes	No
N	**10**	**13**
Responders	**5 (50.0%)**	**9 (69.2%)**
Non responders	**5 (50.0%)**	**4 (30.8%)**

* % positive cells of MYC≥40% and % positive cells of BCL2≥70% (IHC)

Difficult to interpret results with MYC/BCL2 population

- Only 23 patients evaluable
- ORR of 61% *vs* 44% in the PP population

Conclusions

- **Proof of Concept**

  Relapse & Refractory to last regimen DLBCL patients with an ORR of 43.9%

- **Favorable safety profile**
  - → Few related SAEs and related grade 3-4 AEs
  - → No grade 3-4 peripheral neuropathy or keratitis
  - → Reversible and manageable grade 1-2 ocular events
  - → Moderate hematological toxicity

- **Biomarkers**
  - → Potential signal on % of CD19+ at 3+ intensity to be confirmed in further studies
  - → No signal on different response according to COO
  - → Potential signal in Double Hit* patients: **5/10 (50%)** responders in STARLYTE

*% positive cells of MYC≥40% and % positive cells of BCL2≥70% (IHC)