NEOTRIO TRIAL – OPTIMAL NEOADJUVANT SEQUENCING OF ANTI-PD1 AND BRAF TARGETING THERAPY IN RESECTABLE BRAF MUTANT STAGE IIIB/C/D MELANOMA: RESULTS OF HISTOPATHOLOGICAL ANALYSIS

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Background

- Hyalinised fibrosis (HF) in 6 week post neoadjuvant treatment lymph node resection specimens in stage III melanoma is associated with improved relapse-free survival (RFS) with neoadjuvant BRAF targeted therapy(TT)[1] and doublet immunotherapy[2]. Inflammatory/proliferative fibrosis (IF) is associated with poor RFS with neoadjuvant TT[1] .
- Changes to lymphocyte densities and fibrosis and their associations with response to neoadjuvant combination TT and anti-PD-1 are unknown.

We aimed to characterise key histopathological changes with neoadjuvant TT, anti-PD-1 or combination and their association with pathological response.

Methods

Histopathological assessment of longitudinal FFPE samples (core and lymph node dissection specimens) from the phase II NeoTrio (NCT02858921) and NeoCombi (NCT01972347) clinical trials was performed.

Key histopathological characteristics of the tumour bed assessed include;

- Inflammatory fibrosis - % of tumour bed
- Hyalinised fibrosis - % of tumour bed
- Lymphocyte density score (LDS) - absent, mild, moderate, extensive

Statistical Analysis; Histological parameter changes over time were modelled using linear mixed effects model including treatment, pathological response, timepoints and a random intercept.

Results

Figure 1. NeoTrio and NeoCombi Trial Schemas

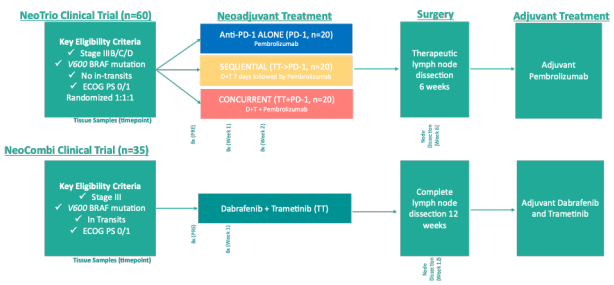


Table 1. Patient Demographics of NeoTrio and Neocombi Clinical Trials

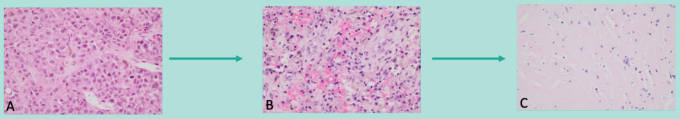
	PD-1 N=20	TT->PD-1 N=20	TT+PD-1 N=20	TT N=35
Age, median (range), yrs	56 (51 - 64)	50 (38 - 63)	53 (42 - 61)	56 (46 - 64)
Female, n (%)	8 (40)	8 (40)	9 (45)	15(43)
ECOG 0, n (%)	20 (100)	19 (95)	20 (100)	32(91)
BRAF subtype, n (%)				
BRAF V600E	16 (80)	16 (80)	17 (85)	34(97)
BRAF V600K/R	4 (20)	4 (20)	3 (15)	1(3)
Lymph Node Site, n (%)				
Neck	8 (40)	3 (15)	5 (25)	3(11)
Axilla	7 (35)	9 (45)	10 (50)	5 (18)
Inguinal or ilioinguinal	5 (25)	8 (40)	5 (25)	15 (54)

Table 2. Pathological Response Rates Across Treatment Arms

	PD-1 N=20	TT->PD-1 N=20	TT+PD-1 N=20	TT N=35
Any pathological response, n(%)	**11 (55)**	**10 (50)**	**16 (80)**	**22 (63)**
pCR	6 (30)	3 (15)	10 (50)	15 (43)
near-pCR	2	3	1	1
pPR	3	4	5	6
pNR	7 (35)	10 (50)	3 (15)	11 (31)
Not evaluable*	2	0	1	2

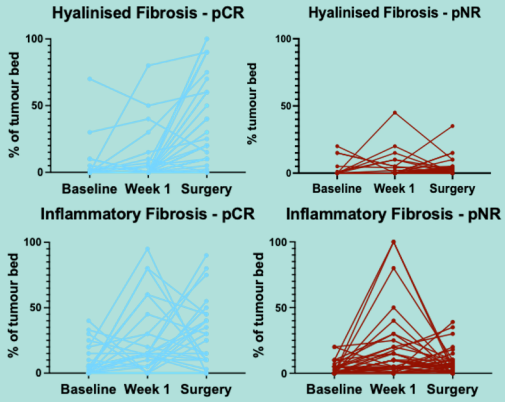
Results Cont.

Figure 2. Histopathology of patient achieving pCR on TT+PD-1



A) Baseline core biopsy; sheets of melanoma cells, minimal immune cell infiltrate. B) Week 1 core biopsy; significant immune cell influx. C) Surgery(week 6 node dissection): near complete replacement with HF

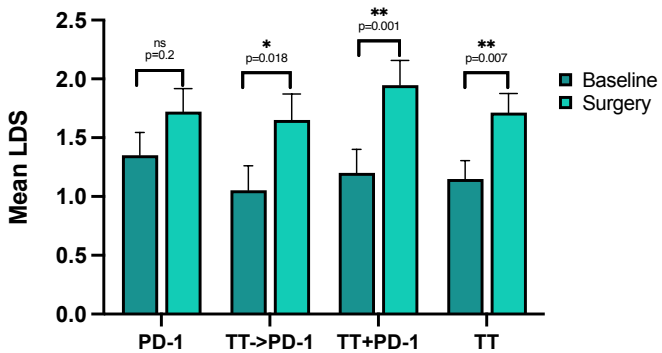
Figure 3. Inflammatory and Hyalinized Fibrosis Across All Treatment Arms



- IF and HF were significantly associated with pCR (p=0.004 and p<0.001 respectively) across the cohort.
- Split by treatment, IF was associated with pCR in combination (TT->PD-1 p=0.02, TT+PD-1 p = 0.013) but not with single modality therapy (PD-1 p = 0.587, TT p=0.13).
- Split by treatment, HF was associated with pCR with TT->PD-1 (p=0.048).

p values derived from linear mixed effects models – changes in fibrosis from baseline in pCR vs non-pCR

Figure 4. Mean Increase in Lymphocyte Density Score (LDS) from Baseline to Surgery Across Treatment Arms



LDS was not associated with pCR in any arms or across the cohort

Conclusion

Concurrent TT+PD-1 achieved the highest pCR rates across the treatment arms.

Hyalinised fibrosis and Inflammatory fibrosis were significantly associated with pCR across the cohort.

Lymphocyte Density Score Increased significantly across all arms with TT with the most significant increase in Concurrent TT+PD-1.

References

1. Tetzlaff M.T., et al., Annals of Oncology, Nov 2020, 31(11):1569-1579
2. Rawson R.V., et al., Annals of Oncology, June 01 2021, 32(6) : 766-777

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