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Escalating Doses of AZD0486, a Novel CD19xCD3 T-cell Engager, Result in High Complete Remissions with Rapid Clearance of Minimal Residual Disease in Patients with Relapsed/Refractory Follicular Lymphoma

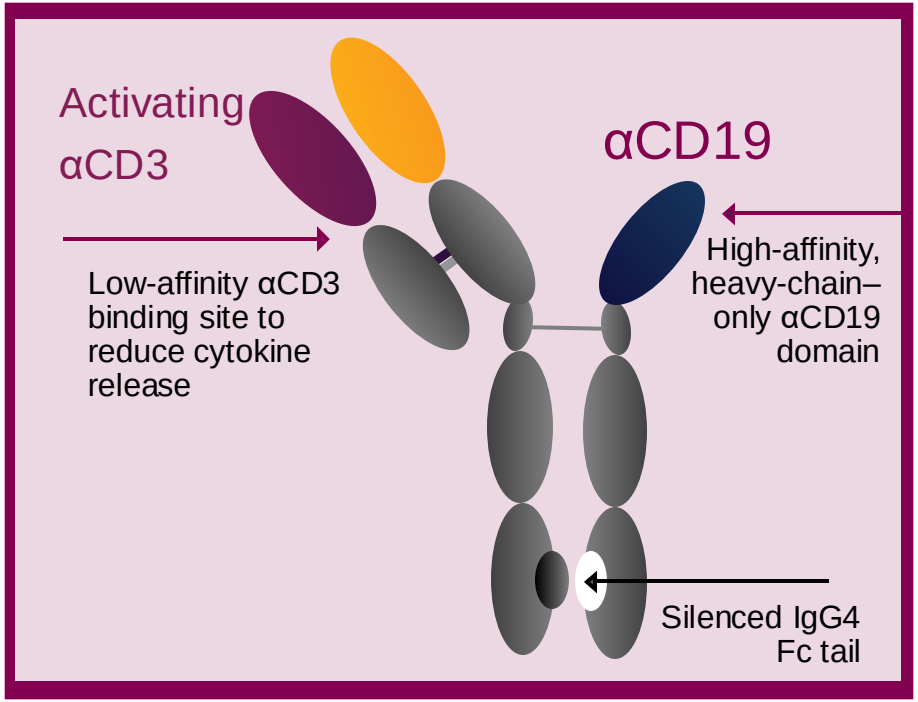
Jing-Zhou Hou,[1] Ranjit Nair,[2] Ryan Jacobs,[3] Tae Min Kim,[4] Seok-Goo Cho,[5] Dai Maruyama,[6] Sumana Devata,[7] Yazeed Sawalha,[8] Dok Hyun Yoon,[9] Constantine S. Tam,[10] Koji Izutsu,[11] Matthew Matasar,[12] Don Stevens,[13] Aravind Ramakrishnan,[14] Denise Brennan,[15] Xu Zhu,[15] Robin Lesley,[16] Yasuhiro Oki,[16] David Sermer,[17] Sameh Gaballa[18]

[1]Lemieux Center for Blood Cancers, UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Atrium Health Levine Cancer Institute, Charlotte, NC, USA; [4]Seoul National University Hospital, Seoul, Republic of Korea; [5]Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [6]Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan; [7]Medical College of Wisconsin, Milwaukee, WI, USA; [8]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [9]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [10]Alfred Hospital and Monash University, Melbourne, Victoria, Australia; [11]National Cancer Center Hospital, Tokyo, Japan; [12]Rutgers Cancer Institute, New Brunswick, NJ, USA; [13]Norton Cancer Institute, Norton Health Care, Louisville, KY, USA; [14]Sarah Cannon Transplant and Cellular Therapy, St. David's South Austin Medical Center, Austin, TX, USA; [15]AstraZeneca, Waltham, MA, USA; [16]AstraZeneca, South San Francisco, CA, USA; [17]AstraZeneca, New York, NY, USA; [18]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Introduction

- AZD0486 is an IgG4 fully human CD19xCD3 bispecific T-cell engager (TCE), with a half-life of 8–12 days[1-3]
- Two step-up dosing (C1D1: 0.27 mg; C1D8: 1 mg; C1D15: target dose) enabled administration of the drug to achieve therapeutic target dose[4,5]
- Here, we present updated efficacy, safety, and PK/PD data of AZD0486 in patients with R/R FL

AZD0486 Structure



1. Malik-Chaudhry HK, et al. *MAbs*. 2021;313:1890411. **2.** Trinklein ND, et al. *MAbs*. 2019;11:639-52. **3.** Hou JZ, et al. *Blood.* 2022;140(Suppl 1):1474-5. **4.** Gaballa S, et al. *Blood.* 2023(suppl 1):1662. **5.** Devata S, et al. *HemaSphere.* 2024;8(Suppl 1):2059-2060.

First-in-Human Phase 1 Study of AZD0486

Key Eligibility Criteria

- Adults with R/R B-NHL
- CD19+ by flow cytometry or IHC
- ≥2 prior lines of therapy
- Prior anti-CD19 therapies, CAR-T cells, and anti-CD20 TCE allowed
- ≥1 measurable lesion
- No active CNS disease
- No circulating disease
- ECOG PS ≤2

Assessments

- Disease response: PET-CT by RECIL by ICR[1]
- CRS and ICANS: ASTCT criteria[2]
- AEs: CTCAE v5.0
- MRD: PhasED-Seq CLARITY assay in plasma ctDNA (sensitivity ~10^{-6})

Endpoints

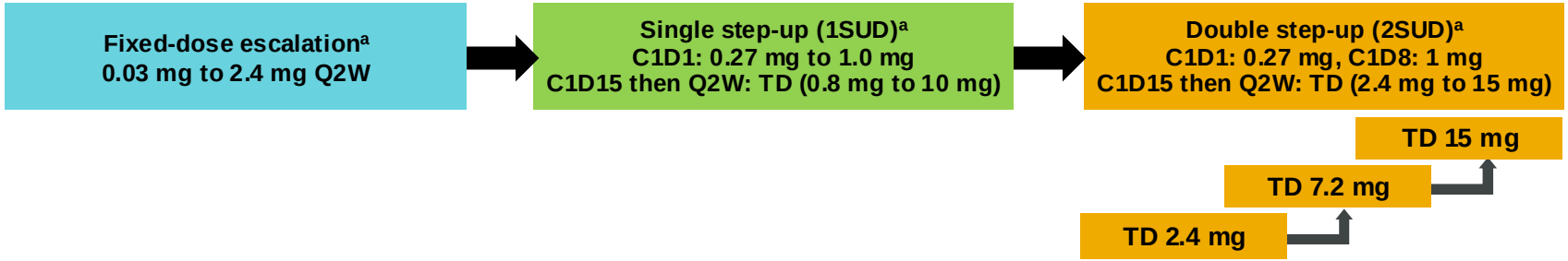
- **Primary:** safety/tolerability, PK, MTD, and RP2D
- **Secondary:** antitumor activity

ICR, independent central review; RECIL, Response Evaluation Criteria in Lymphoma.

1. Younes A, et al. *Ann Oncol.* 2017;28:1436-7. **2.** Lee DW, et al. *Biol Blood Marrow Transplant.* 2016;25:625-38.

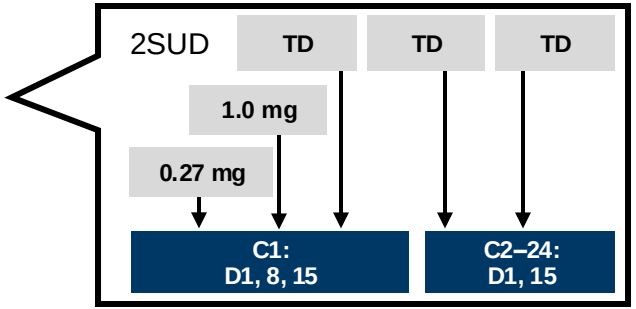
AZD0486 in a First-in-Human Phase 1 Study

Overall Study Design



2SUD Treatment Schedule

- AZD0486 is administered intravenously
- 2SUD on C1D1, C1D8 with target dose (TD) on C1D15, then on D1, D15 each 28-day cycle up to 2 years
  - Cycle 1 doses were inpatient
- Patients with 2 consecutive CRs after cycle 6 may receive AZD0486 every 4 weeks



NCT04594642; data cutoff: 18 June 2024.

[a]In the FL cohort (N=56), 6 (11%) patients received a fixed dose, 12 (21%) received 1SUD, and 38 (68%) received 2SUD.

Most Patients Had Heavily Pretreated FL

Characteristic	N=56[a]	Patients who received target doses of ≥2.4 mg (n=41)
Age, median (range), years	62 (33–86)	63 (33–79)
ECOG PS score 2, n (%)	2 (4)	1 (2)
Ann Arbor stage III–IV, n (%)	45 (80)	35 (85)
CD20-negative disease at study entry, n (%)	9 (16)	6 (15)
Bulky disease[b], n (%)	12 (21)	9 (22)
POD24, n (%)	19 (34)	14 (34)
Median prior lines of therapy (range)	3 (2–12)	3 (2–12)
2 lines, n (%)	20 (36)	14 (34)
≥3 lines, n (%)	36 (64)	27 (66)
Refractory to last line of therapy, n (%)	17 (30)	14 (34)
Prior types of treatment, n (%)		
Lenalidomide	23 (41)	15 (37)
CD19-directed CAR T	7 (13)	6 (15)
CD20 T-cell engager	4 (7)	4 (10)
Allogeneic or autologous SCT	3 (5)	2 (5)
Polatuzumab vedotin	1 (2)	1 (2)

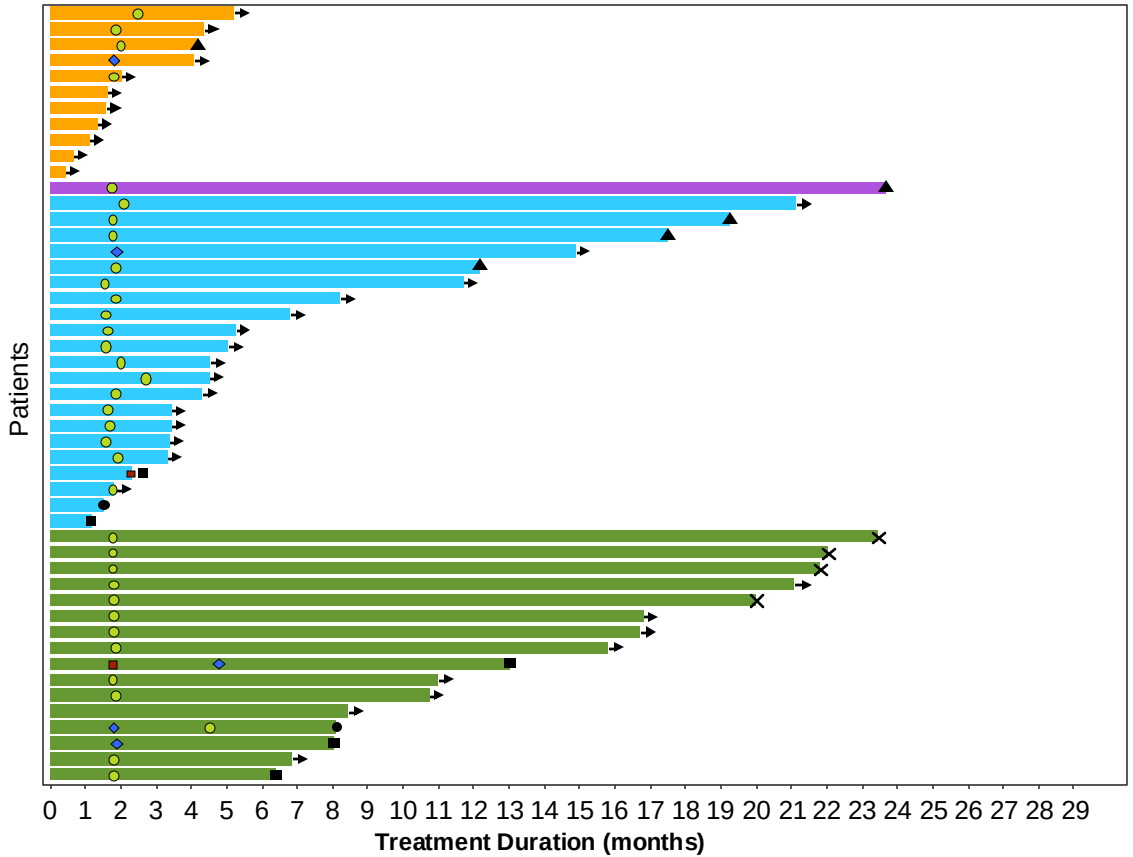
[a]Racial demographics included Asian (34%), Black or African American (2%), White (59%), and Not Reported (5%); 57% of patients were male, 43% were female.
[b]Bulky disease was defined as target lesion ≥7 cm or 3 target lesions each ≥3.

High Response Rates Overall and in High-Risk Populations

Patients	N	ORR	CR rate
All TD ≥2.4 mg	41	95%	85%
Baseline and Disease Characteristics			
POD24	14	100%	100%
Bulky disease	9	78%	56%
CD20 negative disease	6	100%	83%
Refractory disease	6	83%	83%
Prior Therapies			
CD20 TCE	4	75%	75%
CD19 CAR-T	6	83%	67%
Lenalidomide	14[a]	93%	93%

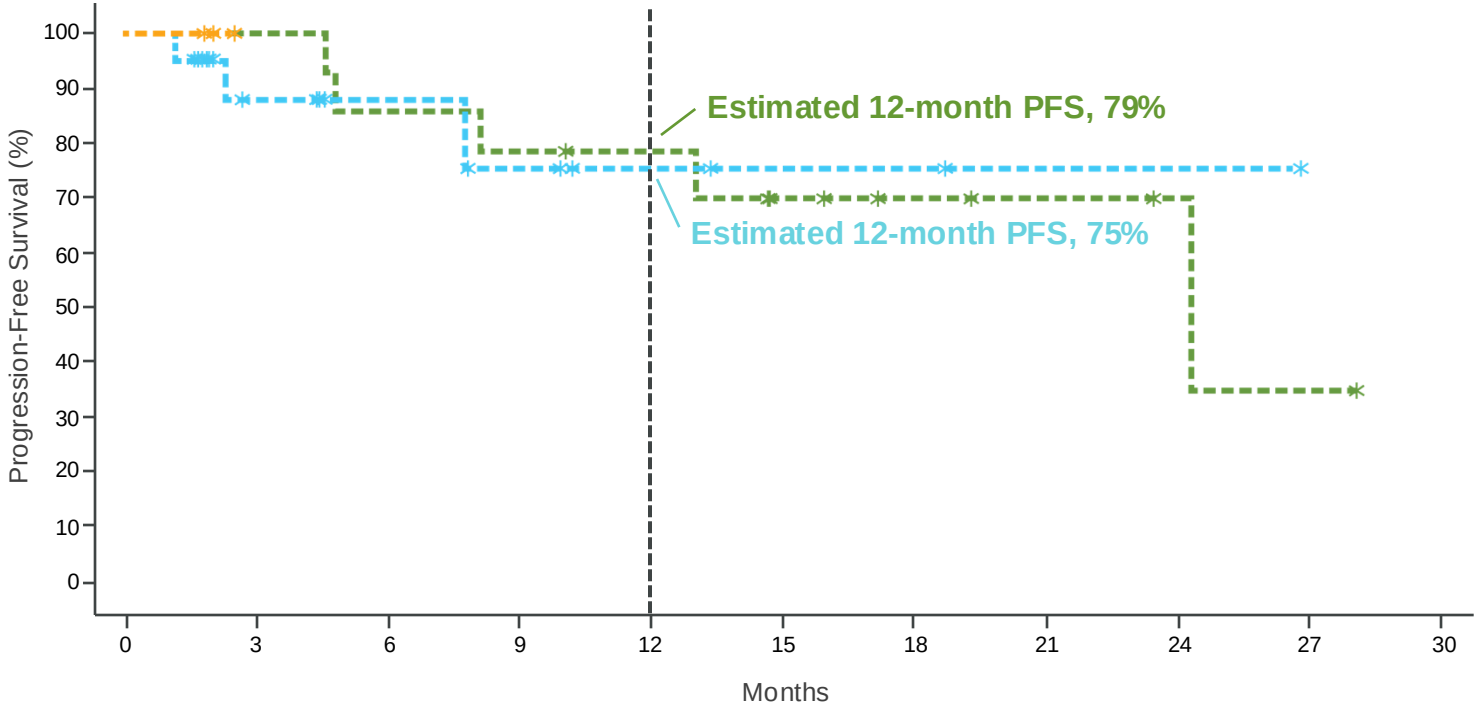
[a]One patient died prior to response assessment.

Responses Were Durable After Treatment With AZD0486



- Median study follow up: 8.4 months (range, 0.5–39.4)
- Median DOR has not been reached
- 2/41 patients in CR relapsed

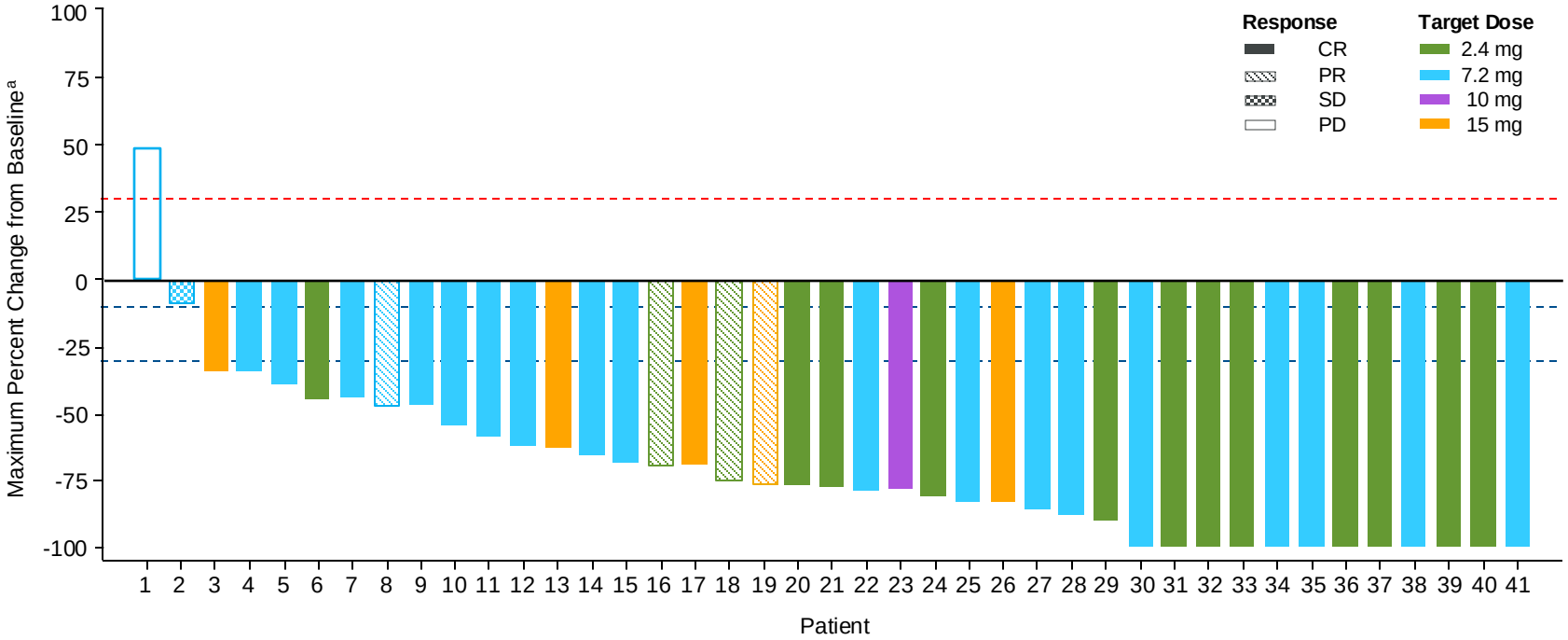
Progression-Free Survival by Target Dose



No. at risk											
2.4 mg	14	14	12	11	9	6	4	3	2	1	0
7.2 mg	21	11	7	5	3	2	2	1	1	0	
15 mg	5	0									

Tumor Regression

- ORR was 95% and CR rate was 85% in patients who received AZD0486 ≥2.4 mg (n=41)



[a]Waterfall chart indicates tumor shrinkage in evaluable patients as assessed by RECIL (change in sum of longest diameters).

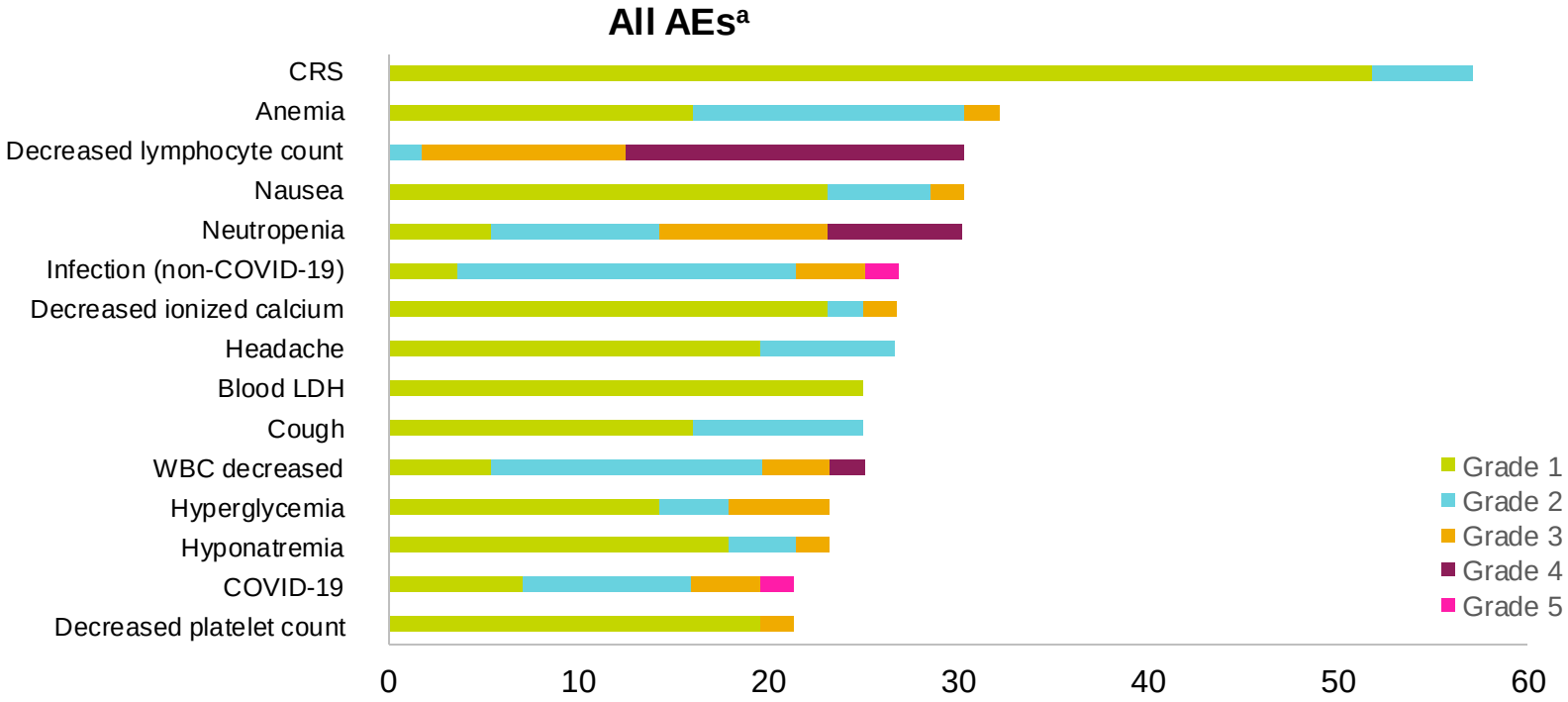
High Rates of uMRD Were Achieved in Patients With CR

Target dose	Within 12 weeks (uMRD/MRD-evaluable[a] CR)	Anytime (uMRD/MRD-evaluable[a] CR)
2.4 mg	**89%** (8/9)	**100%** (9/9)
7.2 mg	**93%** (13/14)	**93%** (13/14)
15 mg	**100%** (3/3)	**100%** (3/3)
≥2.4 mg	**92%** (24/26)	**96%** (25/26)

- MRD was assessed ~every cycle in cycles 1–3, then every other cycle
- MRD was assessed in plasma by Foresight PhasED-Seq CLARITY assay[b]

[a]MRD is considered evaluable if Phased variants (PVs) were detected in baseline tumor or plasma and longitudinal plasma samples were available for PV tracking.
[b]Foresight PhasED-Seq CLARITY assay has a detection limit of <1 part per million in DLBCL. It is indicated for DLBCL, FL, and classic Hodgkin lymphoma.

Adverse Events in All Patients With FL



- The majority of AEs were Grade 1 or 2
- No patients discontinued due to treatment-related AEs

[a]In ≥20% of patients who received fixed, 1SUD, and 2SUD schedules

Only Grade 1 CRS and ICANS in 2SUD Cohorts

AE grade	AZD0486 2SUD cohort (n=38)	
	CRS n (%)	ICANS n (%)
1	19 (50)	1 (3)
2	0	0
3	0	0
4	0	0
5	0	0

- Events occurred during SUD or following administration of the first target dose
  - 2 events of CRS occurred at target dose
  - 0 events of ICANS occurred at target dose
- Tocilizumab was used to manage CRS in 5 (13%) patients
- All patients reached assigned target dose

Conclusions

- AZD0486 showed a high CR rate and was well tolerated in patients with heavily pretreated follicular lymphoma
- ORR 95% and CR rate 85% in R/R FL at target doses ≥2.4 mg
  - Among patients achieving CR, uMRD was achieved in 92% by 12 weeks post-treatment
  - The exposure–response analysis to support the determination of a recommended phase 2 target dose is presented in poster #2794 (Sunday poster session)
- 2SUD allows administration of target doses up to 15 mg with acceptable toxicity
  - All CRS events and the ICANS event in the 2SUD cohorts were grade 1
- Additional studies of AZD0486 in patients with 1L and R/R FL are ongoing

Acknowledgments

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