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Monitoring engorgement of phagocytic circulating stromal cells during chemo-radiotherapy induction predicts survival in unresectable stage 2/3 NSCLC

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ABSTRACT

Circulating stromal cells, i.e. Cancer Associated Macrophage-Like cells (CAMLs), are prevalent in the circulation of non-small cell lung carcinoma (NSCLC) patients (pts), appearing as giant phagocytic macrophages that represent an inflammatory pro-tumorigenic microenvironment. Previously it was shown that pts with engorged CAMLs of ≥50µm after treatment are prognostic for poor clinical outcomes. However, analyzing the dynamic changes in CAMLs over time or in response to treatment, i.e. chemoradiation (CRT) and immunotherapy (IMT) has not been evaluated. We monitored n=182 unresectable NSCLC stage II/III pts treated with CRT alone (n=91) or with concurrent IMT (n=91) to evaluate changes in CAMLs before and after CRT induction at it relates to progression free survival (PFS) or overall survival (OS).

INTRODUCTION

Between 2013 and 2016, there was a sharp decline in population mortality for pts with NSCLC, partly attributed to the success of PD-L1/PD-1 based Immunotherapies (IMT) therapies, such as Atezolizumab (Atezo) and Durvalumab (Durva)[1,2] However, not all patients benefit from these IMT therapies and identifying patients responsive to these treatments has remained elusive. Recently, it was shown that CAMLs, a specialized myeloid immune cell transiting the circulation of NSCLC patients, might predict patients responding to IMTs based on their phagocytic size engorgement[3], through tracking this engorgement after therapy induction has not been studied.

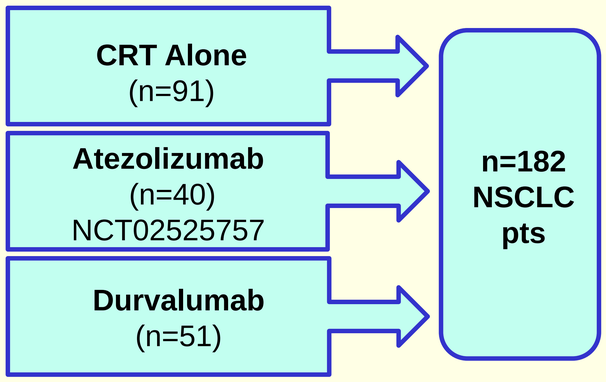

Figure 1. Flow chart of NCLC patient populations

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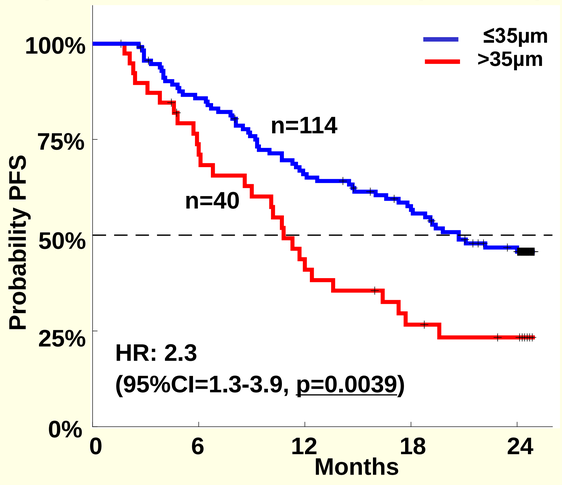
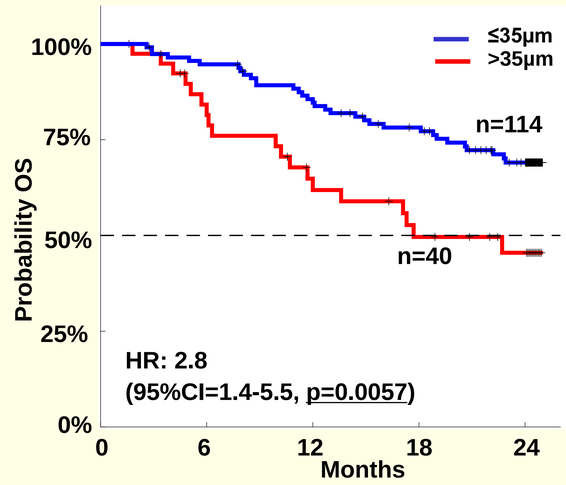
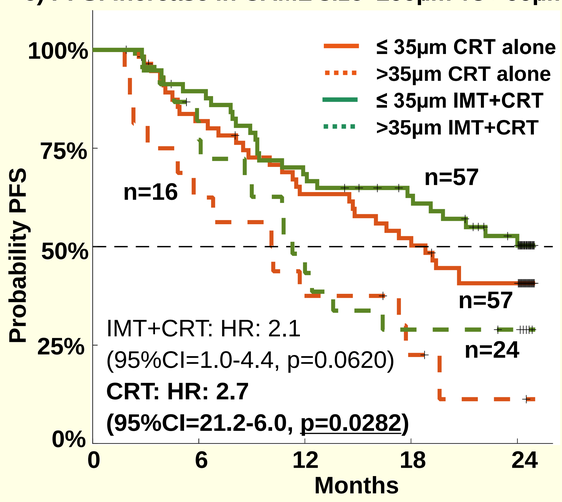
a) PFS: Increase in CAML size ≤35µm vs >35µm



b) OS: Increase in CAML size ≤35µm vs >35µm



c) PFS: Increase in CAML size ≤35µm vs >35µm



d) OS: Increase in CAML size ≤35µm vs >35µm

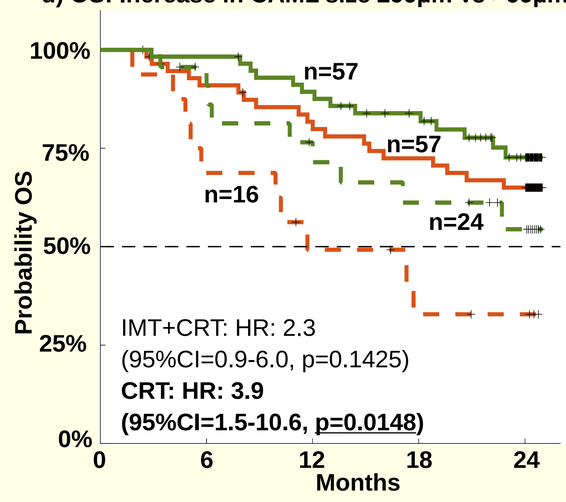


Table 1. Forest Plots for CAML size increase after treatment start for PFS and OS

Change in CAML Size	N value	PFS p value	PFS HR	OS p value	OS HR
+10 µm	89 v 65	0.0214		0.0279	
+15 µm	94 v 60	0.0135		0.0389	
+20 µm	100 v 54	0.0142		0.0277	
+25 µm	106 v 48	0.0043		0.0146	
+30 µm	108 v 46	0.0033		0.0195	
+35 µm	114 v 40	0.0039		0.0057	
+40 µm	122 v 32	0.0183		0.0319	
+45 µm	124 v 30	0.0139		0.0455	
+50µm	128 v 26	0.0219		0.0766	
			1 Log (HR) 10		1 Log (HR) 10

Figure 2. PFS and OS of changes in CAML size by 35 µm. (a) & (b) PFS & OS for all n=182 NSCLC patients. (c) & (d) PFS & OS for IMT population (n=91, green) and CRT alone population (n=91, orange)

MATERIALS & METHODS

We prospectively procured pts from 3 different regimes, treated with CRT alone (n=91), treated concurrently with CRT & Atezolizumab (n=40, clinical trial NCT02525757), or treated concurrently with Durvalumab (n=51) (**Fig 1**). We recruited 182 pts with pathologically confirmed stage II/III unresectable NSCLC. A total of 15 mL blood samples were drawn prior to start of therapy at baseline (BL) and ~5 weeks (T1) after CRT induction. Blood filtration was done using CellSieve™ filters, then CAMLs were identified and measured to evaluate PFS & OS hazard ratios (HRs) by censored univariate and multivariate analyses at 2 years. For analysis, we compared pts based on CAML size increases greater than thresholds versus pts with any changes below the threshold, including decreases and no differences in CAML change.

RESULTS

- Increases in CAML size of 10-50µm between BL and T1 time points correlates with increasingly shorter PFS and OS (**Table 1**).
- Increases in CAML size of 35 micron between BL and T1 was optimal in stratifying pts in terms of PFS and OS **(Figs 2a & 2b).**
- Increases in CAML size of 35 micron significantly stratified pts by PFS and OS treated with CRT but not significantly for pts treated with IMT **(Fig 2 c & d).**

CONCLUSIONS

- Tracking the increase of CAML size in circulation during therapy induction for unresectable stage II/III NSCLC may identify pts less responsive to CRT and possibly IMTs
- Patients treated with IMT had improved PFS and OS.
- Further follow up clinical data is ongoing for the patients treated with IMT

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