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Efficacy of Selpercatinib After Prior Systemic Therapy in Patients with *RET*-Mutant Medullary Thyroid Cancer

Lori Wirth[1], Eric Sherman[2], Manisha Shah[3], Maria E. Cabanillas[4], Bruce Robinson[5], Matthias Kroiss [6], Janessa Laskin[7], Vivek Subbiah[4], Alexander Drilon[1], Jennifer Wright[8], Pearl French[8], Victoria Soldatenkova[8], Antoine Italiano[9] Daniela Weiler[10]

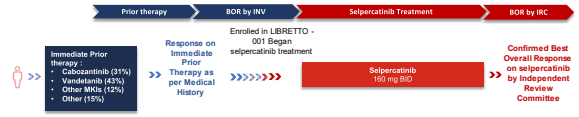
[1]Massachusetts General Hospital, Boston, USA ,[2]Memorial Sloan Kettering Cancer Center, New York, USA,, [3]Ohio State University Comprehensive Cancer Center, Columbus,USA, [4]University of Texas M.D. Anderson Cancer Center, Houston, USA, [5] Royal North Shore Hospital, St. Leonards, NSW, Australia, [6]Universitätsklinikum Würzburg, Germany [7] British Columbia Cancer Agency, Vancouver, Canada, [8] Eli Lilly and Company, Indianapolis, USA,[9]University of Bordeaux, France, [10]Cantonal Hospital, Luzern, Switzerland

Background

- Selpercatinib is a first-in-class, highly selective, and potent RET kinase inhibitor[1] approved in multiple countries for the treatment of *RET*-altered lung or thyroid cancers
- Selective RET inhibitors are now being incorporated into the standard of care for patients with *RET*-altered thyroid cancers in some countries
- Vandetanib and cabozantinib, multitargeted kinase inhibitors (MKIs), also approved for metastatic thyroid cancer, are associated with dose limiting adverse effects[2] due to their broad-spectrum kinase inhibition
- In the ongoing global, LIBRETTO-001 trial (NCT03157128) conducted in 16 countries and 89 sites, selpercatinib demonstrated robust and durable antitumor activity in patients with *RET*-mutant medullary thyroid cancer (MTC), regardless of previous vandetanib and/or cabozantinib therapy, see ASCO poster 9032 [3] For LIBRETTO-001 trial design and patient baseline characteristics, see 6073
- In the absence of randomized controlled data, and with consideraton that response rates cancer therpy usual decline on susquent lines of therapy, the efficacy of selpercatinib were examined in the context of the immediate prior therpy before trial enrollment

Intrapatient Analysis

Objective: A *post-hoc* intra-patient analysis was conducted to compare the best overall response from the last line of prior systemic therapy to the best overall response with selpercatinib (by independent review) using each patient as their own control



- The integrated analysis set (IAS)from Libretto-001 (N=143) was used for this analysis. The IAS efficacy evaluable population included MTC patients enrolled long enough to permit a minimum of 6 months of follow-up from the first dose (data cutoff date: 30-Mar-2020)
- Patients with metastatic *RET*-mutant MTC enrolled on LIBRETTO-001 were retrospectively analyzed for best overall response attained on the prior therapy received immediately prior to enrollment per physician-reported best response in patients' medical history
- The response to prior therapy was compared to the subsequent best overall response (as determined by independent review committee per RECIST v 1.1) observed while on selpercatinib treatment. In this manner, each patient serves as his/her own control

Patient with Objective Response	Patients without Objective Response
Complete Response (CR)	Stable Disease (SD)
Partial Response (PR)	Progressive Disease (PD)
	Not evaluable/Unknown (NE/UNK)

Other Multitargeted kinase inhibitors (MKIs) administered included sorafenib, lenvantinib, alectinib, pazopanib, regorafenib, regorafenib. sunitinib and others. [a]Patients may have received more than one prior treatment

Best response to selpercatinib versus immediate prior therapy

- Efficacy was observed regardless of prior therapy and the ORR on selpercatinib (69%) was markedly higher than responses observed for the last prior therapy received before trial enrollment (10%)
- ORR improvements with selpercatinib were observed regardless of responses observed for prior therapy with cabozantinib (14% vs 66% on selpercatinib) or vandetanib (12% vs 71% on selpercatinib)

	Total population (N=143)	Immediate Prior cabozantinib therapy (N=44)	Immediate Prior vandetanib therapy (N=61)	Immediate Prior other MKI therapy (N=17)
Patients responding to selpercatinib but not to prior therapy, n (%)	89 (62%)	25 (57%)	37 (61%)	12 (71%)
Patients responding to both selpercatinib and prior therapy, n (%)	10 (7%)	4 (9%)	6 (10%)	4 (24%)
Patients responding to prior therapy but not selpercatinib, n (%)	4 (3%)	2 (4%)	1 (2%)	1 (6%)
Patients who did not respond to selpercatinib or prior therapy, n (%)	40 (28%)	13 (30%)	17 (28%)	0 (0%)

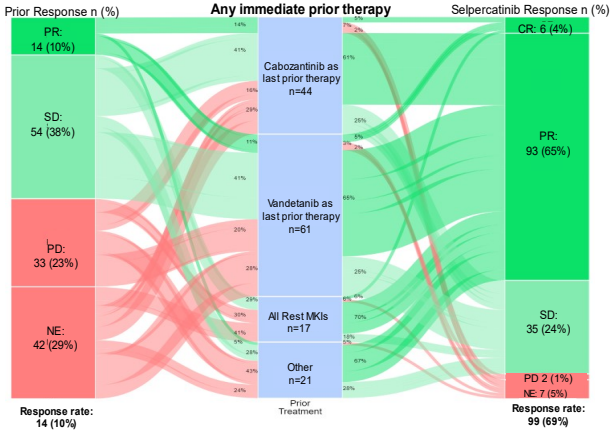
*Other Multitargeted kinase inhibitors (MKIs) administered included sorafenib, lenvantinib, alectinib, pazopanib, regorafenib, regorafenib. sunitinib and others. Patients may have received more than one prior treatment.

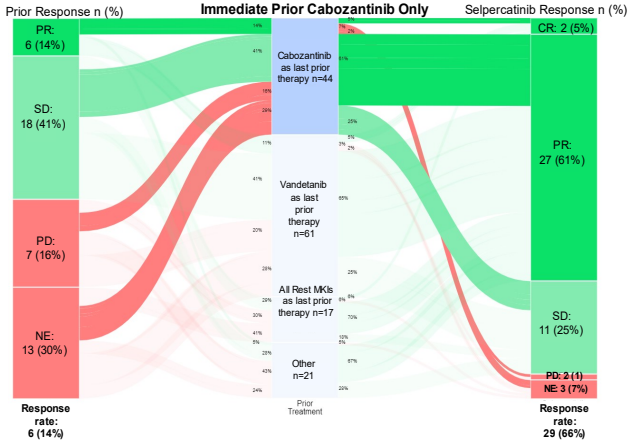
Summary and Conclusion

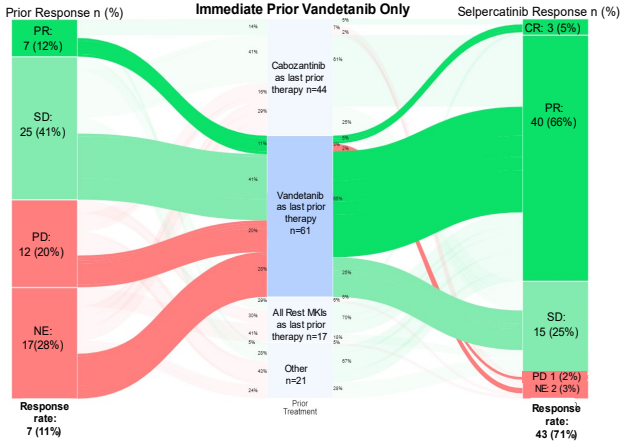
- An exploratory post-hoc longitudinal intrapatient analysis in patients from LIBRETTO-001 with MTC demonstrated ORR improvements with selpercatinib regardless of the type of prior therapy in most patients analyzed herein
- The ORR on selpercatinib (69%) was markedly higher than for responses to immediate prior therapy (10%) received before enrollment.
- Selpercatinib demonstrated robust efficacy regardless of response to immediate prior therapy in patients with *RET*-mutant MTC: cabozantinib (66% vs 14%) or vandetanib (71% vs 12%)
- The response to immediate prior cabo/vande treatment in patients was lower than seen in ZETA[5] and EXAM[6] trials, however patients has previously received 1-8 lines of previous therapies prior to enrollment
- A limitation of this analysis was that immediate prior response assessment was based on physician-reported best response in patients' medical history and may not follow RECIST criteria
- **Patients with no overall response to either cabozantinib or vandetanib may still derive benefit from subsequent selpercatinib treatment**
- **A global, randomized, phase 3 trial (LIBRETTO-531; NCT04211337) evaluating selpercatinib compared with standard frontline therapy, cabozantinib and vandetanib in MTC is ongoing**
- **A separate exploratory post-hoc intrapatient analysis in patients with NSCLC from LIBRETTO-001 also demonstrated ORR improvements with selpercatinib regardless of the response to immediate prior therapy (Poster 9032)[7]**

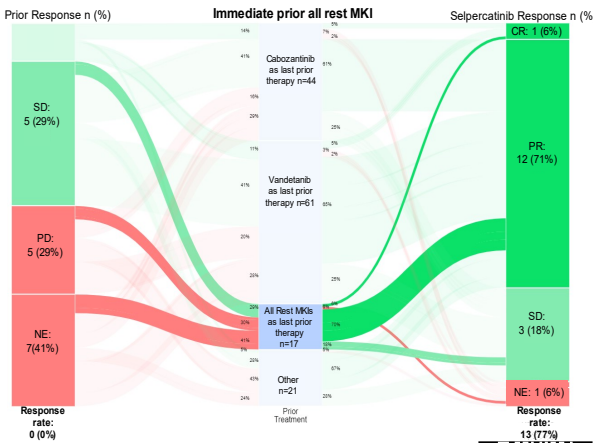
Intrapatient Comparison of BOR: Immediate Prior Therapy vs Selpercatinib

For an interactive data visualization, please use the link adjacent to or scan the QR code









McNemar test

Acknowledgments: We thank all patients, caregivers, investigators and their support staff for participation in this trial. Medical writing support was provided by Elaine Jennings, an employee of Eli Lilly and Company

Disclosure: Lori J. Wirth, MD, has disclosed the following relevant financial relationships:
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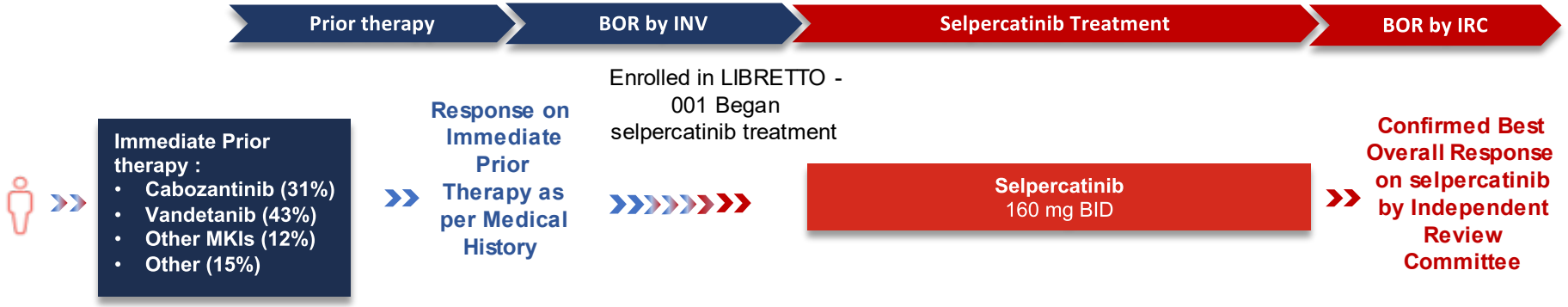

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Intrapatient Comparison of Best Overall Response: Immediate Prior Therapy vs Selpercatinib

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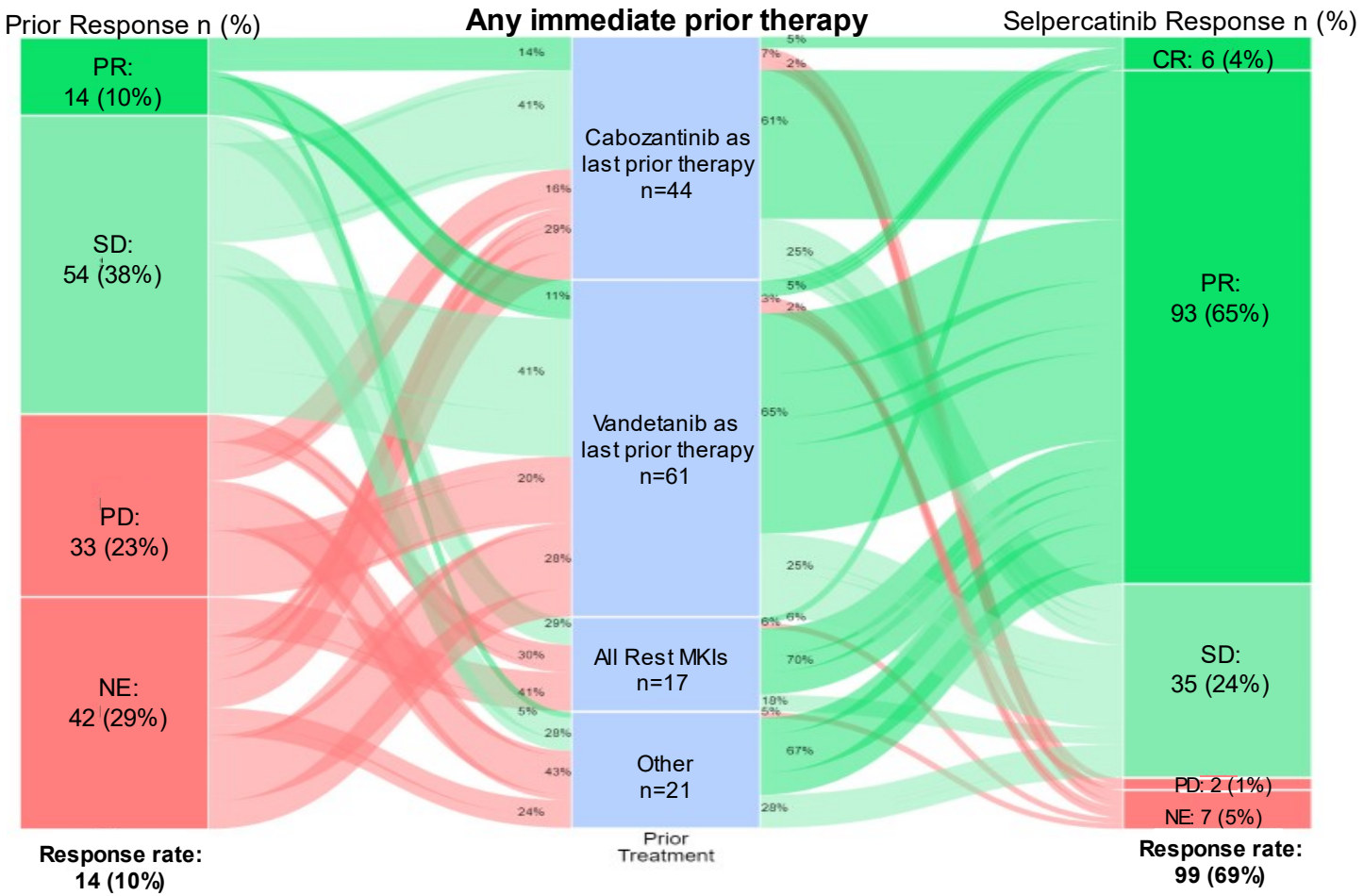
Any Immediate Prior Therapy



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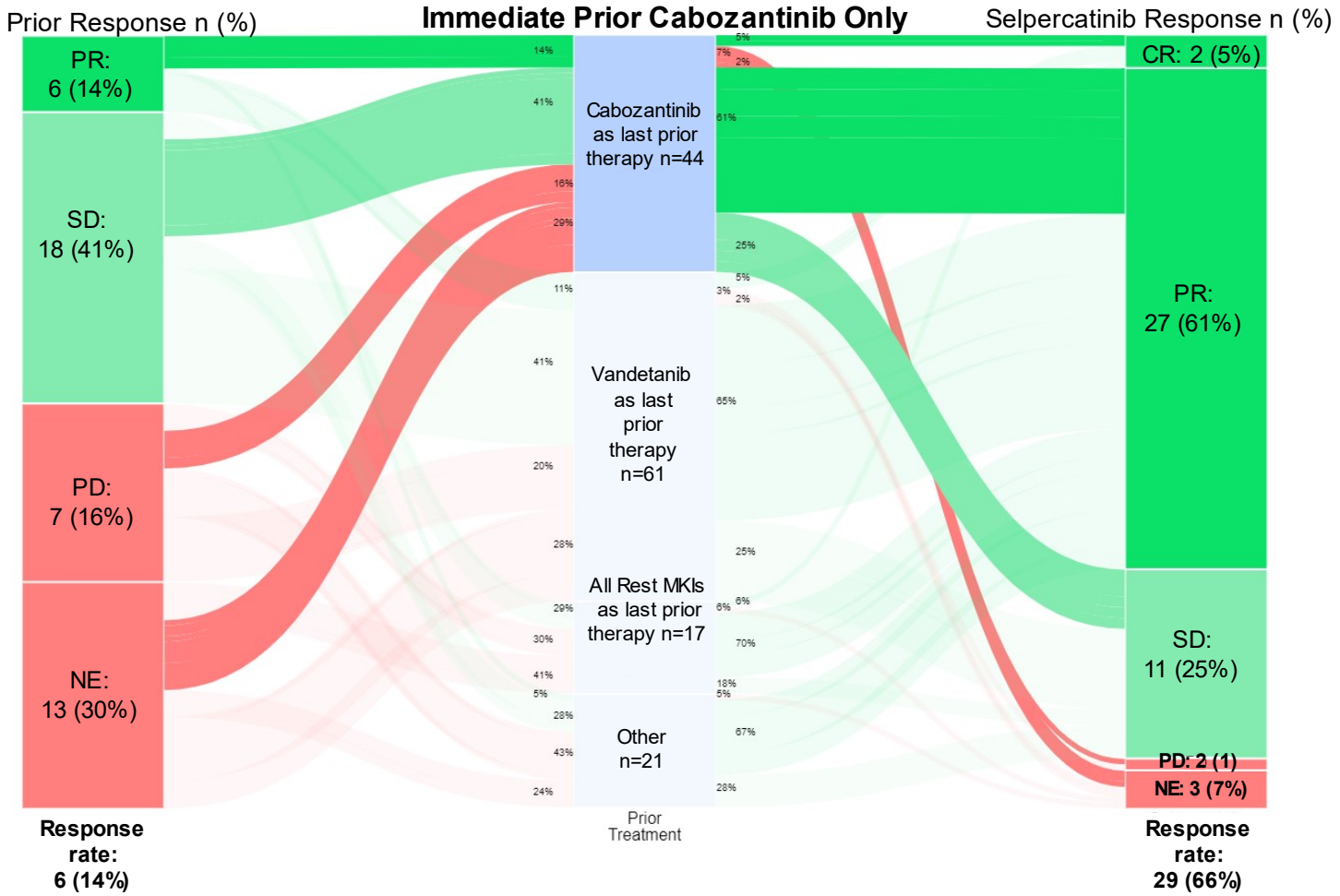
Immediate Prior Cabozantinib



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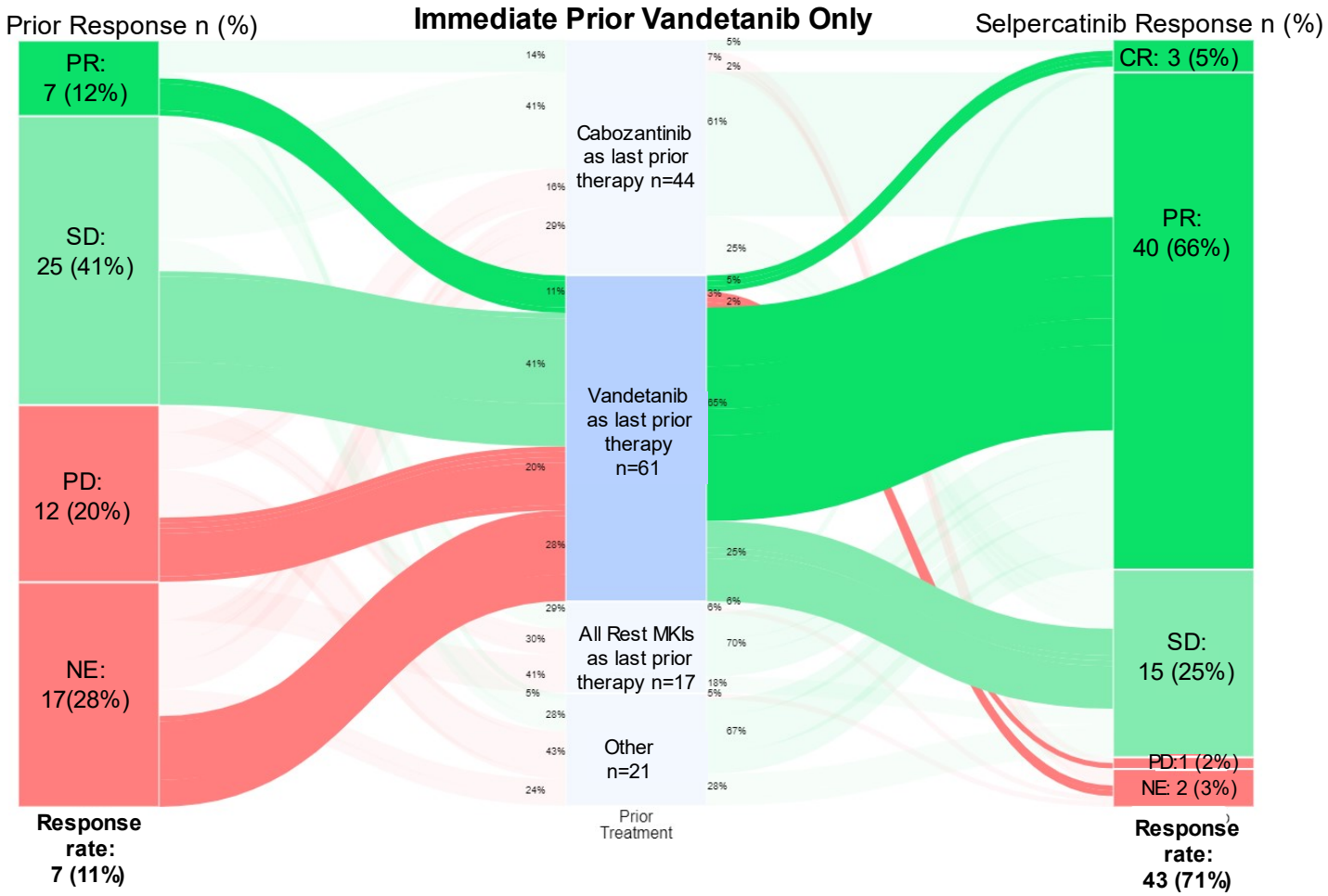
Immediate Prior Vandetanib



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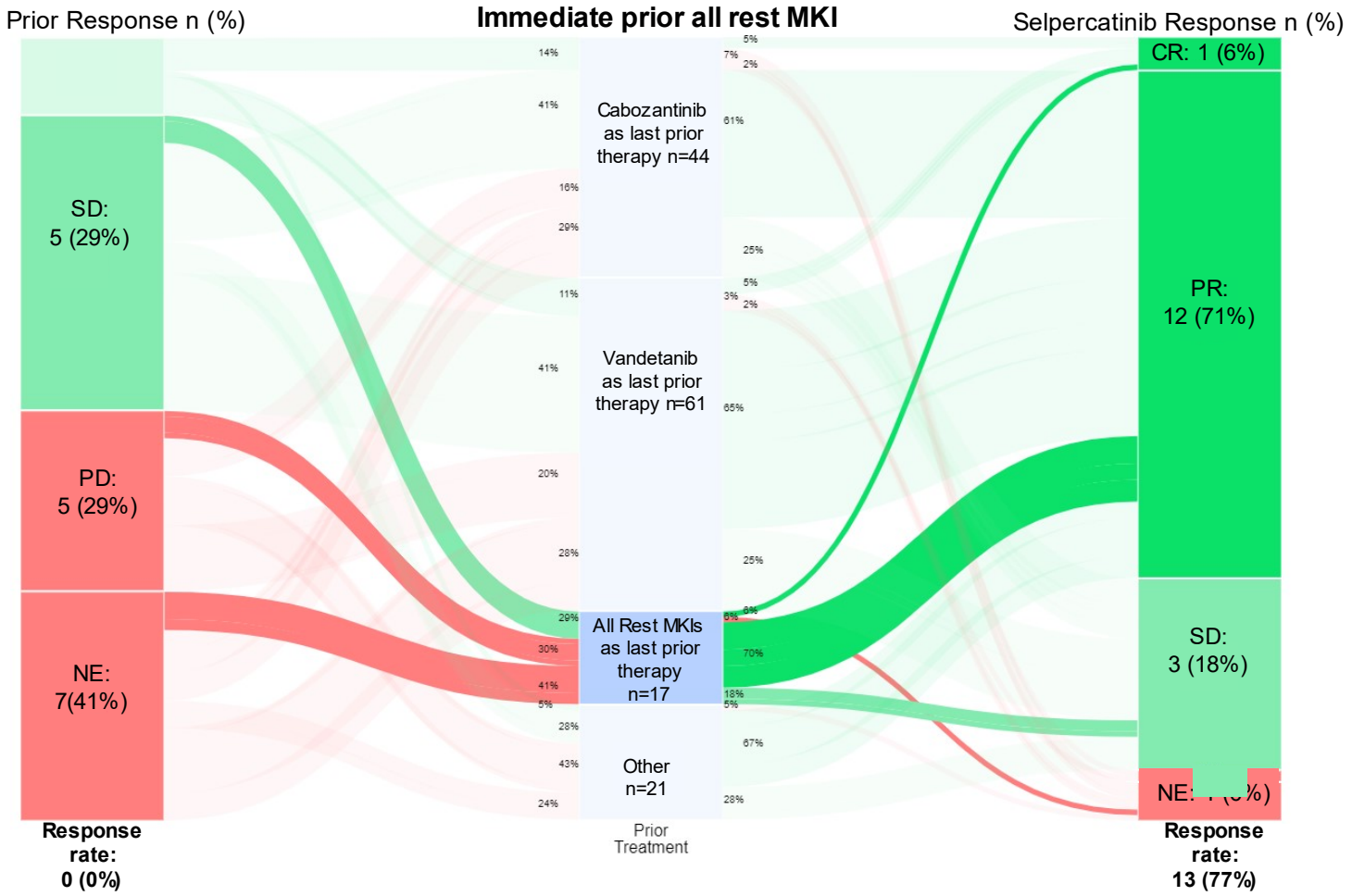
Immediate Prior all rest MKI



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Other: Iovance Biotherapeutics

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[1]Subbiah V. et al, Ann Oncol 2018
[2] Subbiah V. et al., JCO, 2020
[3]Tsang, V. H. M. et al., Curr Opin Oncol 2019
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[6]Wells S.A et al., J Clin Oncol 2012
[7]Schlumberger M. et al., Ann Oncol, 2017
[8]Drilon A. et al., Response to Selpercatinib Versus Prior Systemic Therapy in Patients (Pts) with *RET* Fusion+ Non-Small-Cell Lung Cancer (NSCLC), ASCO 2021, Poster 9032

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