Clinical Efficacy of ONC201 in Recurrent H3 K27M-Mutant Diffuse Midline Glioma Patients

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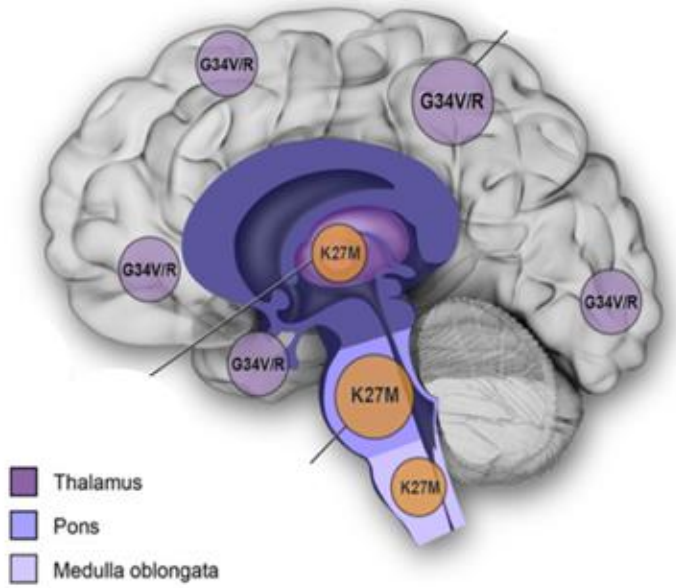
Disclosures

- Astex Pharmaceutics (Investigator Initiated Trial; research)
- FORMA therapeutics (advisory board)

- ONC201 is an investigational drug

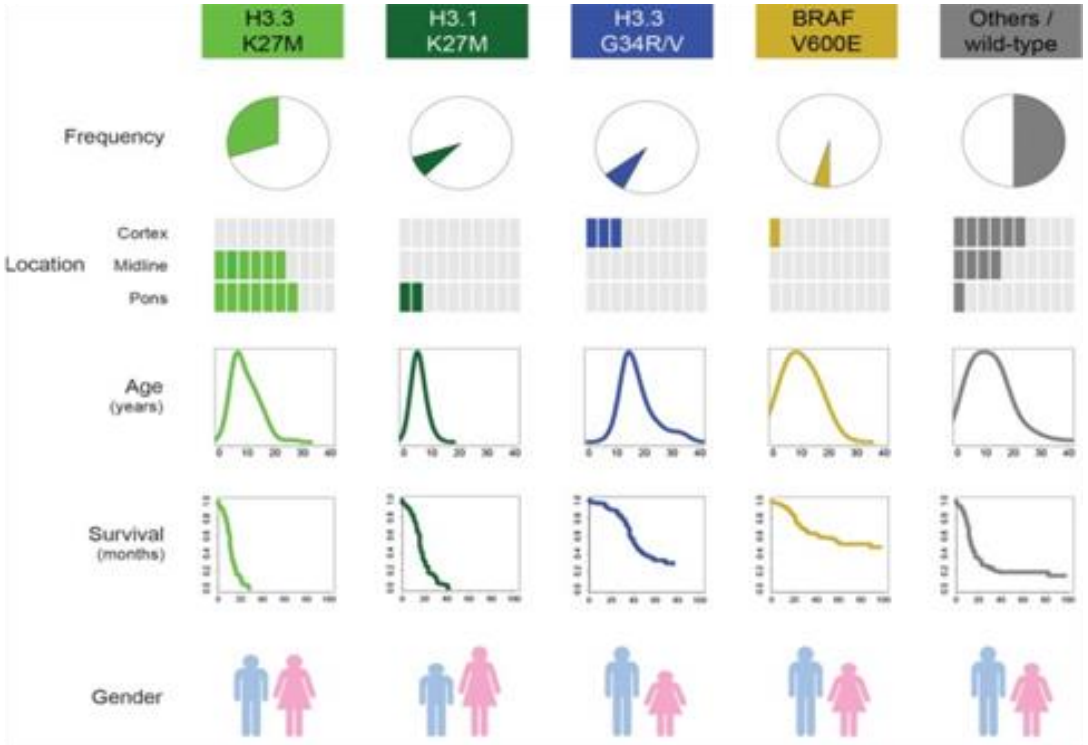
H3 K27M-mutant Diffuse Midline Glioma

- Most frequent histone mutation in glioma[1]
- Defines a distinct Grade IV disease entity in the 2016 WHO classification[2]
- Mutation is predominant in cancers in younger patients and midline of brain (50-90% of midline gliomas)[3]
- No effective therapy after first-line radiation
- No objective responses[5] to systemic therapy reported in recurrent setting



Neuroanatomic and gene associations with histone mutations[1]

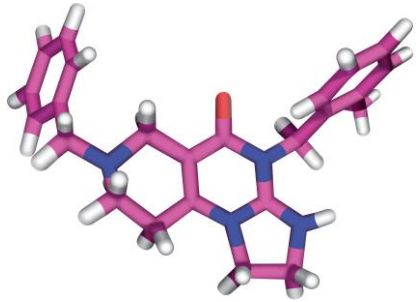
Biologically and clinically defined subgroups of pediatric infiltrating glioma[4]



WHO = World Health Organization.

1. Lulla RR et al. Sci Adv. 2016;2(3):e1501354.; 2. Louis DN et al. Acta Neuropathol. 2016;131(6):803-20.; 3. Solomon, D.A., et al. Brain Pathol 26, 569-580 (2016).; 4. Jones C et al, Neuro Oncol. 2017;19(2):153-161.; 5By Response Assessment in Neuro-Oncology (RANO) criteria

ONC201 Overview

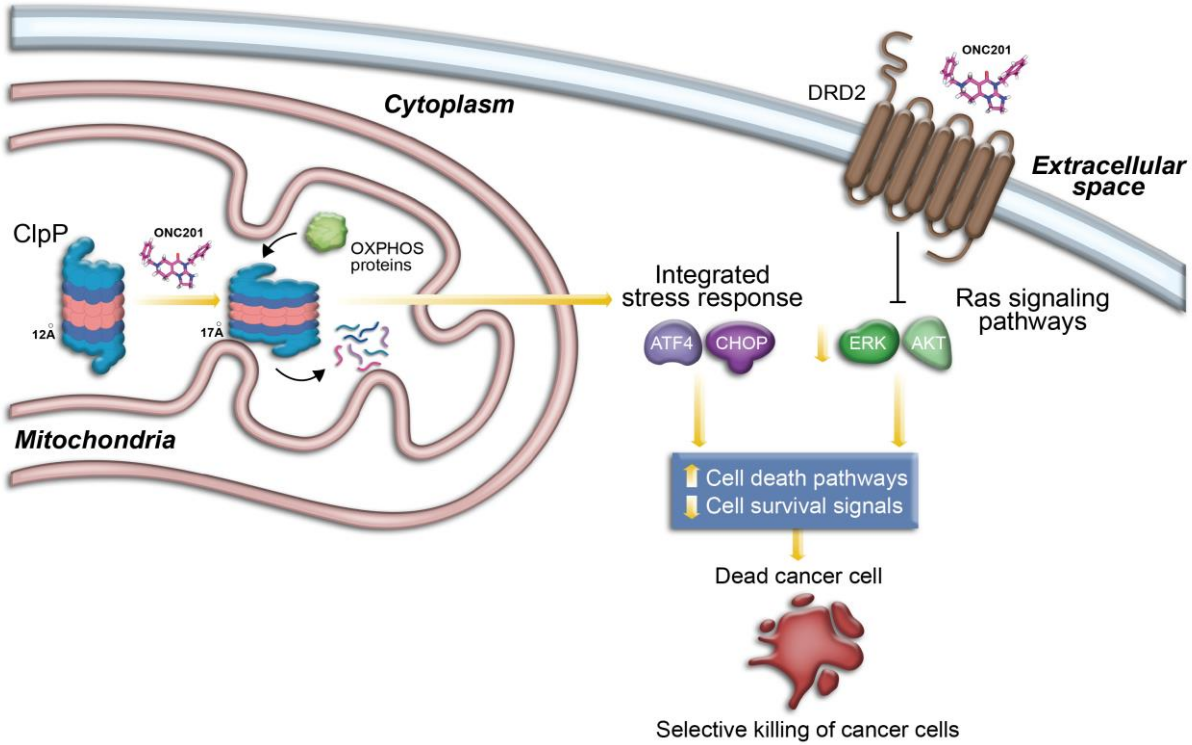


DRD2/3 antagonist[1]
ClpP agonist[1,2]

Oral capsules administered weekly [1,3]

Pharmacodynamic-based dose without DLT[1]

Mechanism of action[1,2,4-6]



AKT = protein kinase B; ATF4 = activating transcription factor 4; CHOP = C/EBP-homologous protein; ClpP = caseinolytic protease P; DLT = dose-limiting toxicity; DRD2 = dopamine receptor D2; ERK = extracellular-regulated kinase; OXPHOS = oxidative phosphorylation.

1. Prabhu VV, et al. *Neoplasia.* 2020;22(12):725-744. 2. Ishizawa J, et al, *Cancer Cell*. 2019;35(5):721-737. 3. Data on file. Oncoceutics, Inc. 4. Allen JA. et al, *Sci Transl Med.* 2013;5(171);171ra17. 5. Ishizawa J, et al. *Sci Signal*. 2016;9(415):ra17. 6. Kline CLB, et al. *Sci Signal*. 2016;9(415):ra18.

Objective and Eligibility Criteria

Objective

To evaluate monotherapy efficacy of ONC201 in recurrent H3 K27M-mutant diffuse midline glioma

Eligibility

- Age ≥2yo and received ONC201 under studies ONC006, ONC013, ONC014, ONC016, or ONC018
- Diffuse glioma with a known H3K27M mutation and involvement of a midline structure of the brain
- Progressive and measurable disease on contrast-enhanced brain MRI by RANO-High Grade Glioma (HGG) criteria
- Prior therapy with at least radiation
- Washouts prior to first ONC201 dose:
  - Radiation: 90 days
  - Temozolomide: 23 days
  - Antibodies (e.g., bevacizumab): 42 days
  - Other anticancer therapies: 28 days
- Baseline Performance Status ≥60
- Corticosteroids stable or decreasing for at least 3 days prior to baseline scan
- Excluded: DIPG, primary spinal tumors, atypical and non-astrocytic histologies, leptomeningeal spread, CSF dissemination

Endpoints

Primary Endpoint[1]

- Overall response rate by RANO-HGG criteria

Secondary Endpoints[1]

- Overall response rate by RANO-Low Grade Glioma (LGG) criteria
- Duration of response
- Time to response
- Best overall response
- Disease control rate
- Progression-free survival
- Overall survival
- Corticosteroid response rate
- Performance status response rate

Analysis

- First 50 patients enrolled who meet eligibility criteria for integrated efficacy analysis[2]
- Censored for all endpoints except overall survival upon initiation of any additional anti-cancer therapy

[1]Radiographic endpoints assessed by RANO-HGG and RANO-LGG criteria with dual-reader blinded independent central review (BICR).
[2]As discussed and prespecified with regulatory authorities

Patient Demographics and Disease Characteristics

	N=50
Age (years), median (range)	30 (8 – 70)
<18 years, N(%)	4 (8%)
18 - <40 years, N(%)	32 (64%)
≥40 years, N(%)	14 (28%)
Gender, N(%)	
Male	27 (54%)
Female	23 (46%)
Race, N(%)	
White	39 (78%)
Other	6 (12%)
Black	3 (6%)
Asian	1 (2%)
Not reported	1 (2%)
Body weight (kg), median (range)	88 (29 – 199)
Performance status (KPS/LPS), N(%)	
60-70	14 (28%)
80	20 (40%)
90-100	16 (32%)

	N=50
Primary tumor location, N(%)	
Thalamic	33 (66%)
Other midline	17 (34%)
Multifocal disease[1], N(%)	23 (46%)
>1 Target lesion, N(%)	9 (18%)
Tumor size[2] (cm^2), median (range)	10.4 (1.6 – 40.8)
H3 K27M detection method	
IHC, N(%)	47 (94%)
NGS, N(%)	3 (6%)
First recurrence, N(%)	37 (74%)
Prior temozolomide, N(%)	44 (88%)
Time from recurrence, days, median (range)	20 (1 – 126)
Time from prior radiation, months, median (range)	7.5 (3 – 104)
Time from initial diagnosis, months, median (range)	10.9 (5 – 105)
Daily steroid dose (mg, dex equiv): median (range)	1.1 (0.0 – 12.0)

[1]Multifocal disease includes non-target lesions
[2]Sum of product of diameters of enhancing target lesions per BICR

Dosing & Disposition

- Dosing
  - Oral 625 mg ONC201 (scaled by body weight for pediatric patients)
  - Once every week with exception of one patient dosed once every 3 weeks
- Last patient enrolled February 26, 2020
- Data cutoff for analysis May 31, 2021
- Median follow-up 18.8 months
- Disposition
  - 5 patients remain on study treatment though 4 are on past progression
  - No patient came off study for toxicity

[1]Discontinuation due to treatment-related toxicity has not been reported
[2]Progression as assessed by BICR

Serious Adverse Events

	Any attribution, N (%)	Related, N (%)
Any SAE[1]	**25 (50%)**	**1 (2%)**
Gastrointestinal disorders		
Nausea	2 (4%)	0
Vomiting	2 (4%)	0
General disorders and administration site conditions		
Disease progression	2 (4%)	0
Nervous system disorders		
Brain edema	2 (4%)	0
Encephalopathy	4 (8%)	0
Headache	3 (6%)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	2 (4%)	0
Vascular disorders		
Embolism	2 (4%)	0
Pulmonary embolism	2 (4%)	1 (2%)[2]

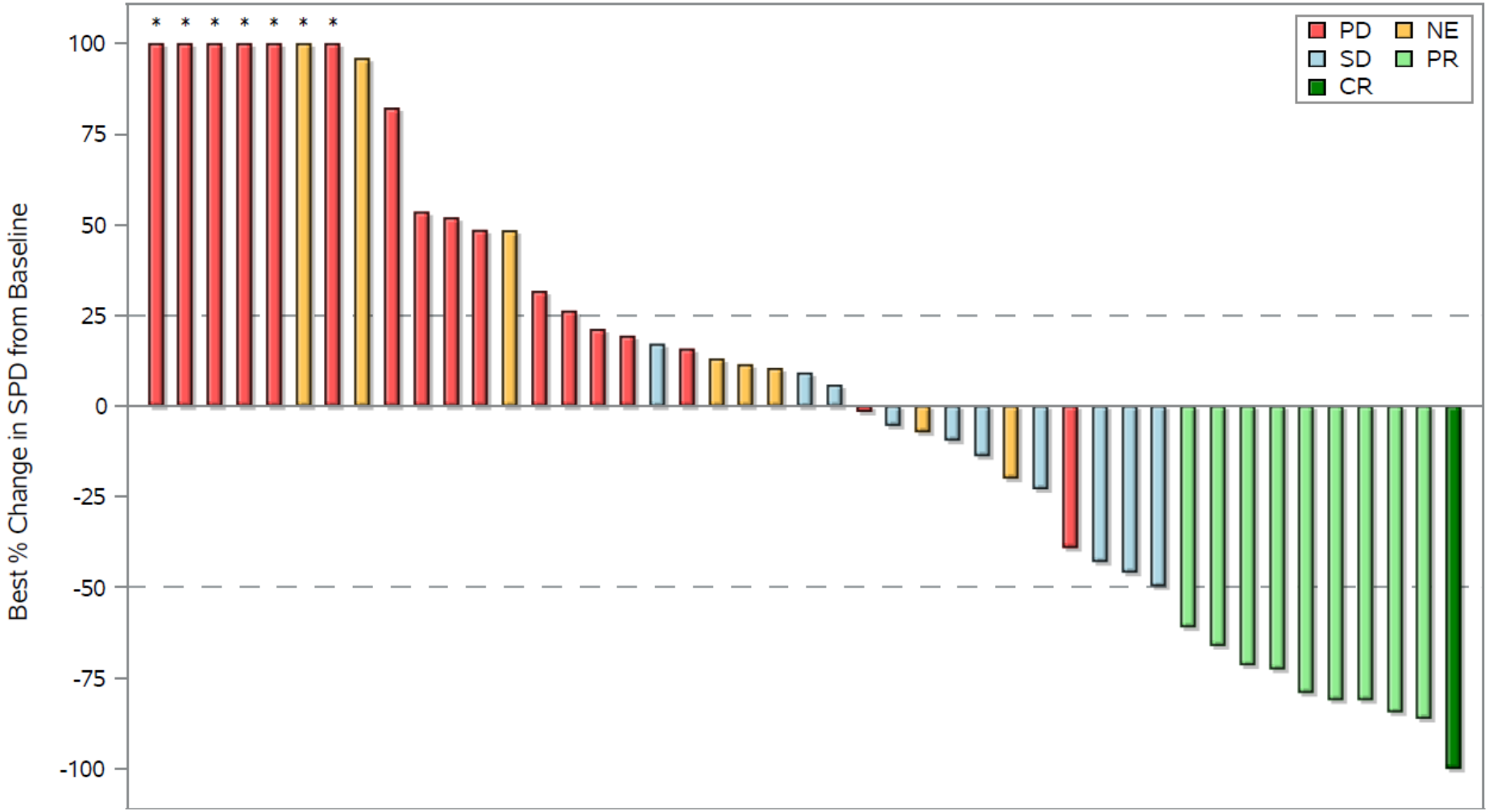
[1]Specific preferred terms occurring in more than one patient are listed; 25 patients had at least one SAE
[2]Possibly related per investigator assessment; unlikely related per sponsor assessment. Patients had morbid obesity and other comorbidities. Patient continued ONC201 for 7 months after event without additional SAE.

Overall Response Rate (RANO-HGG)

RANO-HGG[1]	N=50
ORR (CR + PR)	**10 (20%)** 95% CI: 10 – 34%
Complete Response (CR) Partial Response (PR) Stable Disease (SD) Not Evaluable (NE)[2] Progressive Disease (PD) Not Applicable (NA)[3]	1 (2%) 9 (18%) 10 (20%) 8 (16%) 18 (36%) 4 (8%)
Disease Control Rate (CR + PR + SD)	**20 (40%)** 95% CI: 26 – 55%

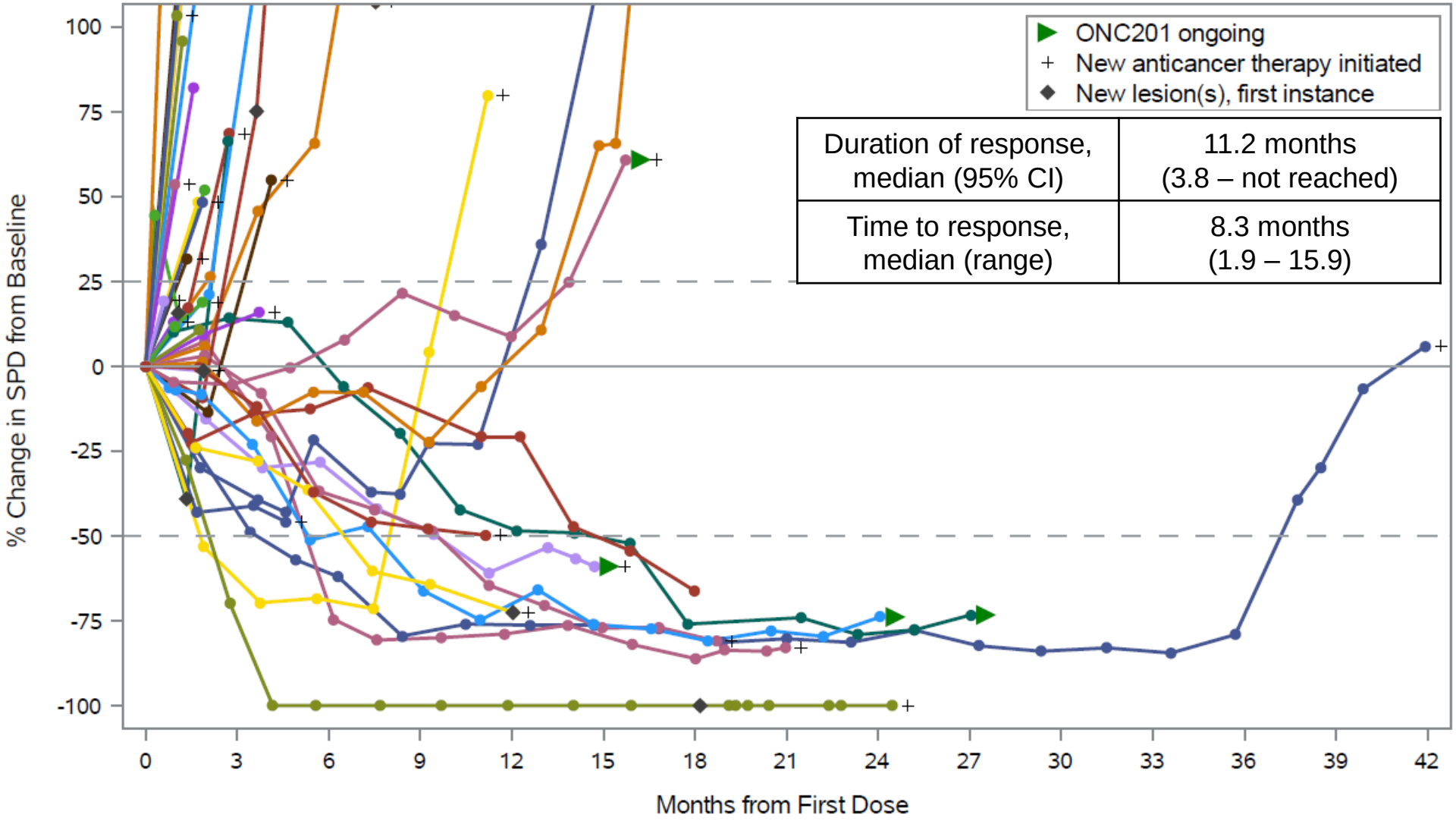
[1]Integrated RANO HGG criteria assessment by dual reader BICR
[2]Five overall radiographic SD accompanied by increase in corticosteroids; 3 overall radiographic PD accompanied by decrease in corticosteroids
[3]Three patients did not have on-treatment monotherapy MRIs available for BICR; one patient censored prior to first on-treatment MRI

Waterfall Plot (RANO-HGG)



* Change > 100%, CR=complete response, PR=partial response, SD=stable disease, NE=not evaluable, PD=progressive disease
SPD=sum of products of perpendicular diameters (target enhancing lesions per BICR)
Only patients with measurable target enhancing lesions by BICR at baseline and with post-baseline evaluations are included.
Three patients did not have on-treatment monotherapy MRIs available for BICR; one patient censored prior to first on-treatment MRI; one patient did not have measurable target lesion.

Spider Plot (RANO-HGG)



Duration of response, median (95% CI)	11.2 months (3.8 – not reached)
Time to response, median (range)	8.3 months (1.9 – 15.9)

SPD=sum of products of perpendicular diameters (target enhancing lesions per BICR)
Only patients with measurable target enhancing lesions by BICR at baseline and with post-baseline evaluations are included.
Three patients did not have on-treatment monotherapy MRIs available for BICR; one patient censored prior to first on-treatment MRI ; one patient did not have measurable target lesion.

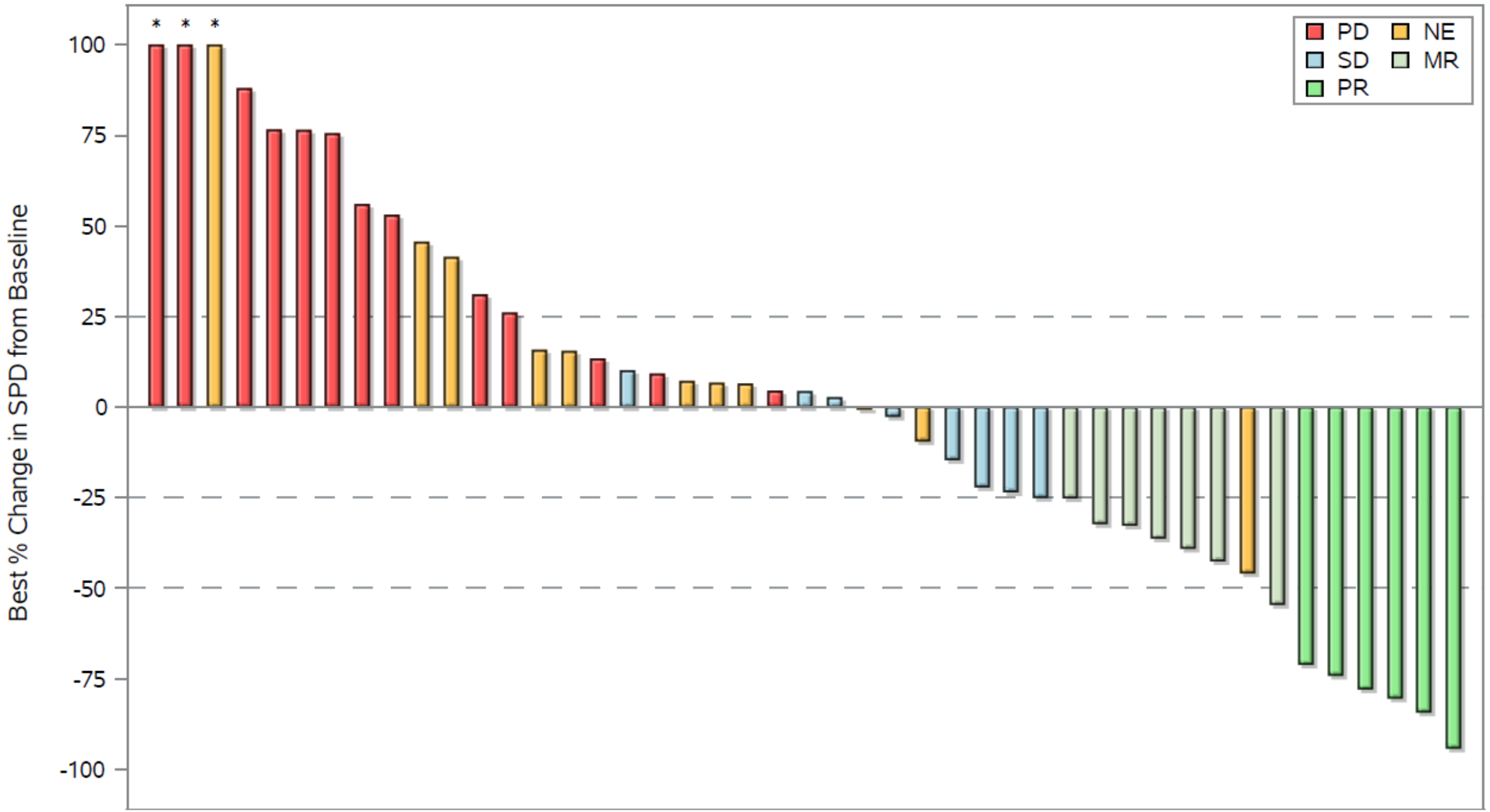
Overall Response Rate (RANO-LGG)

RANO-LGG[1]	N=50
ORR (CR + PR + MR)	**13 (26%)** 95% CI: 15 – 40%
Complete Response (CR)	0 (0%)
Partial Response (PR)	6 (12%)
Minor Response (MR)	7 (14%)
Stable Disease (SD)	8 (16%)
Not Evaluable (NE)	11 (22%)[2]
Progressive Disease (PD)	14 (28%)
Not Applicable (NA)	4 (8%)[3]
Disease Control Rate (CR + PR + MR + SD)	**21 (42%)** 95% CI: 28 – 57%

30.0% (95% CI: 17.9-44.6%) achieved an objective response by RANO-HGG and/or RANO-LGG criteria

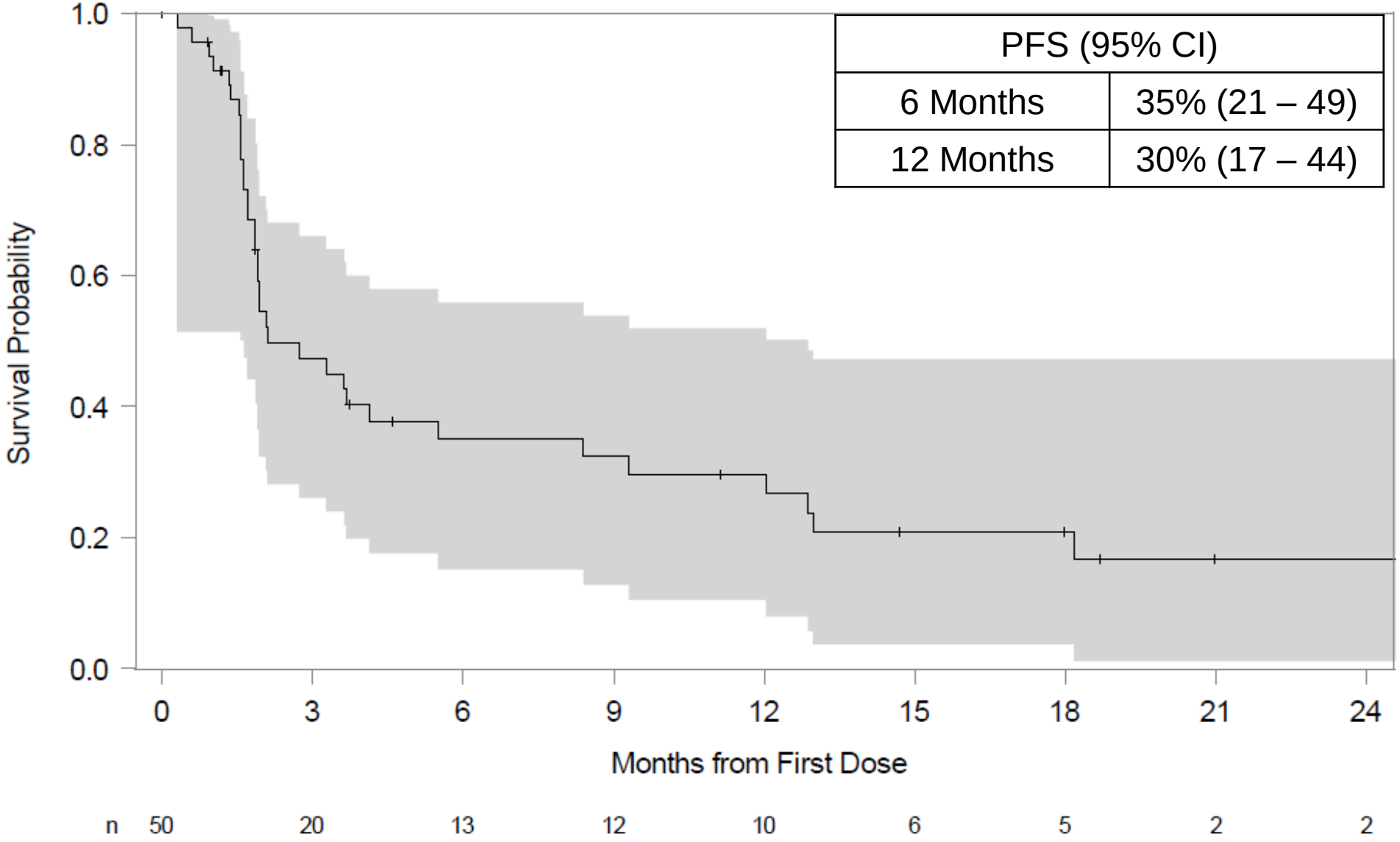
[1]Integrated RANO LGG criteria assessment by dual reader BICR
[2]Eight overall radiographic SD accompanied by increase in corticosteroids; 3 overall radiographic PD accompanied by decrease in corticosteroids
[3]Three patients did not have on-treatment monotherapy MRIs available for BICR; one patient censored prior to first on-treatment MRI

Overall Response Rate (RANO-LGG)



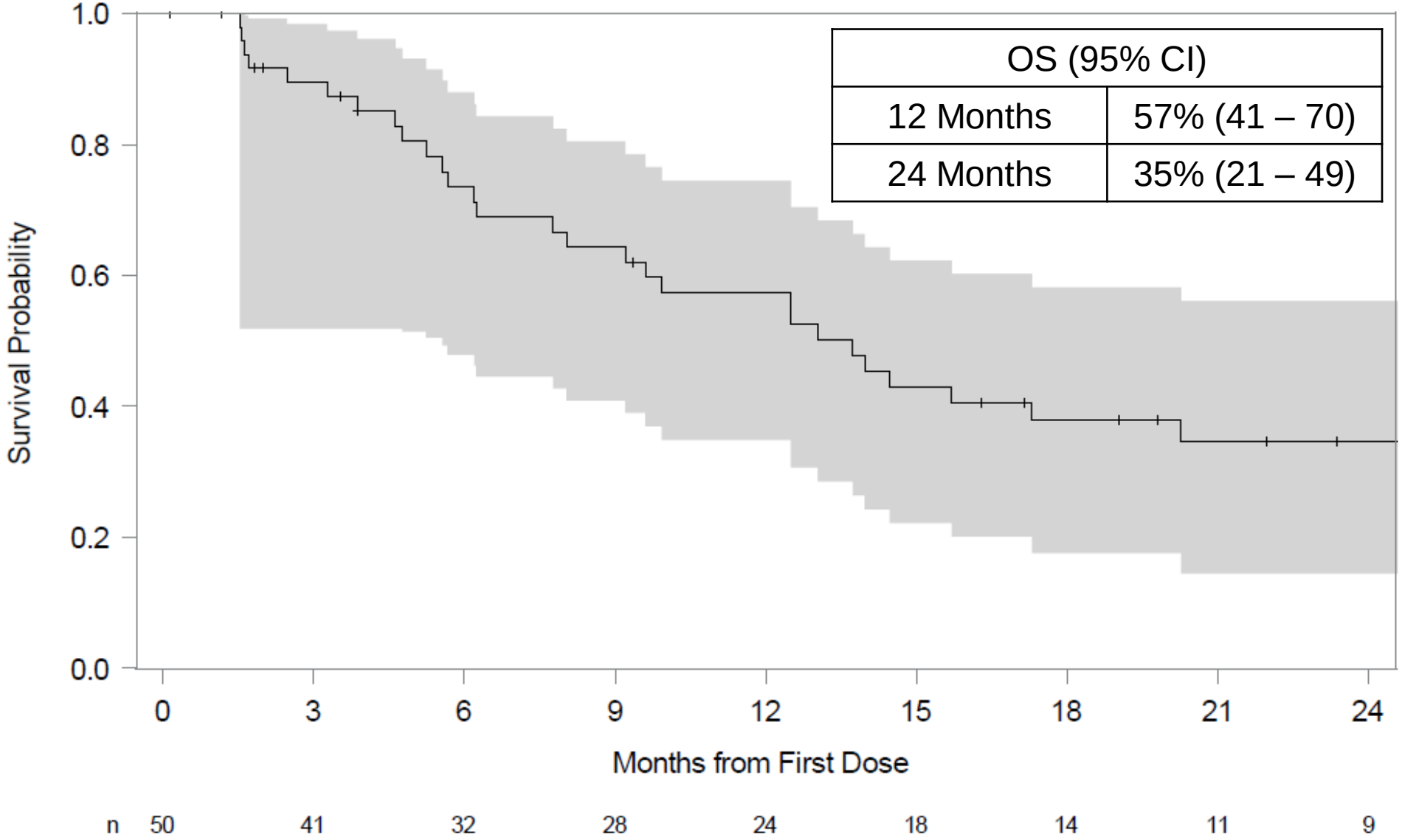
* Change > 100%, PR=partial response, MR=minor response, SD=stable disease, NE=not evaluable, PD=progressive disease
SPD=sum of products of perpendicular diameters (target non-enhancing lesions per BICR)
Only patients with measurable target lesions by BICR at baseline and with post-baseline evaluations are included.
Three patients did not have on-treatment monotherapy MRIs available for BICR; one patient censored prior to first on-treatment MRI.

Progression-Free Survival (RANO-HGG)



PFS (95% CI)	
6 Months	35% (21 – 49)
12 Months	30% (17 – 44)

Overall Survival

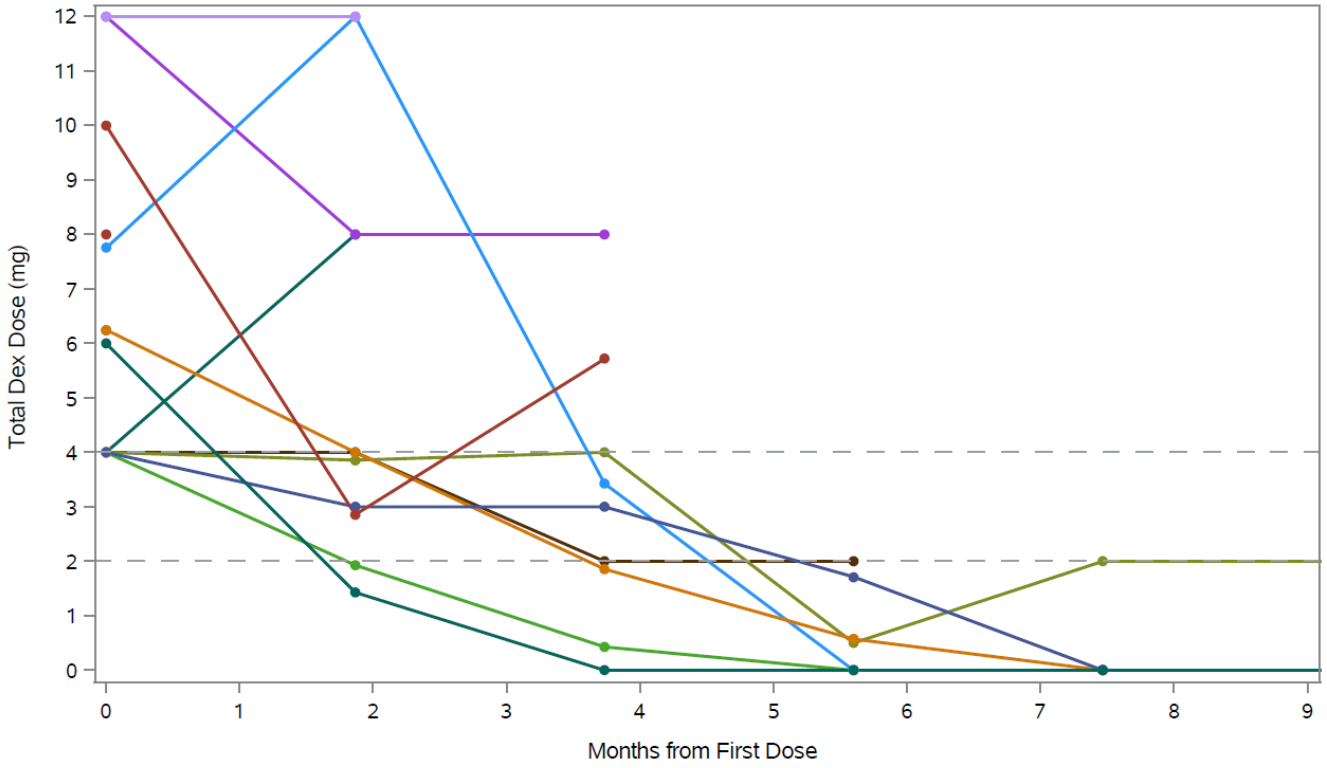


OS = overall survival

Performance Status and Corticosteroid Use

Corticosteroid Response[1]	
Response rate, % (n) (95%CI)	47% (7/15) (21 – 73%)
Time to response, months median (range)	3.7 (1.9 – 5.6)
Performance Status Response[2]	
Response rate, % (n) (95% CI)	21% (7/34) (9 – 38%)
Time to response, months median (range)	3.5 (1.9 – 22.4)

Corticosteroids[3]



[1]Corticosteroid response: ≥50% reduction in average daily corticosteroid dose compared to baseline with stable or improved KPS/LPS. Must be confirmed at next analysis timepoint. Corticosteroids were converted into a dexamethasone equivalent dose. Baseline ≥4mg dexamethasone at baseline were evaluable.
[2]Performance status response: increase in KPS/LPS compared to baseline with stable or reduced corticosteroid use. Must be confirmed at next analysis timepoint. Baseline KPS/LPS ≤80 were evaluable.
[3]Average daily over 1 week around analysis window presented (every 8 weeks)

Summary

- ONC201 monotherapy exhibited durable and clinically meaningful efficacy in recurrent H3 K27M-mutant DMG patients
  - RANO-HGG criteria assessed by dual reader BICR
    - ORR 20% (95% CI: 10 – 34%)
    - Median DOR 11.2 months (95% CI: 3.8 – not reached)
    - Median time to response 8.3 months (range 1.9 – 15.9)
    - Disease control rate 40% (95% CI: 26 – 55%)
    - PFS at 6 months 35% (95% CI: 21 – 49%); PFS at 12 months 30% (95% CI: 17 – 44%)
  - RANO-LGG criteria assessed by dual reader BICR
    - ORR 26% (95% CI: 15 – 40%)
  - Overall survival
    - 12 months: 57% (95% CI: 41 – 70%)
    - 24 months: 35% (95% CI: 21 – 49%)
- Improvements observed in performance status and reduction in corticosteroid use
- One SAE was considered possibly related to ONC201 by investigator and unlikely related to ONC201 by sponsor

Acknowledgments

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