

SENLOAD study: association of baseline CD8 T-cell senescence with survival in unresectable stage III NSCLC

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Background

- Standard of care for patients with unresectable locally advanced (LA) non-small cell lung cancer (NSCLC) is concomitant platinum-based chemotherapy radiotherapy (CRT) followed by immune checkpoint blocker (ICB) consolidation.
- Loss of CD28 and expression of CD57, and KLRG1 have been previously identified as markers of T-cell immunosenescence.
- The impact of T-cell immunosenescence, a mechanism of anti-PD-1/L1 resistance in advanced NSCLC (aNSCLC), needs to be assessed in unresectable LA NSCLC.
- We present here the preliminary results of the SENLOAD study.

Methods

- SENLOAD is a prospective translational study embedded within STING study (NCT04932525): baseline pre-CT (V0), before RT (V1), before ICB (V2), after 8 weeks of ICB (V3) and at progression (V4) (figure 1).
- For this analysis, 86 patients with evaluable baseline samples were included.
- Baseline senescence was defined using V0 when available or V1 otherwise, generating a unified baseline variable (VBaseline) reflecting real-world sampling constraints. Baseline assessment occurred around treatment initiation (median 0 days; IQR -4 to 21).

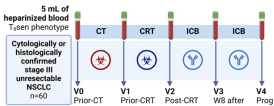


Figure 1. Pipeline of SENLOAD study

- The percentage of CD28-, CD57+, KLRG1+ among CD8+ T cells (T_{sen}, figure 2) was assessed by blood flow cytometry. Patients were classified SIP+ when T_{sen} rate was >25% of CD8+ T cells [1].
- The primary objective was to evaluate baseline SIP as a prognostic factor for progression-free survival (PFS) in patients treated with CRT followed by ICB.

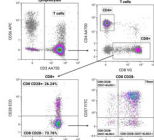


Figure 2. Gating strategy for the analysis of circulating T_{sen} cells by flow cytometry

[1] Ferrara R, Naigeon M, Auclin E, et al Clin Cancer Res. 2021

Results

Patients characteristics are shown in table 1.

Characteristic	Overall (N=86)
Age at diagnosis, median (IQR), years	66 (59-71)
Sex	
Female	34 (40%)
Male	52 (60%)
ECOG performance status	
0	40 (47%)
1	43 (50%)
2	3 (3%)
Histology	
Non-squamous	59 (69%)
Squamous	27 (31%)
Stage	
IIA	2 (2%)
IIIA	38 (44%)
IIIC	39 (45%)
IIIC	21 (25%)
Oncogenic driver status	
Unknown	41 (48%)
Wild-type	45 (52%)
Platinum chemotherapy	
Carboplatin-based	41 (48%)
Cisplatin-based	45 (52%)
Chemotherapy	
Concurrent	40 (47%)
Sequential	46 (53%)
Radiotherapy	
Yes	79 (92%)
No	7 (8%)
Best response to CRT	
CR	3 (3%)
PR	46 (53%)
SD	32 (37%)
PD	12 (14%)
Unknown	2
Durvalumab consolidation	
Yes	56 (65%)
No	22 (25%)
Unknown	8
Progression during treatment	
No	49 (57%)
Yes	37 (43%)
VO Tsen (% of CD8, median (IQR))	23% (15-41)
V1 Tsen (% of CD8, median (IQR))	24% (15-42)
Missing	22
Baseline Tsen (% of CD8, median (IQR))	23% (15-39)
Diagnosis to baseline, median (IQR), days	-46 (29-65)
Treatment start to baseline, median (IQR), days	0 (-4 to 121)

Table 1. Clinicopathological characteristics.

The previously reported SIP cut-off of 39.5% [1] was not predictive of OS or PFS. When analyzed as a continuous variable, baseline SIP demonstrated a non-linear association with OS, but not PFS. In a penalized spline Cox model, the overall effect was significant (LRT=9.21, p=0.02), with a borderline non-linear component (p=0.055), supporting a non-monotonic relationship between senescence burden and survival (figure 3).

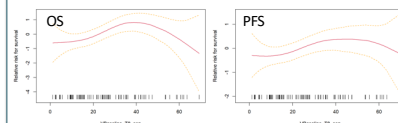


Figure 3 : Association Between Baseline Tsen and Overall Survival.

With a median follow-up of 42.2 months, median OS was not reached and median PFS was 23.3 months. An outcome-oriented analysis identified 25% (IQR 13-39) as the exploratory cohort-derived cut-off for both OS and PFS. Patients with SIP ≥25% had shorter PFS (13.0 vs 27.8 months) and a trend toward shorter OS (figure 4). The multivariable analyses shown SIP as prognostic factor. (figure 5).

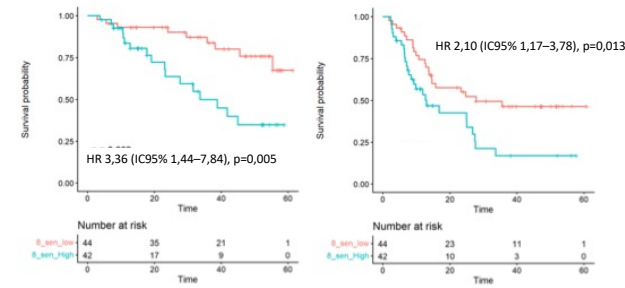


Figure 4. Probability of OS (left) and PFS (right) according to Tsen status with optimal exploratory threshold calculated on the patients in the study (high >25%, low ≤25%).

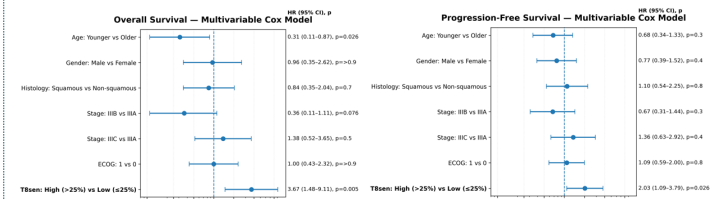


Figure 5 : Multivariable Cox Regression Analyses for Overall and Progression-Free Survival.

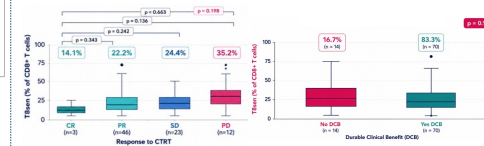


Figure 6. Baseline Tsen rate according to response to CRT (left), DCB (Durable Clinical Benefit: CR+PR+SD>6 months) (right); p = 0.13 respectively.

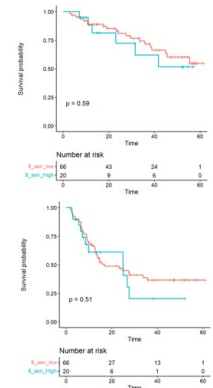


Figure 7. Probability of OS (above) and PFS (below) according to Tsen status (high >39.5%, low ≤39.5%, Ferrara et al CCR 2021).

Conclusion

- In SENLOAD, baseline CD8 T-cell senescence showed a non-linear association with survival outcomes in unresectable LA NSCLC treated with CRT ± IO.
- Previously proposed thresholds were not validated.
- An exploratory 25% threshold identified a high-risk population and remained independently associated with OS and PFS after multivariable adjustment.
- These findings support prospective validation and favor continuous modeling of senescence.