

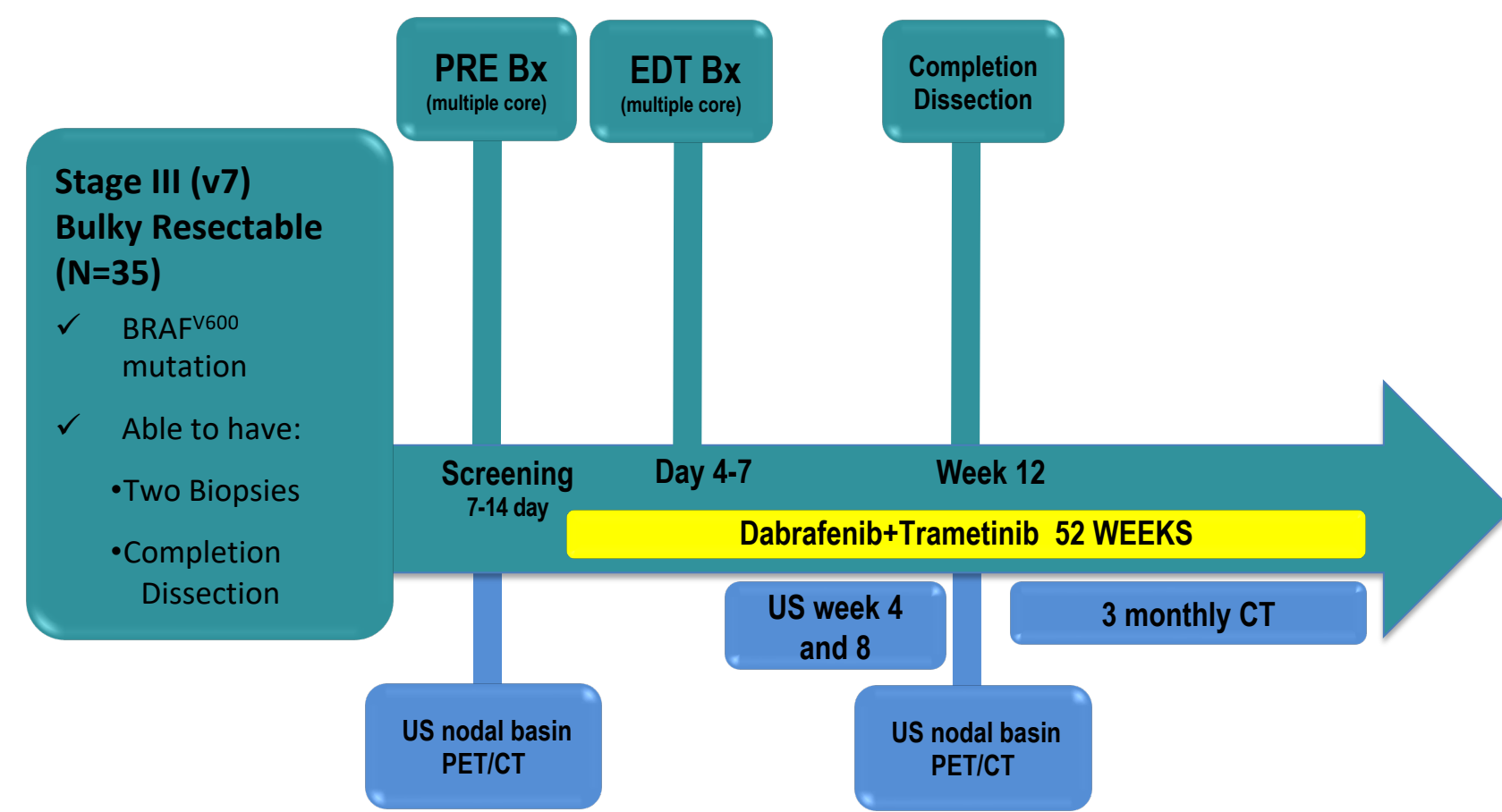
Background

- Neoadjuvant D+T has a high pathologic response rate and impressive short-term survival.^{1,2}
- The NeoCombi trial (NCT01972347) enrolled 35 patients with resectable stage III melanoma, with last patient commencing treatment April 19th 2017.¹

Objectives

- We now report 5-year outcomes from this trial.

Methods



Primary Endpoints

- Complete Pathological Response Rate at Week 12
- RECIST Response Rate at Week 12

Secondary Endpoints

- Surgical Morbidity
- Relapse Free Survival
- Overall Survival
- Toxicity
- Correlation of biomarkers with clinical endpoints

Treatment

- Dabrafenib 150 mg twice daily + Trametinib 2 mg once daily
- 12 weeks prior to therapeutic dissection of pre-therapy tumor bed (neoadjuvant)
- 40 weeks after therapeutic dissection (adjuvant)

Key Eligibility

- BRAF V600 mutation-positive melanoma
- Histologically confirmed resectable bulky stage IIIB/C melanoma
- ≥18 years
- ECOG Performance Status ≤1

Assessments

- CT and PET scans at baseline and Week 12
- CT monitoring q12w to 2y then q6mo to 3y.
- Ultrasound of pre-therapy tumor bed at baseline, week 4, 8 and 12
- Biopsies at baseline and Week 1.
- Therapeutic dissection of pre-therapy tumor bed at Week 12
- Blood for translational and pharmacokinetic analyses at baseline, Week 1,4,8,12, then 4 weekly.
- Pathologic response determined as per INMC criteria and defined as complete (pCR), near complete, partial (pPR) or no response (pNR).³

Results

Table 1. Patient Characteristics

	N= 35
Age, median (range), years	57 (22-83)
Female, n (%)	15 (43%)
BRAF V600E, n (%)	34 (97%)
ECOG 0, n (%)	32 (91%)
LDH Elevated, n (%)	13 (37%)
Stage (AJCC v7), n (%)	
IIIB	6 (17%)
IIIC LN +/- intransit	22 (63%)
IIIC Intransit only	7 (20%)

At data cut August 17th 2021, median F/U was 60 mo (95% CI 56-72).

Figure 1. Pathological Response

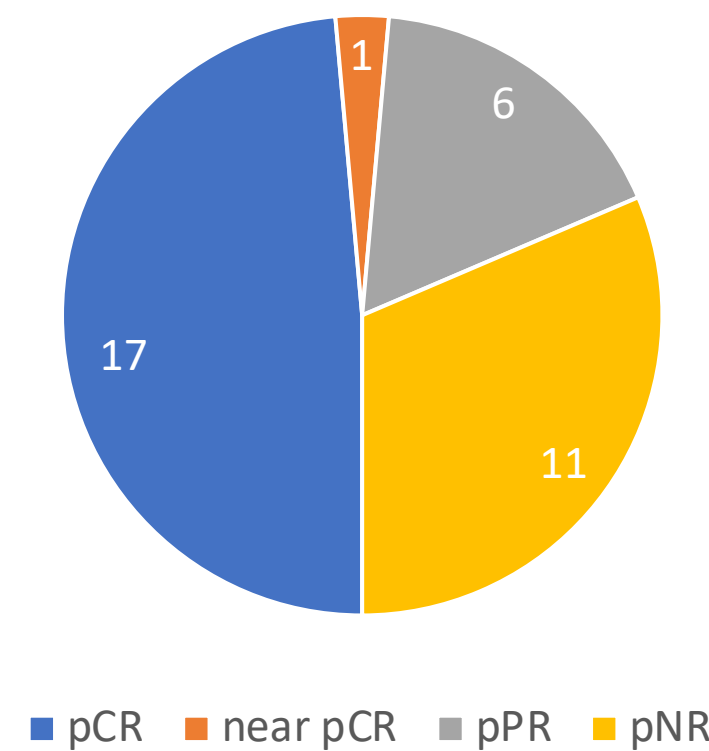


Figure 2. Nature of recurrence (N=21)

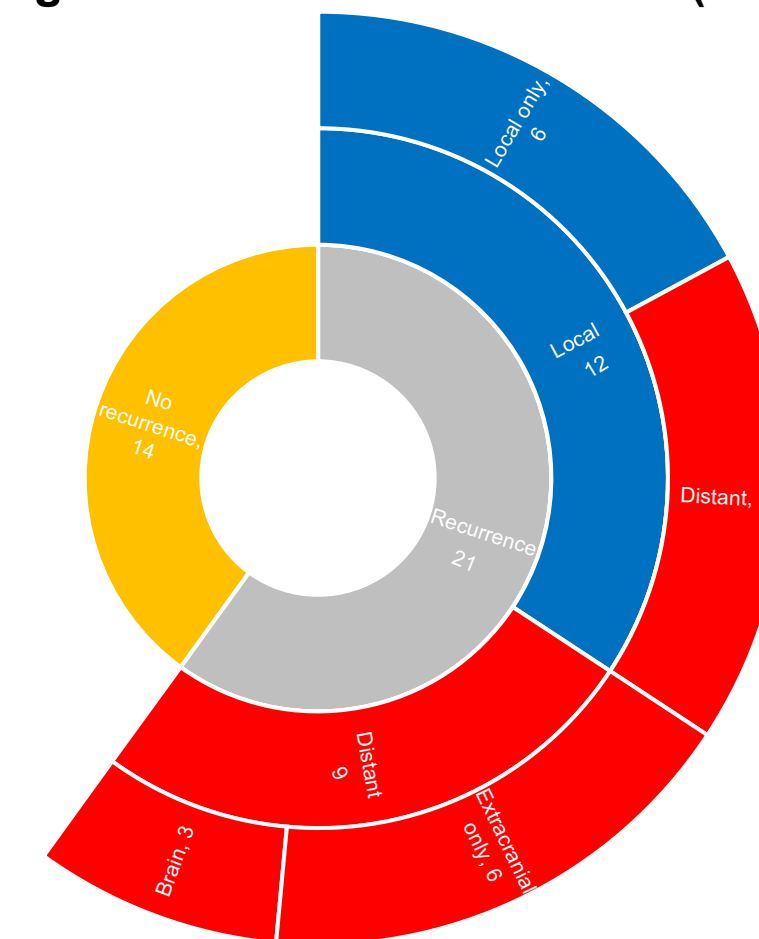


Table 2. Management of local recurrence

	Local (n=12)
Surgery alone	5
Surgery + neo/adjuvant	4 [#]
Systemic therapy alone	2 [~]
Observation	1

[#] 2 neoadjuvant (ipi/nivo, pembro), 2 adjuvant nivo ~ pembro, nivo/rela

Table 3. Management of distant recurrence

Drug class	1 st line (N=15)	Later (N=9)*
Ipilimumab + nivolumab	7	3
PD1 monotherapy	4	1
PD1 + investigational	2	1
Nivolumab + relatlimab	-	2
BRAF/MEKi	2	6
BRAF/MEKi + PD1	-	1
Chemotherapy	-	1

*Some patients had more than one therapy

Conclusions

- Despite early activity with neoadjuvant D+T, patients remain at high risk of recurrence.
- While those with pCR have improved survival than non-pCR, recurrences frequently occur in contrast to immunotherapy.⁴
- Targeted therapy also appears to have inferior survival than immunotherapy in the neoadjuvant setting.

Results - Survival

Figure 3a) Recurrence-free survival*

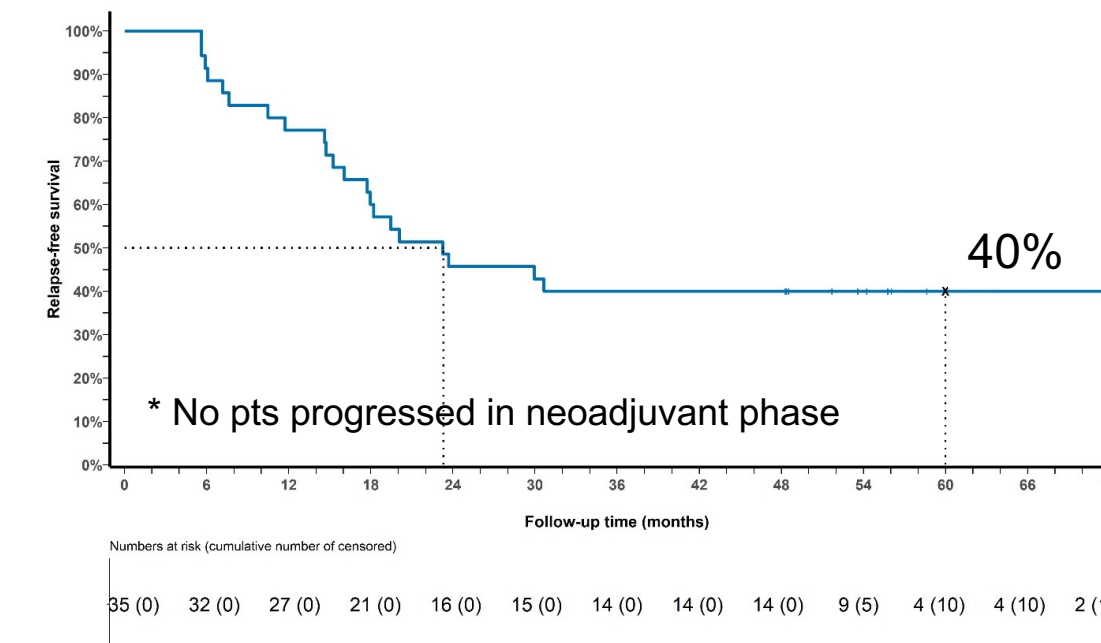


Figure 3b) Distant metastasis-free survival

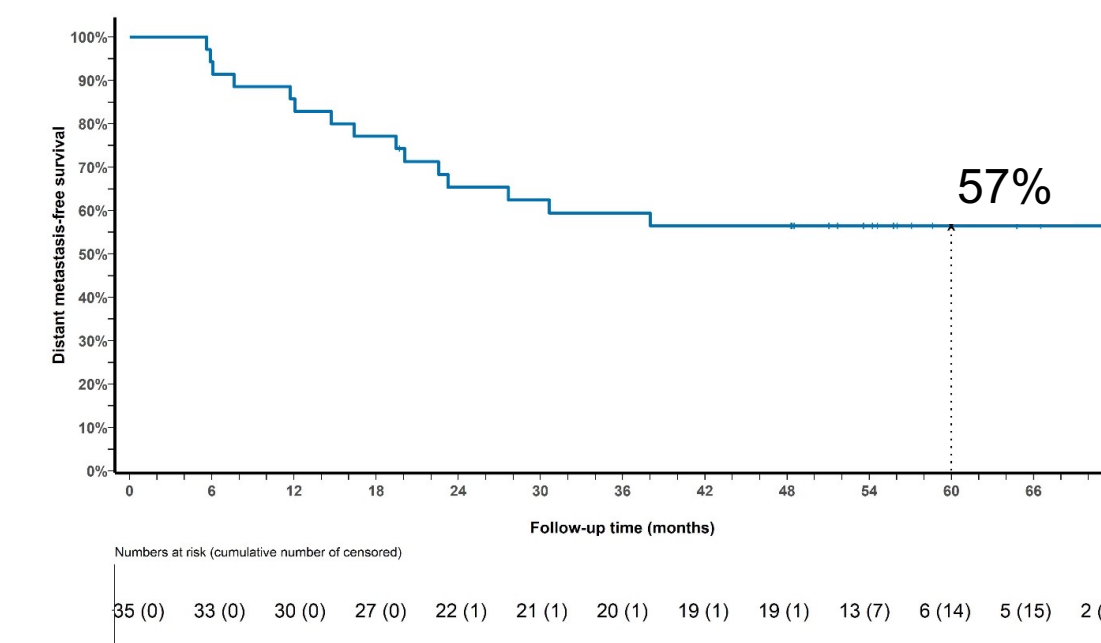
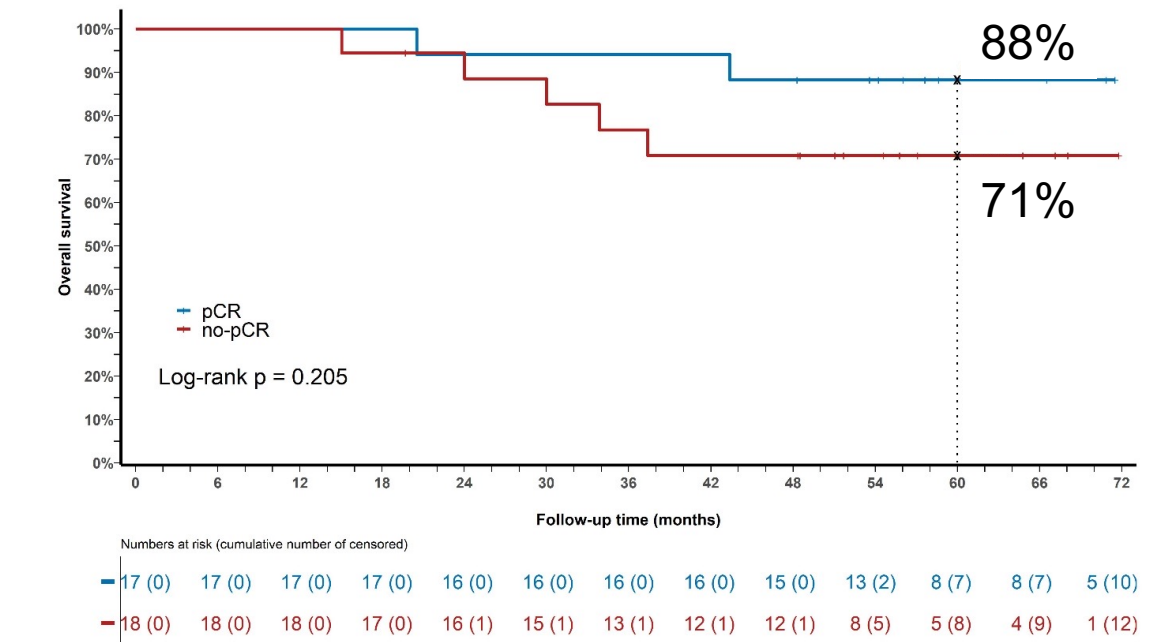
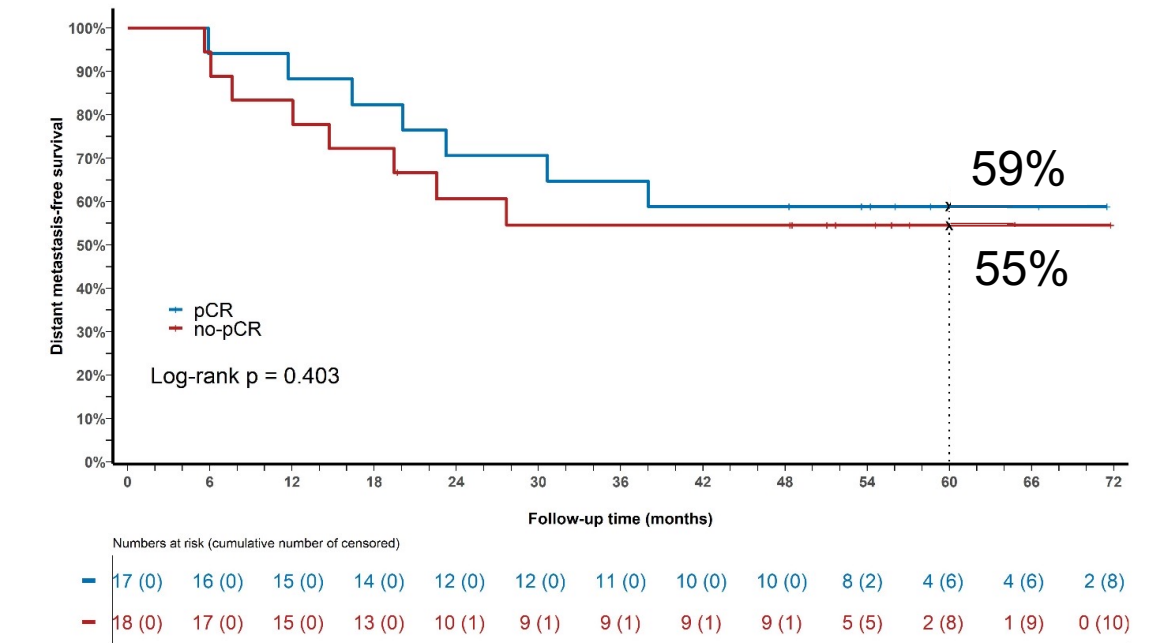
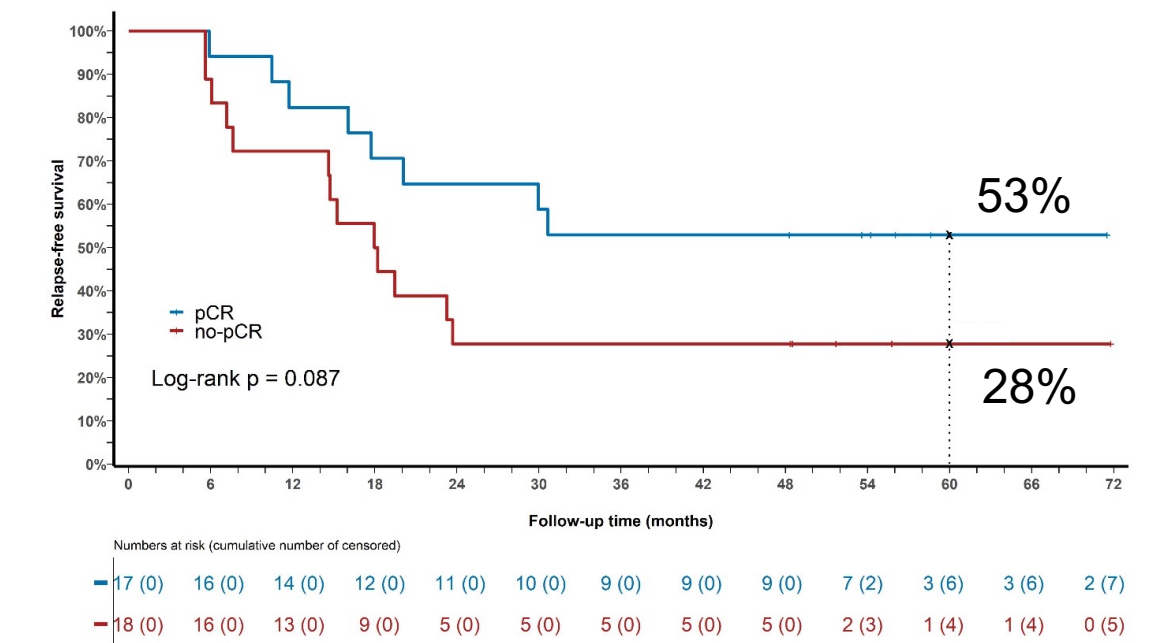
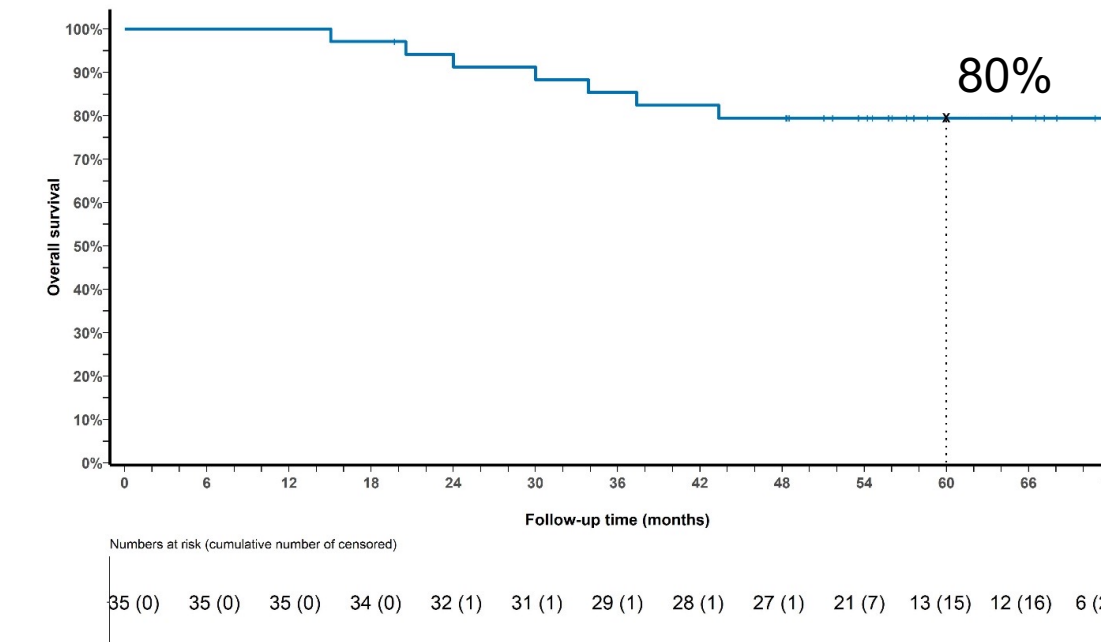


Figure 3c) Overall survival



References

- Long GV, et al. Lancet Oncol 2019.
- Amaria RN, et al. Lancet Oncol 2018.
- Tetzlaff MT, et al. Ann Oncol 2018.
- Menzies AM, et al. Nat Med 2021.

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