Neoadjuvant cytoreductive treatment with BRAF/MEK inhibition of prior unresectable regionally advanced melanoma to allow complete surgical resection, REDUCTOR trial

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Background

- Approximately 5% of patients with regionally metastatic melanoma have unresectable (or high risk of R1 resection) locally advanced disease at presentation.
- Cytoreductive treatment causing sufficient downsizing of the tumor could enable radical resection.
- BRAF and MEK inhibition is known for high response rates and quick responses in metastatic melanoma.

Trial Design

- Two-stage phase II trial in which a total of 25 patients will be treated with neoadjuvant dabrafenib and trametinib, with no subsequent adjuvant treatment.

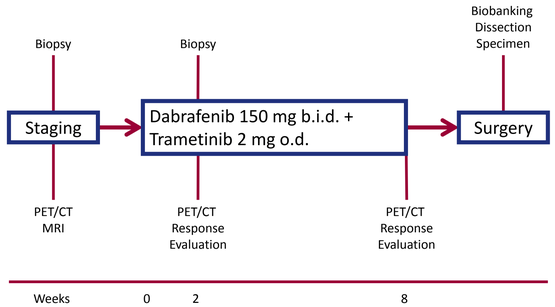

Fig 1. Study scheme with start of dabrafenib and trametinib at baseline (week 0).

Objectives

Primary objective

To evaluate the potency of short-term neoadjuvant cytoreductive therapy with dabrafenib and trametinib (BRAF and MEK inhibitor respectively) to allow radical surgical resection in patients with unresectable BRAF-mutated, locally advanced stage III or oligometastatic stage IV melanoma.

Secondary Objectives

- Recurrence-free survival (RFS, only patients that undergo surgical resection)
- Progression free survival (PFS, only patients that do not undergo surgical resection)
- Time to next treatment
- Overall survival (OS)

Results

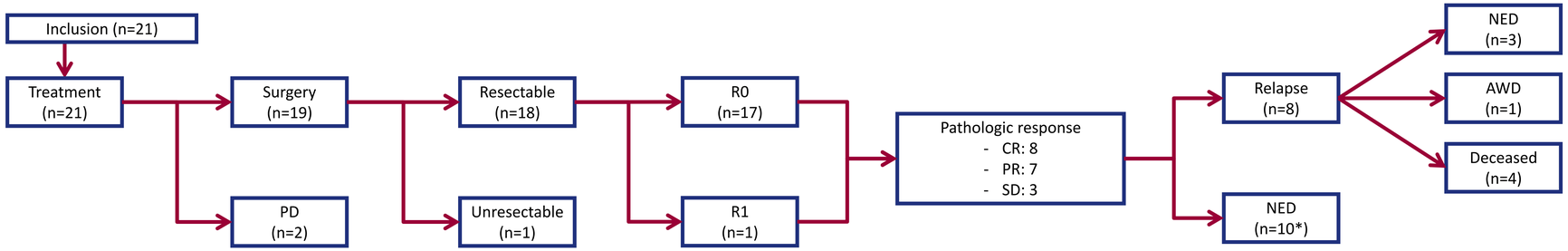

Fig 2. Flowchart of included patients.
List of abbreviations: AWD, alive with disease; CR, complete response; NED, no evidence of disease; PD, progressive disease; PR, partial response; R0, radical resection; R1, microscopic irradical resection; SD, stable disease.

*Follow-up in 2 patients <3 months.

Follow-up data (n=19)	
Median follow-up	28 months (range 4-46)
Median RFS	9 months (range 3-37)
Median OS	Not reached
1-year OS	94%
2-year OS	82%

Toxicity (n=21)	
Total	81%
Grade 1	48%
Grade 2	19%
Grade 3	14%
Most common	Fever

Case Presentation

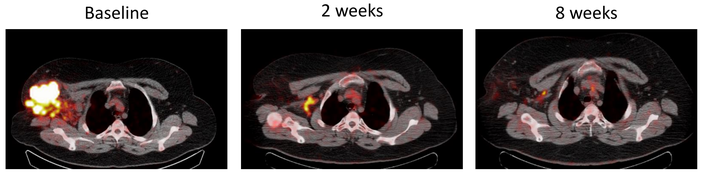

Fig 3. Example of metabolic response, already visible after 2 weeks of treatment.

Key inclusion criteria

- BRAF mutation-positive (V600E/K)
- Unresectable locally advanced stage III or oligometastatic stage IV (≤3 metastases) melanoma
- Treatment naïve
- Evaluable disease by CT/MRI or PET with ≤ 3 metastases/organ sites.
- ECOG 0-1

Key exclusion criteria

- Non-cutaneous melanoma
- Any radiotherapy, surgery or immunotherapy <4 weeks prior to start
- Second malignancy
- Active GI-disease
- Presence of any CNS metastases

Conclusions

- Neoadjuvant dabrafenib and trametinib shows to be a potent cytoreductive treatment, allowing radical resection of metastases in 17/21 (81%) patients with prior unresectable locally advanced melanoma.
- Patients with no recurrence remained disease-free for a prolonged period of time. If there was recurrent disease, this usually occurred within months after surgery.
- This may present an opportunity for further tailored adjuvant therapy.

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