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## BACKGROUND

- Monalizumab (mona, M), a IgG4 Ab targeting the NKG2A receptor, has limited activity as monotherapy in RM SCCHN.
- Targeting the NKG2A-HLA-E pathway with PD(L)1 blockade improved tumor control in mice. Preliminary data of mona and durvalumab (durva, D), have shown encouraging activity in pretreated MSS colorectal cancer.

## METHODS

- The UPSTREAM trial was a biomarker-driven umbrella trial of targeted therapies and immunotherapies for RM SCCHN (post-platinum, ECOG 0-1, measurable disease) (Fig 1).
- The immunotherapy 2 (I2) cohort (red frame Fig 1) was a phase II, randomized, open-label substudy evaluating the efficacy of the combination of durva (iv, 1500mg Q4W) and mona (iv, 750mg Q2W or Q4W) (D+M) vs physician's choice (control, ctrl) (2:1 ratio).
- Patients non-eligible for the biomarker-driven cohorts and pretreated with anti-PD-(L)1, were included in the I2 cohort.
- The primary endpoint was objective response rate (RECISTv1.1) during the first 16 weeks (2-stage Simon design applied to the D+M arm, H1 15%, H0 3%, 1-sided  $\alpha$  10%, power 90%). Secondary endpoints included response duration, toxicity, PFS, and OS.

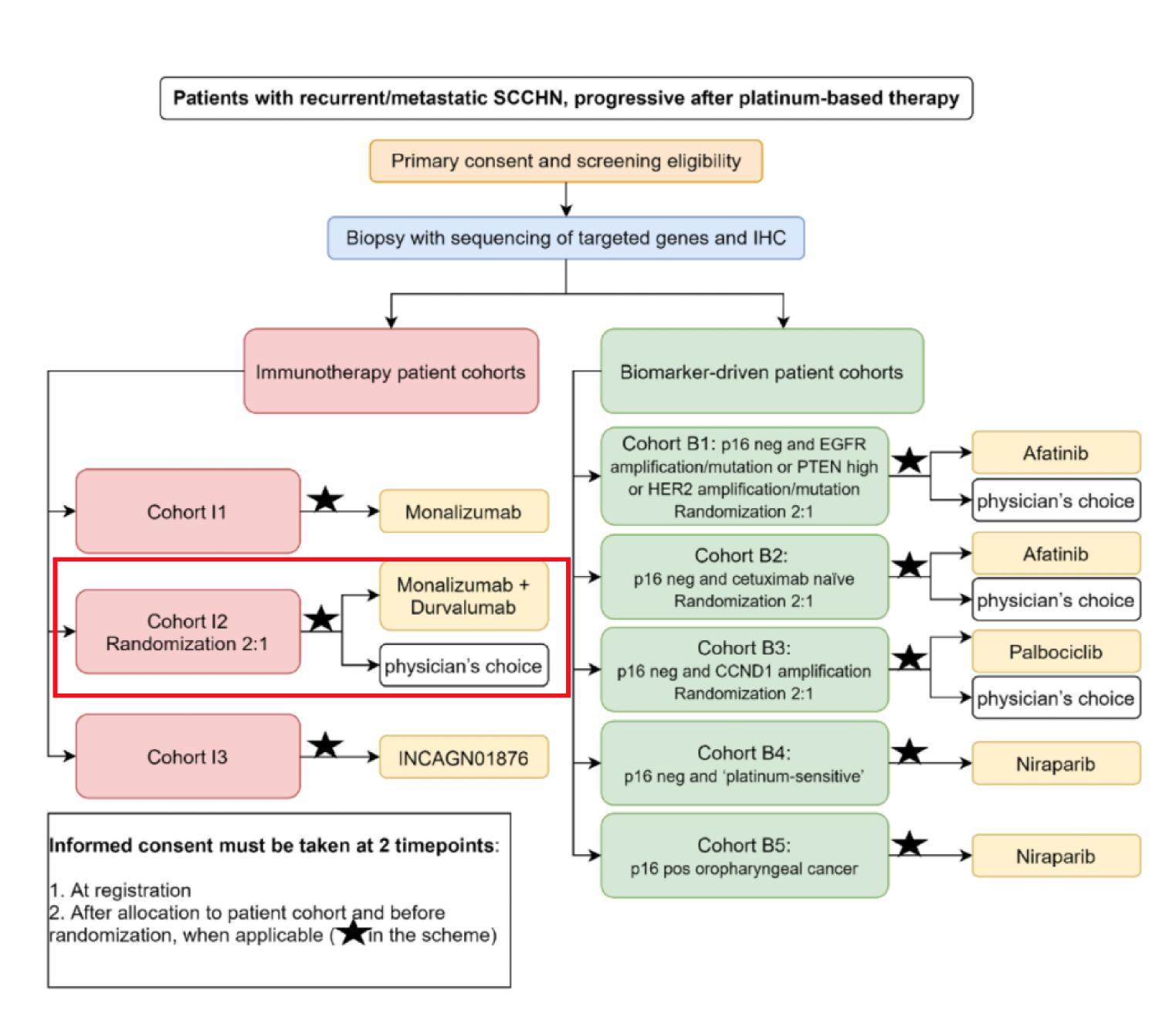


Fig 1. Study design UPSTREAM trial

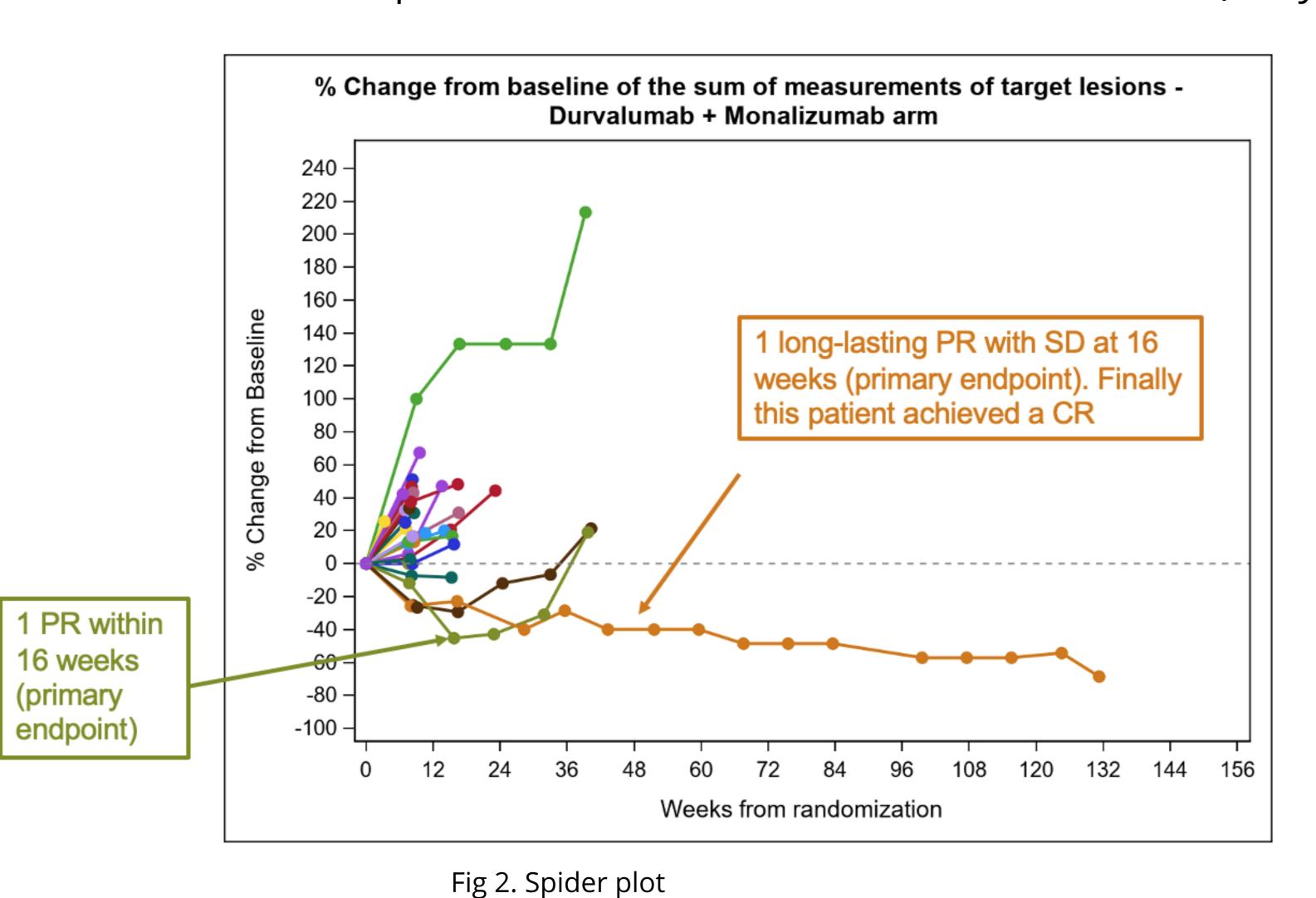
## RESULTS

- 66 RM SCCHN patients were included in the I2 cohort (D+M: n=45, ctrl: n=21) between February 2019 and December 2021, of whom 60 patients were evaluable (D+M: n=42, ctrl: n=18). Patients in the ctrl am were treated by following chemotherapy regimens: docetaxel (n=3) / paclitaxel (n=4) / methotrexate (n=7) / carboplatin (n=1) / gemcitabine (n=1) / carboplatin-5FU-cetuximab (n=1).
- The reason for allocation to the I2 cohort was the quality of the biopsy that did not allow to assess the tumor biomarkers in 26 patients (39%). The other patients were allocated to I2 because they did not harbor one of the predefined biomarkers or because the allocated biomarker-driven cohorts were closed for accrual.

Table 1: Patient's characteristics I2				
	durva + mona (n=42)	Control (n=18)	Total (n=60)	
Median age (range)	62	63	62	
Male, n (%)	31 (74%)	14 (78%)	45 (75%)	
ECOG PS, n (%)				
0	11 (26%)	3 (17%)	14 (23%)	
1	31 (74%)	15 (83%)	46 (77%)	
Primary disease, n				
Oral cavity	8 (19%)	3 (17%)	11 (18%)	
Oropharynx	16 (38%)	9 (50%)	25 (42%)	
P16 pos	4 (25%)	3 (33%)	7 (28%)	
Hypopharynx	7 (17%)	5 (28%)	12 (20%)	
Larynx	11 (26%)	1 (5%)	12 (20%)	

Table 1 (continued) Patient's characteristics I2				
	durva + mona (n=42)	Control (n=18)	Total (n=60)	
Type of recurrence				
Only loco-regional	9 (21%)	6 (33%)	15 (25%)	
LR + distant	26 (62%)	4(22%)	30 (50%)	
Distant only	7 (17%)	8(44%)	15 (25%)	
Prior lines of				
1 line	4 (9%)	4 (22%)	8 (13%)	
2 lines	26 (62%)	10 (56%)	36 (60%)	
3 lines	12 (29%)	4 (22%)	16 (27%)	
Prior	42 (100%)	18 (100%)	60 (100%)	
Prior cetuximab	34 (81%)	13 (72%)	47 (78%)	
Prior IO	42 (100%)	18 (100%)	60(98%)	

- Grade >/= 3 treatment-related adverse events were reported in 4 patients (9%) in the the D+M arm and in 26% of patients in the ctrl arm. The most frequent treatment-related adverse events in the D+M arm was fatigue (19% versus 26% in the control arm), diarrhea (12% versus 5%), pruritus (9% versus 0%), nausea (7% versus 0%) and vomiting (7% versus 0%).
- In D+M 1 partial response (PR) was recorded during the first 16 weeks of treatment (ORR 2.4%, 95% CI: 0.1 12.6%) and stable disease (SD) was observed in 11 patients (26%). 1 PR was reported in the ctrl arm and SD in 8 (44%). In the D + M arm, the one patient with response had a duration of response of 3.7 months. In the control arm, the one patient with response had a duration of response of 3.9 months. The spider plot (Fig 2) shows the change from baseline in tumor size for target lesions in the D+ M arm. Interestingly, one patient with SD at week 16 had a complete response after 3 years of treatment.
- In the D+M arm, 8 patients died before first disease evaluation (early death), 7 of them due to progressive disease.



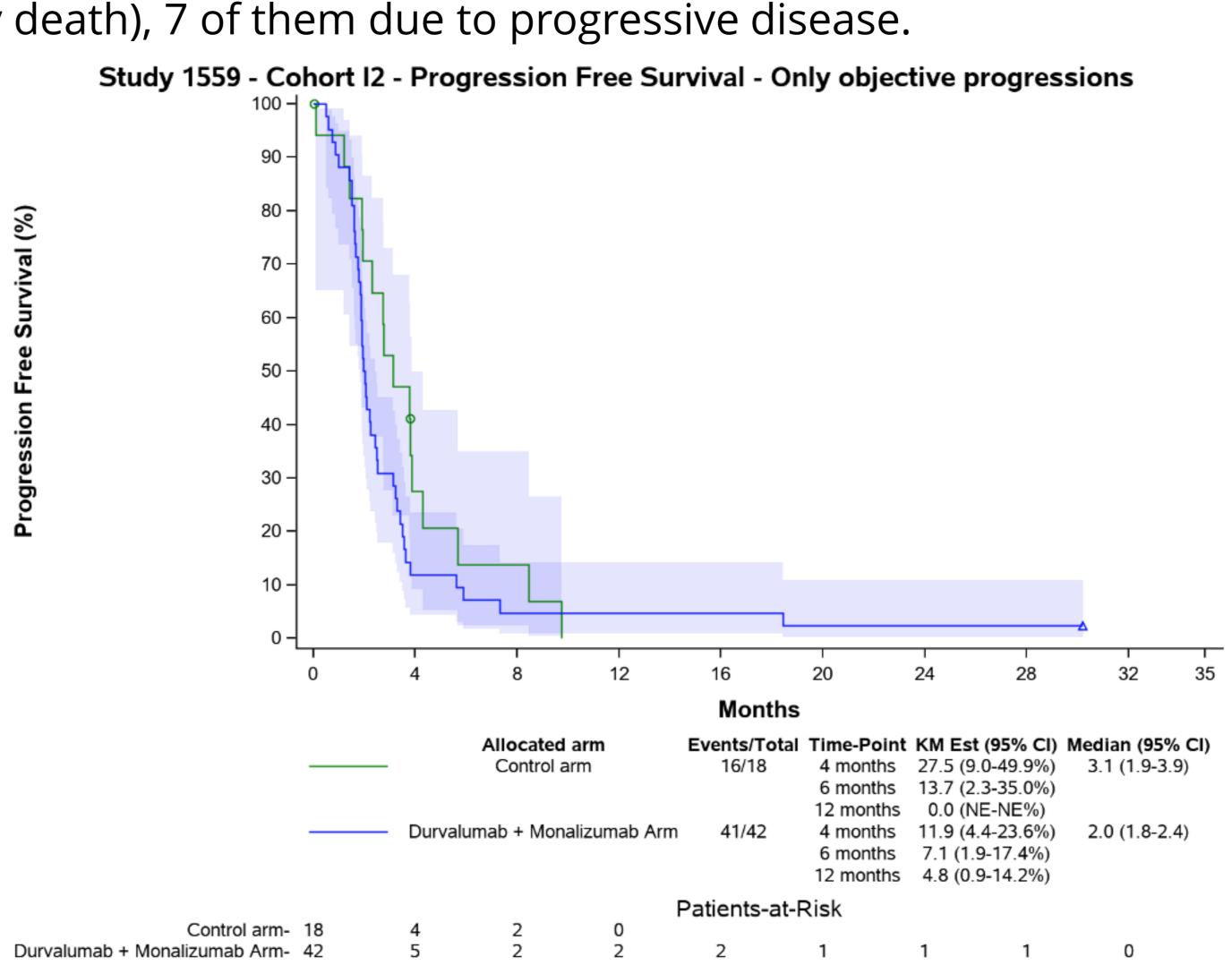
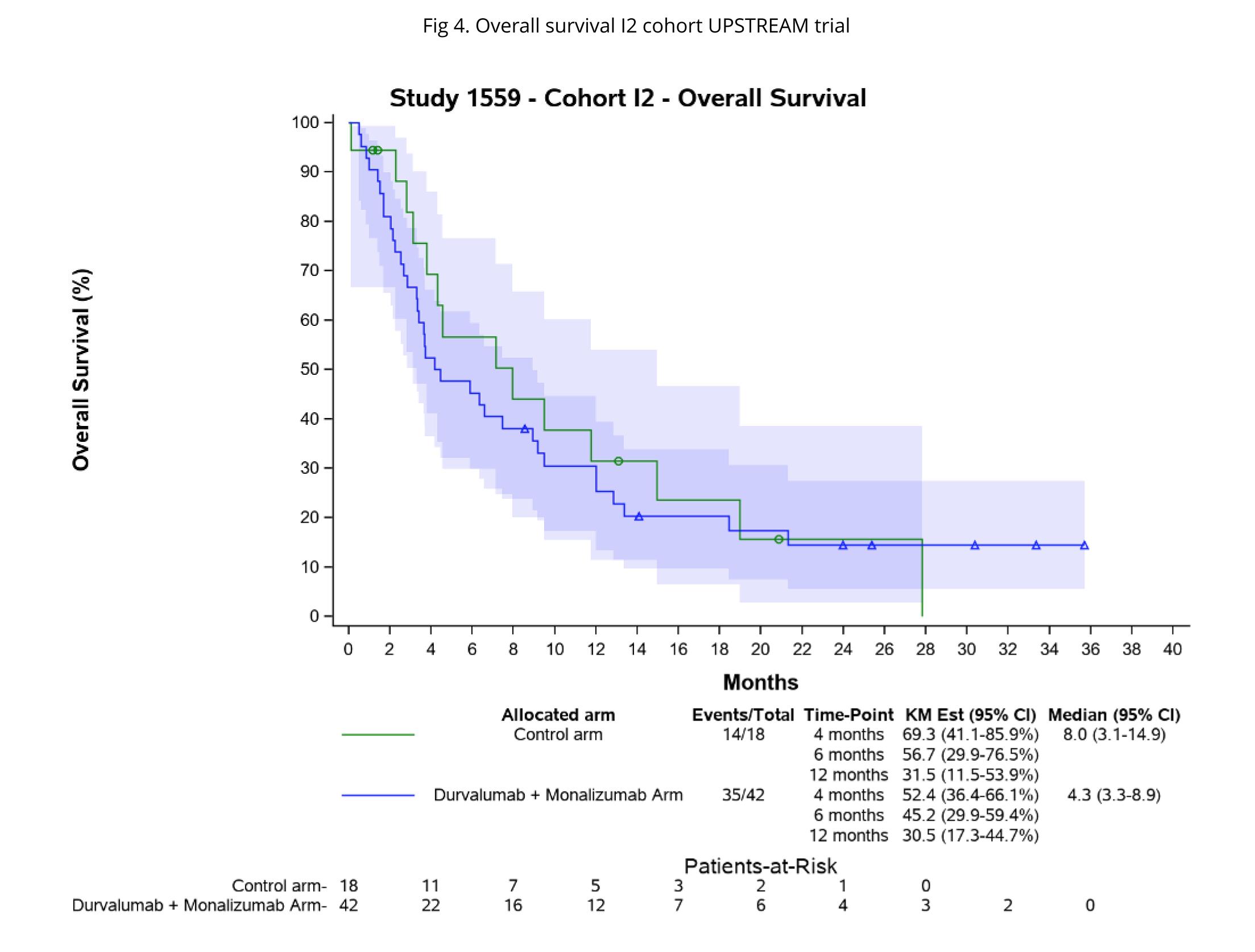


Fig 3. Progression-free survival I2 cohort UPSTREAM trial

• The median PFS was 2.0 mo (95% CI: 1.8-2.4) and 3.1 mo (95% CI: 1.9-3.9) in the D+M arm and ctrl arm, respectively. (Fig 3). The median OS was 4.3 mo (95% CI: 3.3-8.9) and 8.0 mo (95% CI: 3.1-14.9) in the D+M and ctrl arm, respectively. (Fig 4)



## CONCLUSION

- The substudy of mona and durva did not meet its primary objective in this heavily pretreated population previously exposed to anti-PD-(L)1. (ORR: 2.4% Median PFS: 2.0months Median OS: 4.3months).
- The combination of mona and durva was safe.
- In the mona and durva arm, 8 patients died before first disease evaluation (early death), 7 of them due to progressive disease.
- Interestingly, one patient with SD at week 16 had a complete response after 3 years of treatment.

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Dr Rachel Galot has no conflicts of interest to declare

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