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Results from the first-in-human phase 1 study of LY4170156, an antibody drug conjugate (ADC) targeting folate receptor alpha (FRα) in recurrent platinum resistant high-grade serous ovarian cancer (HGSOC)

Isabelle Ray-Coquard[1], Chrisann Kyi[2], Bhavana Pothuri[3], Ana Oaknin[4], Nehal Lakhani[5], Takafumi Koyama[6], Shigehisa Kitano[7], William B. McKean[8], Ainhoa Madariaga[9], Meena Okera[10], Myong Cheol Lim[11], Alejandro Perez-Fidalgo[12], Giuseppe Curigliano[13], Domenica Lorusso[14], Ramez N. Eskander[15], Shannon N. Westin[16], Chunxiao Wang[17], Marine Manvelyan[17], Emin Avsar[17], David M. O'Malley[18]

[1]Centre Leon Berard, University Claude Bernard, Lyon, France; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Division of Gynecologic Oncology, Laura & Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA; [4]Medical Oncology Service, Vall d'Hebron Institute of Oncology, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [5]START Center for Cancer Research, Grand Rapids, MI, USA; [6]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; [7]Department of Advanced Medical Development, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [8]Utah Cancer Specialists, START Center for Cancer Research, Salt Lake City, UT, USA; [9]Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain; [10]Medical Oncology, Cancer Research SA, Adelaide, Australia; [11]National Cancer Center, Goyang-si, Gyeonggi-do, Republic of Korea; [12]Department of Medical Oncology, Hospital Clinico Universitario de Valencia, Valencia, INCLIVA, Spain; [13]European Institute of Oncology, IRCCS, Milan, Italy and University of Milano, Milano, Italy; [14]Gynaecological Oncology Unit, Humanitas Hospital, San Pio X, Milan, and Humanitas University, Rozzano (MI), Italy; [15]Obstetrics, Gynecology, and Reproductive Science Department, University of California San Diego, La Jolla, CA, USA; [16]Department of Gynecologic Oncology and Reproductive Medicine, The MD Anderson Cancer Center, Houston, TX, USA; [17]Eli Lilly and Company, Indianapolis, IN, USA; [18]Division of Gynecologic Oncology, The Ohio State University, James Comprehensive Cancer Center, Columbus, OH, USA

OBJECTIVES

Determine the safety and efficacy of LY4170156 in patients with high-grade serous ovarian cancer (HGSOC) and other solid tumors (NCT06400472)

CONCLUSIONS

- LY4170156 was well-tolerated among HGSOC pts with no grade ≥3 drug related ocular, neuropathy, or alopecia events
- LY4170156 showed promising clinical activity in heavily pre-treated patients across all FRα expression levels and regardless of prior mirvetuximab soravtansine-gynx treatment
- FRAmework-01, is a global phase 3 trial investigating LY4170156 monotherapy in patients with PROC, and in combination with bevacizumab in patients with PSOC (NCT07213804)

Study is sponsored by Eli Lilly and Company

European Society for Medical Oncology (ESMO) 13th Annual Meeting; Berlin, Germany; October 17-21, 2025

Isabelle Ray-Coquard (isabelle.ray-coquard@lyon.unicancer.fr)

Declaration of Interests: advisory board (personal)– Roche, GSK, Mersana, Deciphera, Amgen, Oxnea, Merck Sereno, Agenus, Novartis, Macrogenics, Clovis, EQRX, Esai, SUTRO, BMS, Adaptimmune, Daiichi-Sankyo, Immunogen, SEAGEN, PMVPharma, AbbVie, LOXO LILLY, PHARMAND, Genmab, Incyte, Regeneron Pharmaceuticals; advisory board (institutional) – AstraZeneca; translational research (institutional) - BMS (COLIBRI trial), MSD (NEOPREMBROV trial); past president (non-financial interest) - GINECO; and principal investigator (non-financial interest) – PAOLA1

Background

- Folate receptor alpha (FRα) is overexpressed in ovarian cancer and is a clinically validated target for therapeutic intervention
- Mirvetuximab soravtansine-gynx is an FRα ADC with a DM4 microtubulin payload which is approved for the treatment of platinum-resistant ovarian cancer (PROC)
  - limited to high FRα tumor expression levels
  - associated with ocular toxicity and neuropathy
- LY4170156 is an ADC composed of an Fc-silent, FRα specific humanized IgG1 ADC linked to exatecan, a topoisomerase-I inhibitor, via a proprietary cleavable polysarcosine (PSAR) linker at a homogenous DAR of 8[1]
- LY4170156 demonstrated preclinical *in vivo* efficacy across all FRα expression levels and mirvetuximab soravtansine-gynx resistant ovarian models, as well as across multiple tumor types[1]

Study Design

- Key inclusion criteria are
  - Diagnosis of recurrent platinum-resistant ovarian cancer and other select metastatic and advanced solid tumors
  - Patients who progressed on prior mirvetuximab soravtansine-gynx were eligible
  - ≥18 years of age and ECOG PS 0-1
- Dose escalation utilized a mTPI-2 design and evaluated LY4170156 at dose levels ranging from 2-6 mg/kg Q3W IV
  - Dose escalation was followed by a randomized dose optimization cohort in HGSOC (2 mg/kg, 4 mg/kg, and 6 mg/kg)
  - 3-6 patients were enrolled per dose level to evaluate dose-limiting toxicities (DLTs) in Cycle 1 (21 days)
  - Selected dose levels were backfilled up to a total of 20 patients
- Key endpoints were safety, PK[2], RP2D determination, and antitumor activity per RECIST v1.1
- Data cutoff date was 30 Jul 2025

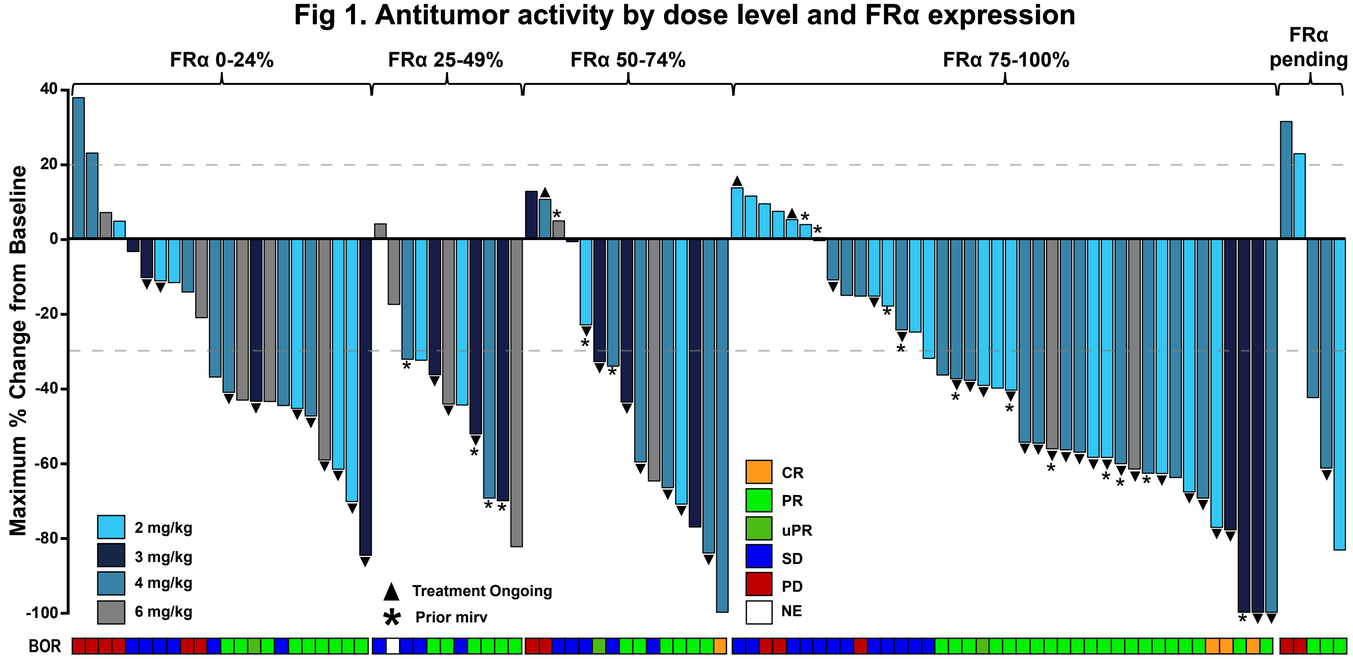
Results

Table 1. Baseline Characteristics

Characteristics	LY4170156 N=105[a]
Median age, years (range)	63 (40-89)
Race, n (%)	
White / Asian	68 (65) / 16 (15)
Black or African American / Not Reported	2 (2) / 19 (18)
ECOG PS, n (%)	
0 / 1	38 (36) / 67 (64)
Histology, n (%)	
Serous	97 (92)
Endometrioid	3 (3)
Carcinosarcoma	1 (1)
Other	4 (4)
FRα expression by IHC central testing, n (%)	
<75% at 2+ and/or 3+ intensity	54 (51)
≥75% at 2+ and/or 3+ intensity	46 (44)
Pending	5 (5)
Median prior systemic regimens (range)	5 (1-11)
Selected Prior Therapy, n (%)	
Mirv / Bevacizumab	18 (17[b]) / 92 (88)
PARPi / Topotecan	69 (66) / 10 (10)
Platinum-resistant[c]	101 (96)

[a]4 doses of LY4170156 were evaluated: 2 mg/kg (n=35), 3 mg/kg (n=17), 4 mg/kg (n=39), and 6 mg/kg (n=14). [b]61% had FRα ≥75%. [c]3 had missing data

Fig 1. Antitumor activity by dose level and FRα expression



Efficacy Evaluable Patients	FRα 0-24% (n=25)	FRα 25-49% (n=12)	FRα 50-74% (n=16)	FRα ≥75% (n=46)	FRα pending (n=5)	Total (N=104)
ORR[a], % (n/N)	40 (10/25)	50 (6/12)	50 (8/16)	54 (25/46)	60 (3/5)	50 (52/104)
CR, n	-	-	1	3	-	4
PR, n	10[b]	6	7[b]	22[b]	3	48[c]
DCR[d], % (n/N)	68 (17/25)	83 (10/12)	81 (13/16)	83 (38/46)	60 (3/5)	78 (81/104)

Efficacy evaluable patients are those who have a baseline assessment and at least one post-baseline response assessment or discontinued treatment prior to the first post-baseline response assessment. [a]ORR includes patients with CR and PR (confirmed, and unconfirmed [ongoing and pending confirmation]). [b]Includes 1 unconfirmed PR, ongoing and pending confirmation. [c]Includes 3 unconfirmed PRs, ongoing and pending confirmation. [d]Includes 2 SDs with non-measurable lesions not shown in the waterfall plot. FRα expression levels at 2+ and/or 3+ intensity were assessed using Ventana RxDx IHC assay.

Fig 2. Treatment Duration in Responders

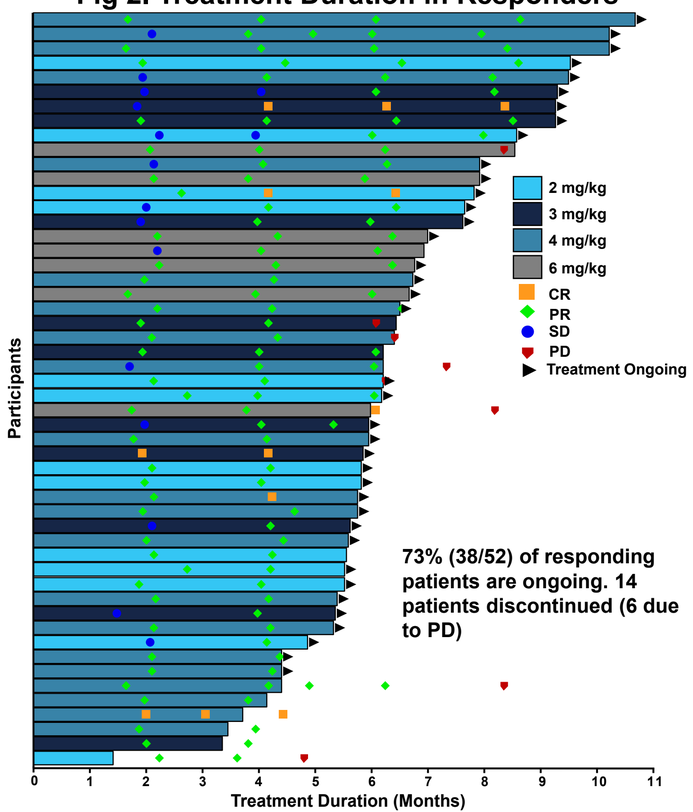


Table 2. Safety

Treatment-Emergent AEs (≥20%), All Doses and Patients	2 mg/kg (n=35)		3 mg/kg (n=17)		4 mg/kg (n=39)		6 mg/kg (n=14)		Total (N=105)	
Adverse Event, %	Any	G ≥3	Any	G ≥3	Any	G ≥3	Any	G ≥3	Any	G ≥3
Nausea	60	3	47	-	69	-	79	14	64	3
Fatigue[a]	60	3	41	-	46	-	71	7	53	2
Anemia	20	9	41	18	44	31	71	57	39	25
Vomiting	46	3	24	0	33	-	36	7	36	2
Neutropenia[a]	17	6	35	18	41	31	57	57	34	24
Diarrhea	26	-	29	-	44	3	29	0	33	1
Abdominal pain	43	6	6	-	23	-	14	7	26	3
Constipation	34	3	12	-	18	-	29	-	24	1
Decreased appetite	11	-	24	-	31	-	36	-	24	-
Dose reductions due to TEAEs, %	-		24		36		64		26	

[a]Consolidated terms: fatigue includes fatigue and asthenia; neutropenia includes neutropenia and neutrophil count decreased

- 50 pts are ongoing, 12 discontinued due to AEs (10 due to related AEs)
- 8% had grade 4 neutropenia, 2% had febrile neutropenia (no prophylactic GCSF used)
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References:

[1]Viricel W, et al. *Cancer Res, 2023,* 83 (7_Supplement): 1544

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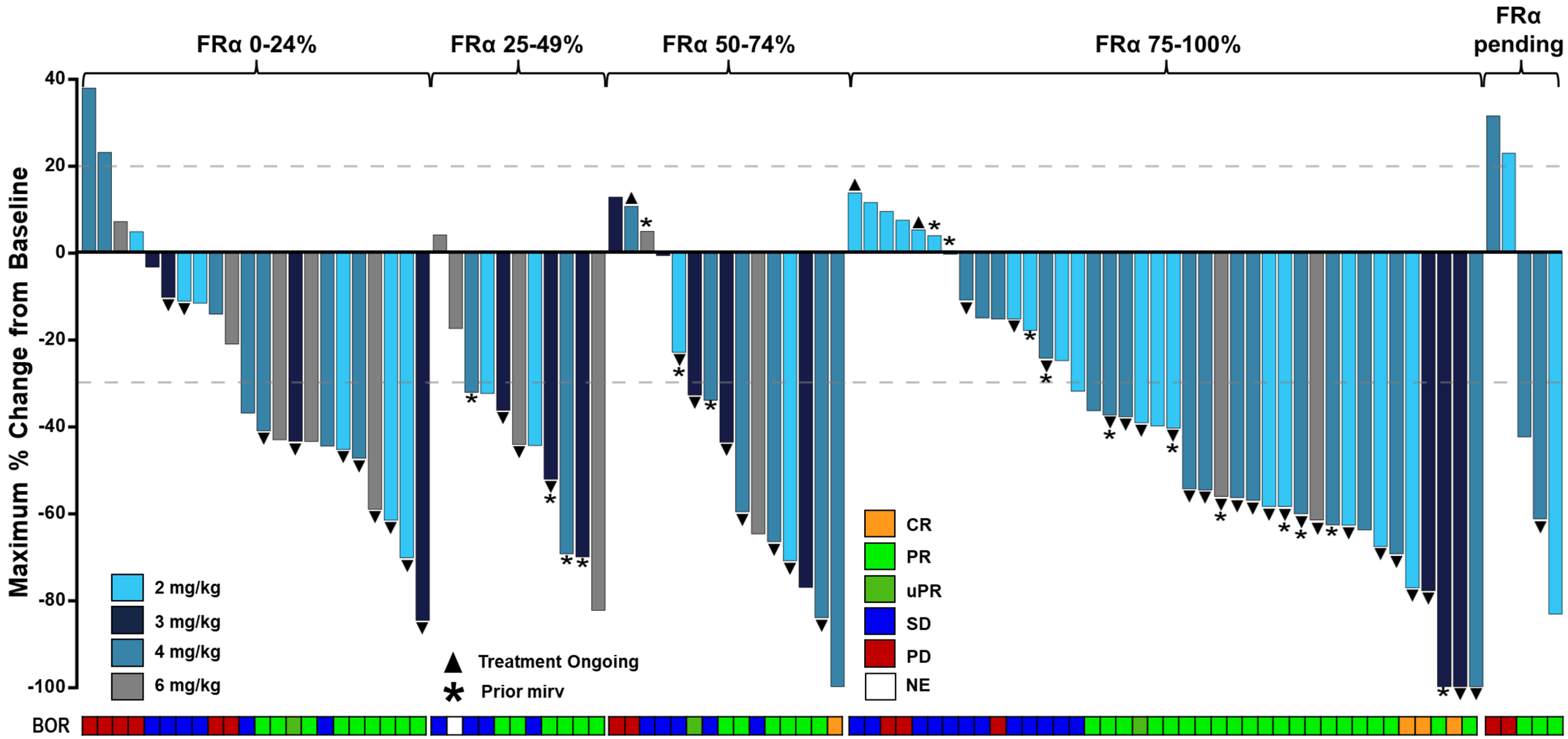

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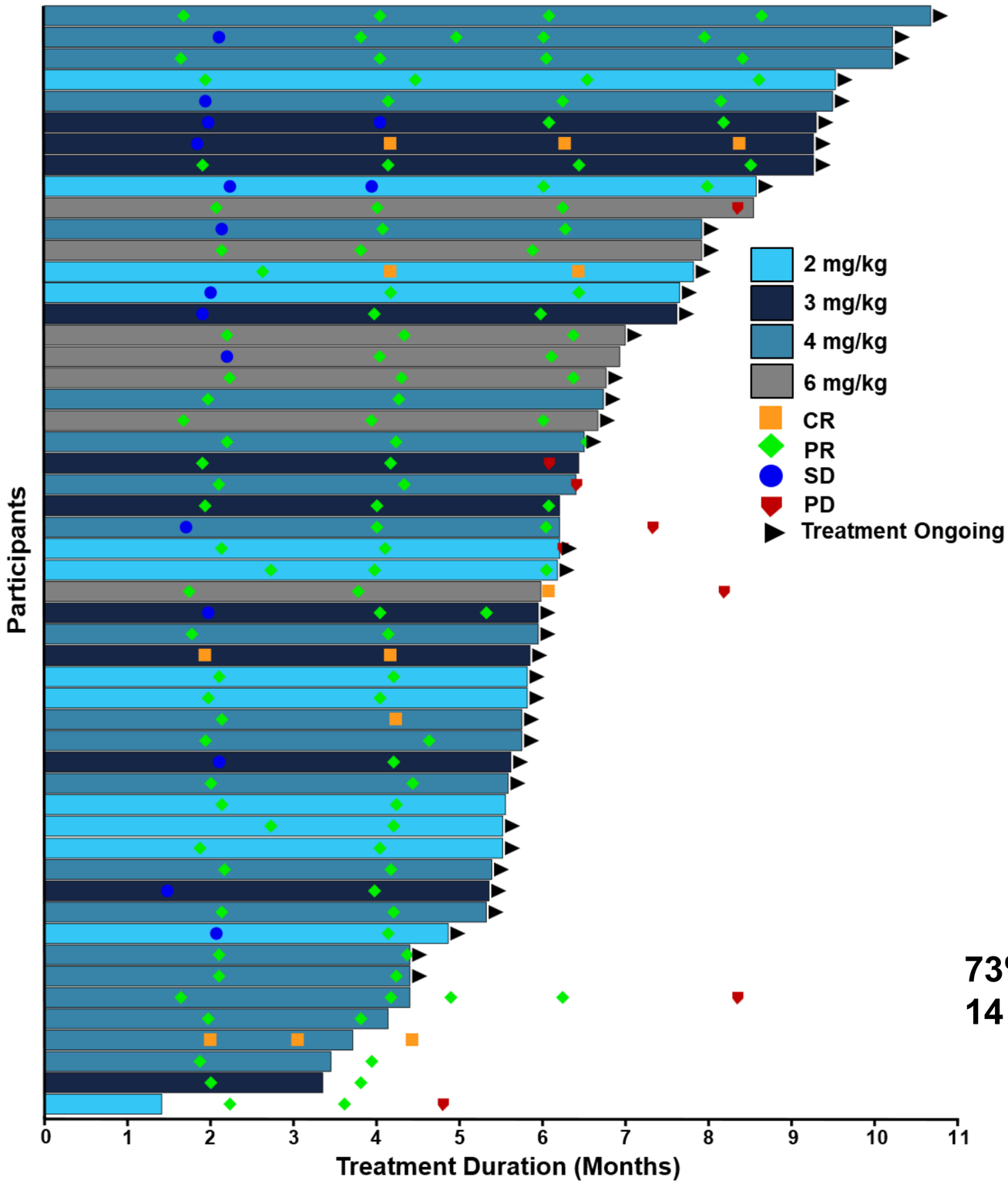

73% (38/52) of responding patients are ongoing.
14 patients discontinued (6 due to PD)

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