FNP:798P

Histopathological Analysis of Neoadjuvant Sequential or Combination Targeted Therapy (TT) and anti-PD-1; Combined Analysis of NeoTrio and NeoCombi Clinical Trials

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Background

- Hyalinised fibrosis (HF) 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, melanophages populations 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 assessed include;
  - Inflammatory fibrosis - % of tumour bed
  - Hyalinised fibrosis - % of tumour bed
  - Melanophages - % of tumour bed
  - Lymphocyte density score (LDS) - absent, mild, moderate, extensive
- A linear mixed effects model was used to analyse histological changes from baseline across timepoints(paired) within treatment arms and their associations with response.

Figure 1. NeoTrio and NeoCombi Trial Schemas

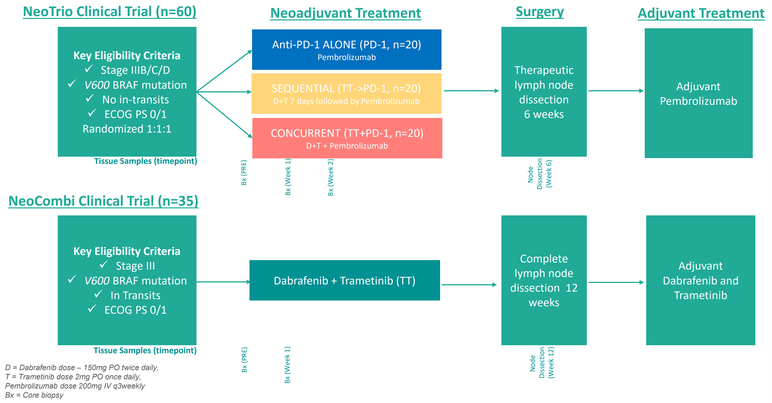


Table 1. Patient Demographics of NeoTrio and Neocombi Clinical Trials

	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)

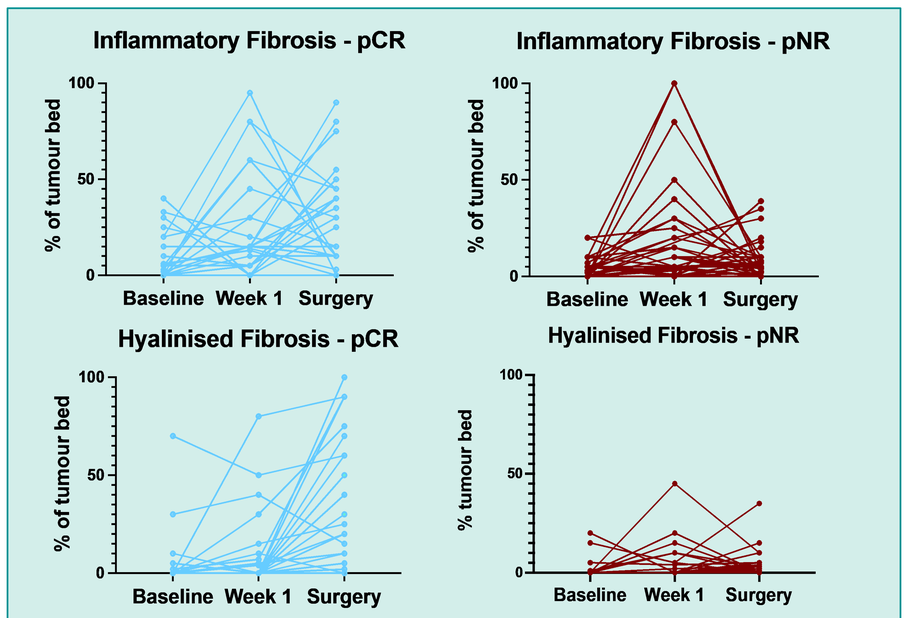
Results

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

** 5 pts did not undergo surgery due to progression in neoadjuvant period.*

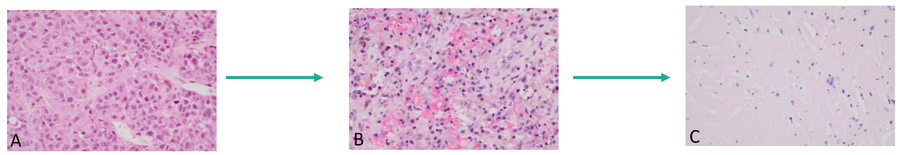
Figure 2. Inflammatory and Hyalinized Fibrosis Across All Treatment Arms



- 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).

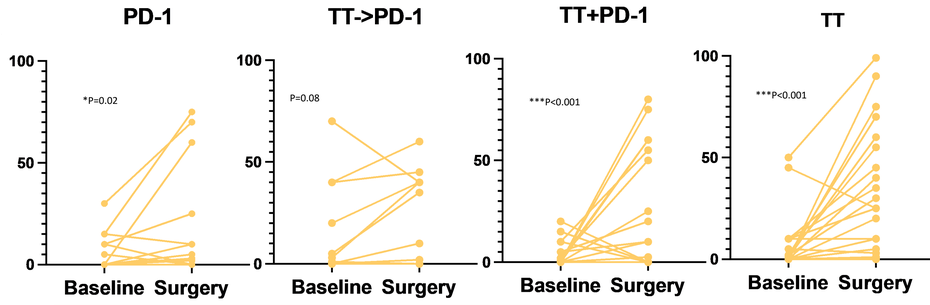
p values derived from linear mixed effects models – changes in fibrosis from baseline in pCR vs non-pCR

Figure 3. Histopathology of patient achieving pCR on TT+PD-1



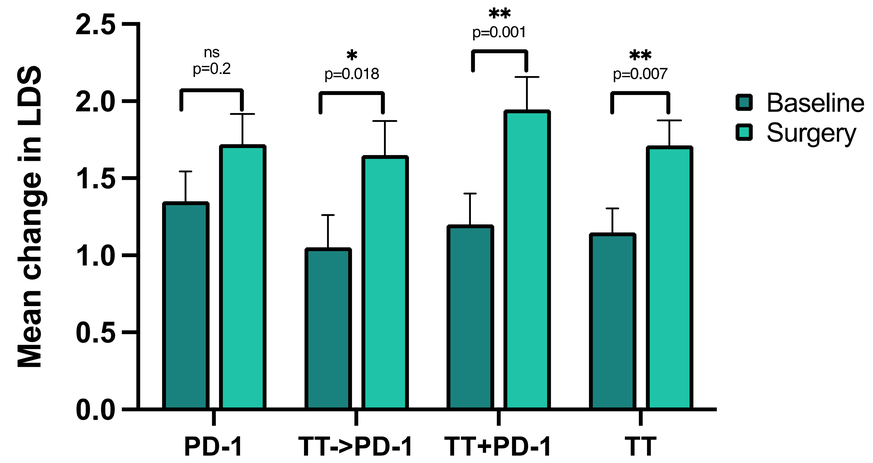
A) Baseline core biopsy; sheets of melanoma cells, minimal immune cell infiltrate. B) Week 1 core biopsy; significant immune cell influx. C) Surgery(week 6 node dissection): near complete replacement with HF

Figure 4. Increase in % of Melanophages from Baseline to Surgery Across Treatment Arms



Anti-PD-1 alone was the only treatment arm to demonstrate a significant association with pCR (p=0.009)

Figure 5. 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

- Hyalinised fibrosis is associated with complete pathological response across the cohort.
- Inflammatory fibrosis is associated with pCR across the cohort and strongly associated with pCR in combination treatment.
- This study is the first to demonstrate increased melanophages treated with neoadjuvant anti-PD-1 monotherapy are associated with pCR.

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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