



Monitoring populations of tumor-macrophage fusion cells in blood prognosticates PFS and OS in pan-metastatic cancers over 2 years

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ABSTRACT

Tumor associated macrophages are known to fuse with cancer cells in the blood through a dysfunctional CD47-mediated phagocytic immune pathway resulting in the formation of tumor-macrophage fusion cells (TMFCs), which are observed as heterokaryon (incomplete fusion), synkaryon (full fusion) or hetero-to-synkaryon transition (partial fusion). Previous studies in lung and breast cancer demonstrated that subtypes of TMFCs in blood may correlate with highly aggressive disease unlikely to respond to certain systemic therapies (i.e. chemotherapy). We initiated a prospective study to evaluate the blood of n=100 metastatic pan-cancer patients (pts) receiving systemic therapy for the presence of full, partial, and incomplete TMFCs to compare their progression-free survival (PFS) and overall survival (OS).

MATERIALS & METHODS

We conducted a prospective pilot study of pathologically confirmed metastatic cancer pts with breast (n=23), prostate (n=21), pancreas (n=17), colon (n=19), or lung (n=20) with active progressive disease, prior to the induction of new systemic therapies, i.e. chemotherapy (n=39), PD-L1 immunotherapy (n=27), hormone therapy (n=20), or targeted therapy (n=23), (Table 1). TMFCs were isolated from 7.5ml peripheral blood using CellSieve microfiltration and identified by their enlarged multinucleated structure (>30 µm), which was categorized into 3 distinct subtypes: full fusion marked by a single multinucleated nuclei, partial fusion marked by 2 contacting nuclei, or incomplete fusion marked by 2 distinct non-contacting nuclei. TMFC subtypes and other clinical parameters were compared to pts' PFS and OS by cox proportional univariate and multivariate analysis over 24 months (Table 2).

RESULTS

- We identified TMFCs in 78% of all pts (n=78/100), averaging 10 per pt
- 37% of pts were found to have >1 TMFC, with n=70 pts having full fusion, 23 partial fusion, & 28 incomplete fusion (Table 1)
- At 24 months, pts with incomplete fusion TMFCs had significantly worse PFS (HR=2.9; p=0.0023) & OS (HR=2.4; p=0.0304) (Fig 1)
- In an ad-hoc analysis, pts with incomplete fusion and treated with targeted therapy (n=7) had significantly improved PFS (HR=4.8; p=0.0052) & OS (HR=3.9; p=0.0300) (Fig 2)
- There was no significant PFS differences in pts without incomplete fusion TMFCs being treated with targeted therapies

Table 2. Forest Plot of Clinical Parameters

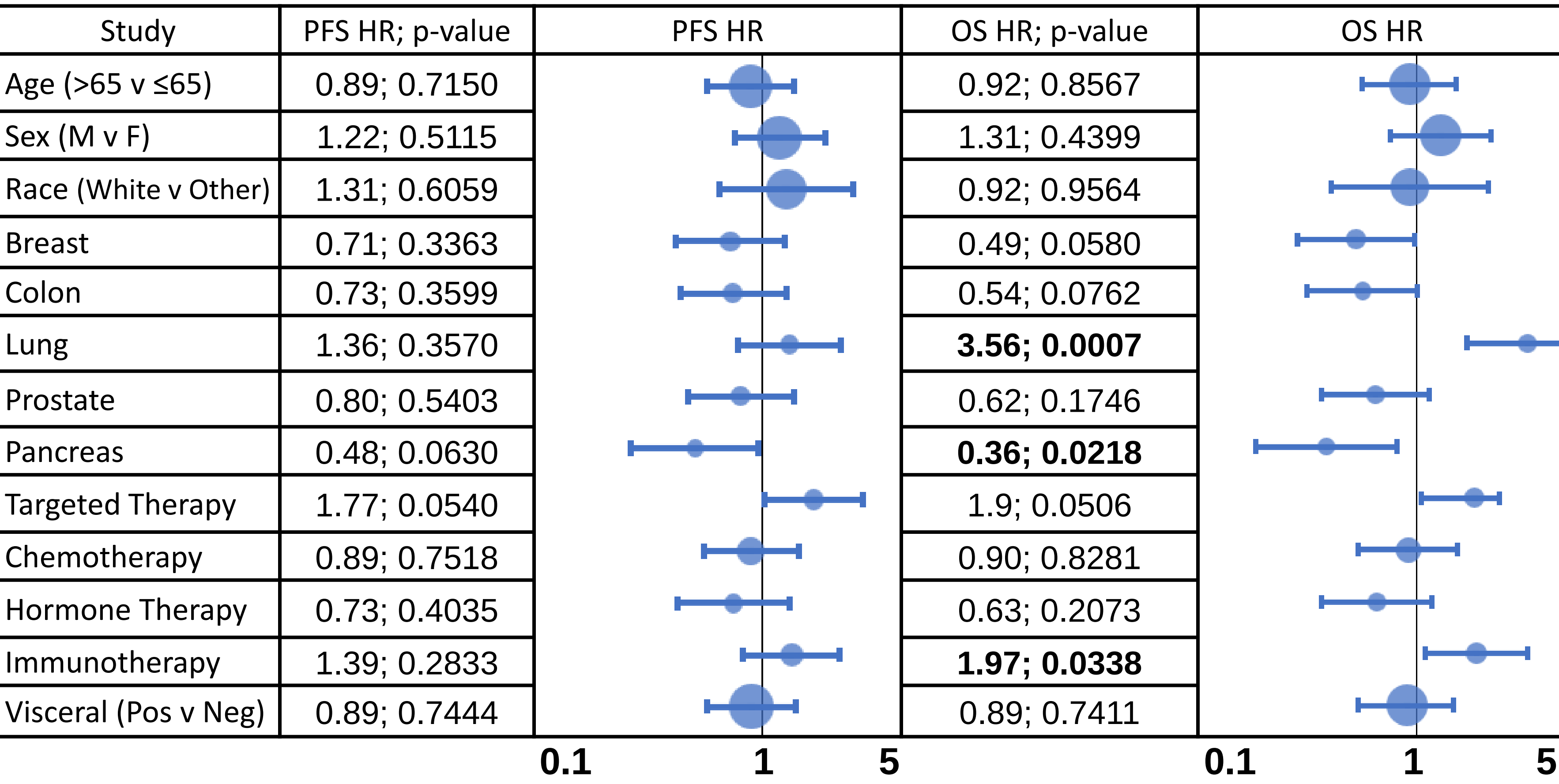


Table 1. Demographic Table

Median Age (Range)	64 (33-92)
Sex	
Male	57 (58%)
Female	41 (42%)
Race	
White	66 (66%)
Black	6 (6%)
Hispanic	1 (1%)
Unknown/Other	27 (27%)
Cancer Type	
Breast	23 (23%)
Colon	19 (19%)
Lung	20 (20%)
Pancreas	17 (17%)
Prostate	21 (21%)
Therapy Type	
Targeted Therapy	23 (21%)
Chemotherapy	39 (26%)
Hormone Therapy	20 (18%)
Immunotherapy	27 (25%)
Metastasis	
Visceral	51 (52%)
Non-Visceral	48 (48%)
ECOG	
0	44 (45%)
1	48 (48%)
2	7 (7%)
TMFC Subtype	
Full	70 (70%)
Partial	23 (23%)
Incomplete	28 (28%)
None	22 (22%)

Figure 1

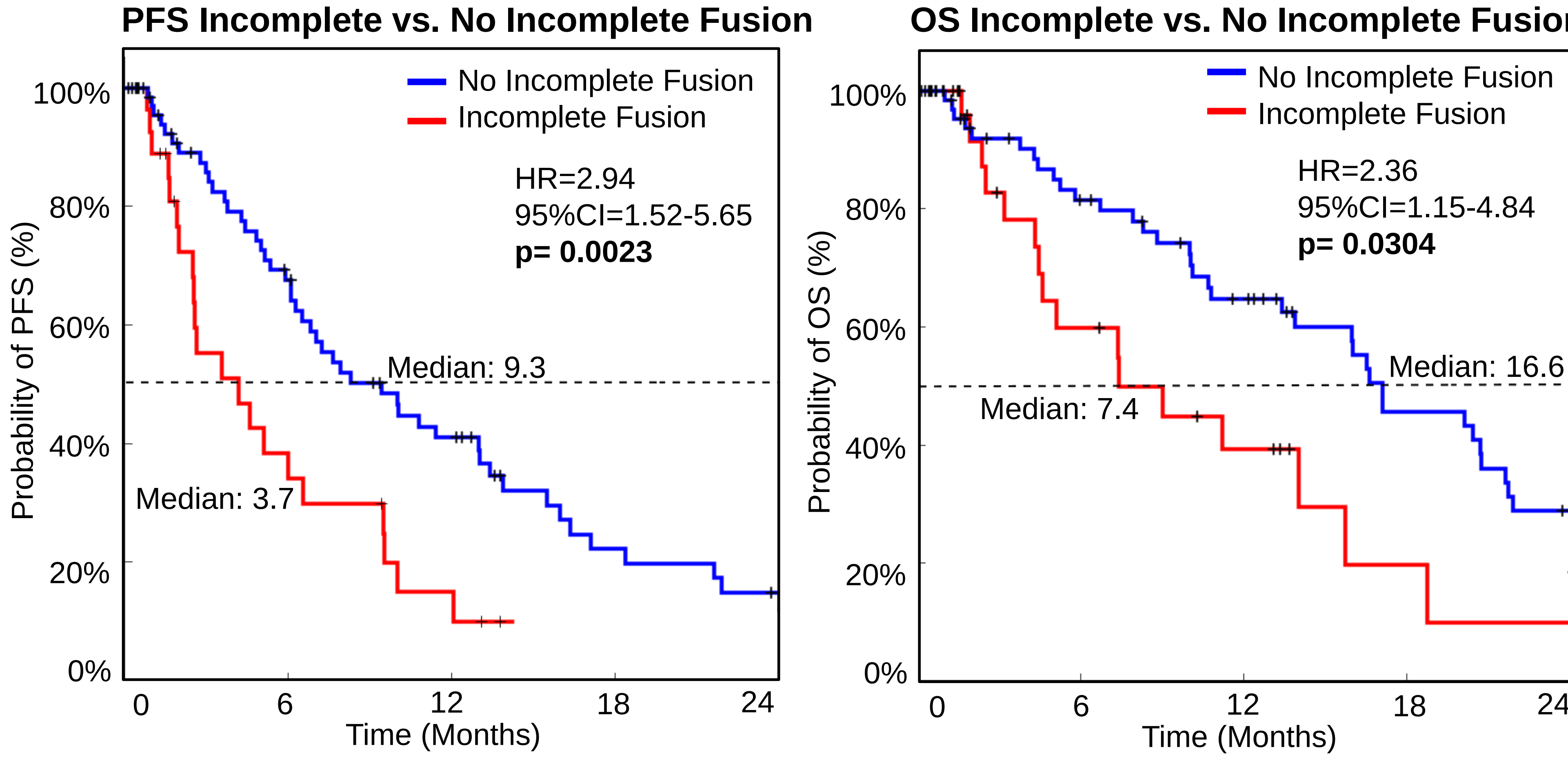
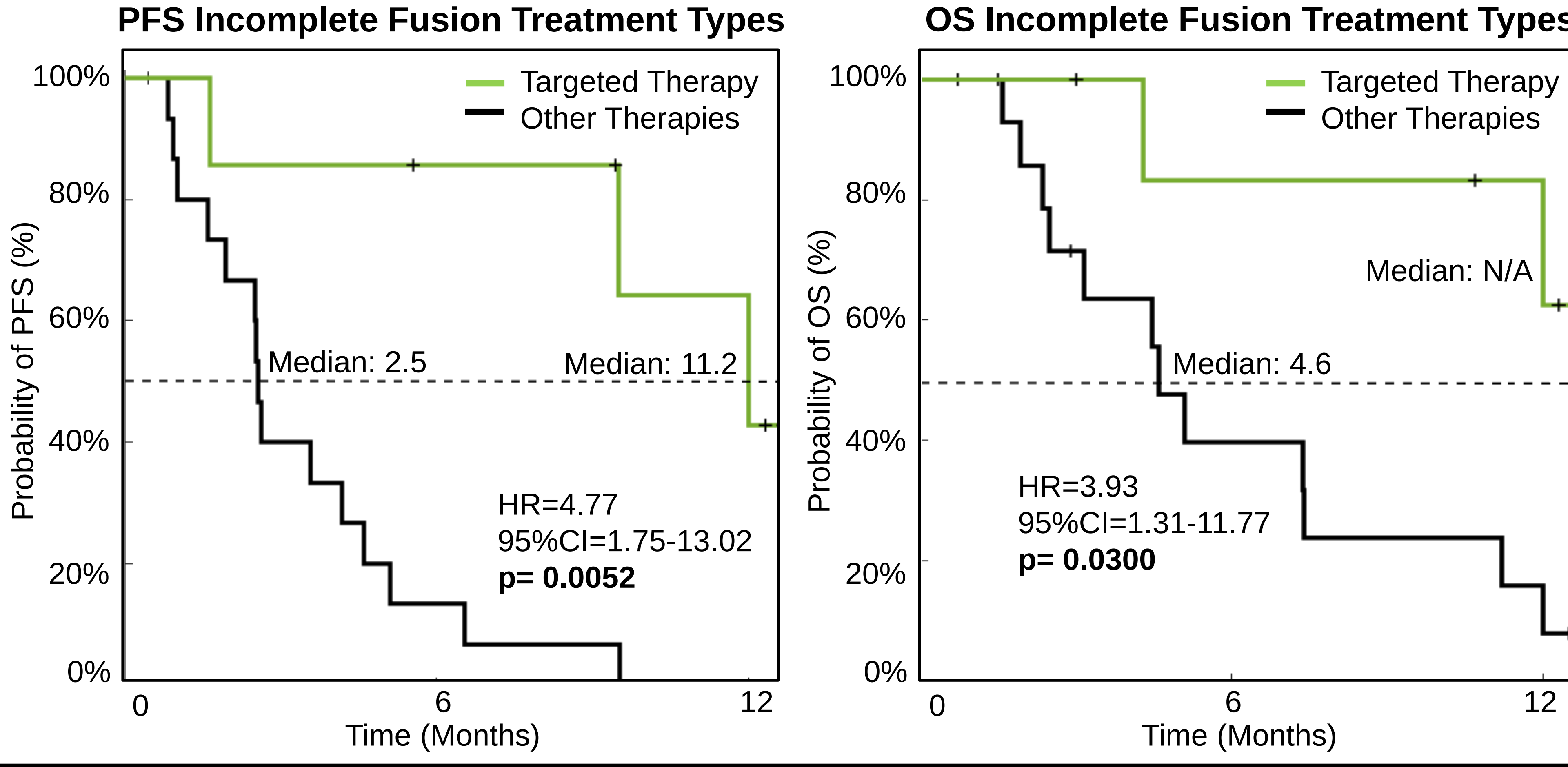


Figure 2



CONCLUSIONS

- In a pan metastatic cancer setting, we found that incomplete fusion in circulating TMFCs associates with poorer outcomes at 24 months
- It appears that pts with incomplete TMFCs may have had better outcomes when treated with targeted therapies compared to other therapy types
- These preliminary findings suggest the need for larger scale prospective studies to further evaluate relationships between TMFCs and therapeutic response in these disease populations

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