Concurrent versus sequential immune checkpoint inhibition in stage III NSCLC patients treated with chemoradiation

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Introduction

- Durvalumab maintenance treatment after completion of concurrent chemoradiotherapy (CRT) in patients with inoperable stage III non-small cell lung cancer (NSCLC) is the international standard.
- The concurrent administration of an anti–programmed cell death-protein 1 (PD-1) or anti–programmed death-ligand 1 (PD-L1) with radiotherapy may improve the response rate in preclinical models [2] and has been investigated in the first prospective study [3].
- In this prospective study, we investigated the impact of simultaneous versus sequential immune checkpoint inhibition in patients receiving platinum-based CRT

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- Prospective study

- Study duration- January 2016 to December 2020
- 39 NSCLC patients in stage IIIA/B/C

Total 39 patients- 38 (97.4%) patients received platinum-based concurrent CRT with curative intent (≥60Gy)

SIM-I cohort →11 (28.2%) patients received concurrent PD-1 inhibition (nivolumab) up to 1 year after the end of CRT

SEQ-I cohort → 28 (71.8%) patients received sequential PD-L1 inhibition (durvalumab)

Therapy-associated adverse events were assessed weekly during the CRT and at 6 weeks, 3,6,9, and 12 months after the end of the CRT. The index date for oncologic endpoints was defined as the end of radiotherapy.

Results

	Overall cohort	SIM-I cohort	SEQ-I cohort
Median follow up	27.2 months	33.3 months	24.7 months
Median OS	NA (not achieved)	NA	NA
Median PFS	NA	22.8 months	NA
PFS at 12 months	-	82%	63%
PFS at 24 months	-	44%	59%

Survival Rates

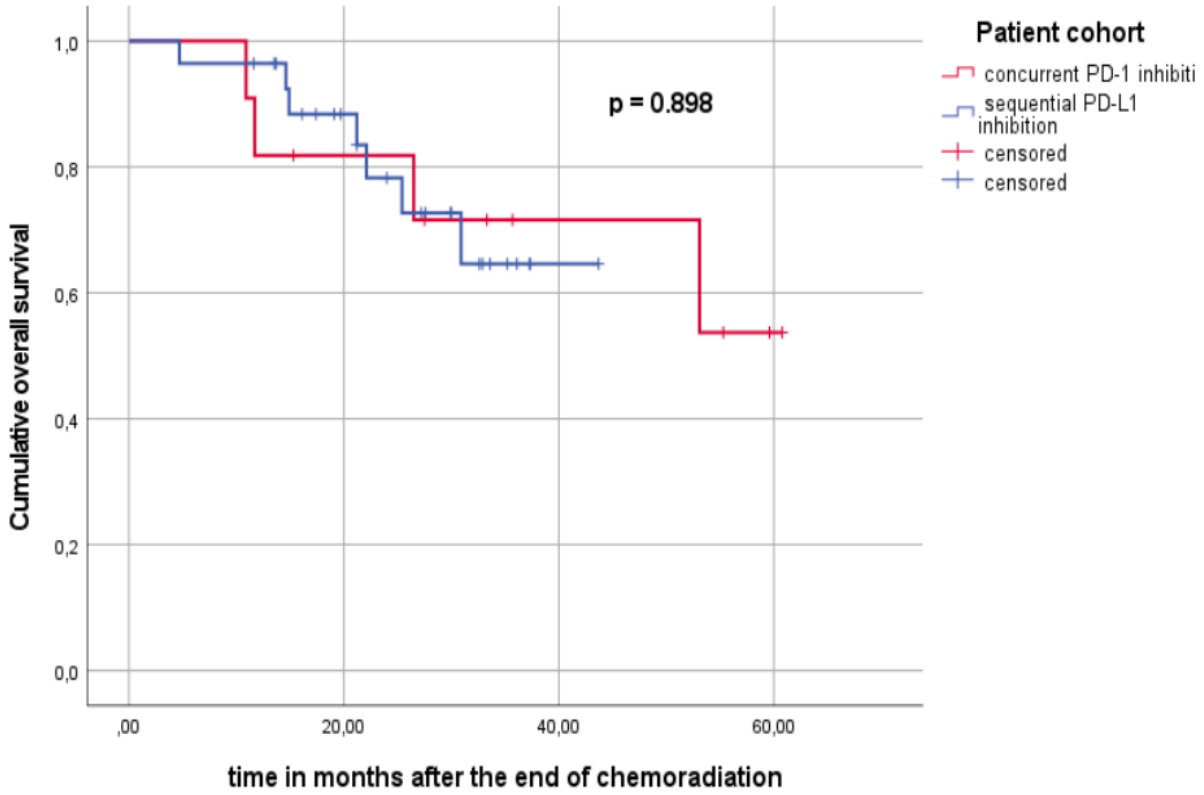


Figure I: Kaplan-Meier curves for overall survival according to concurrent versus sequential checkpoint inhibition

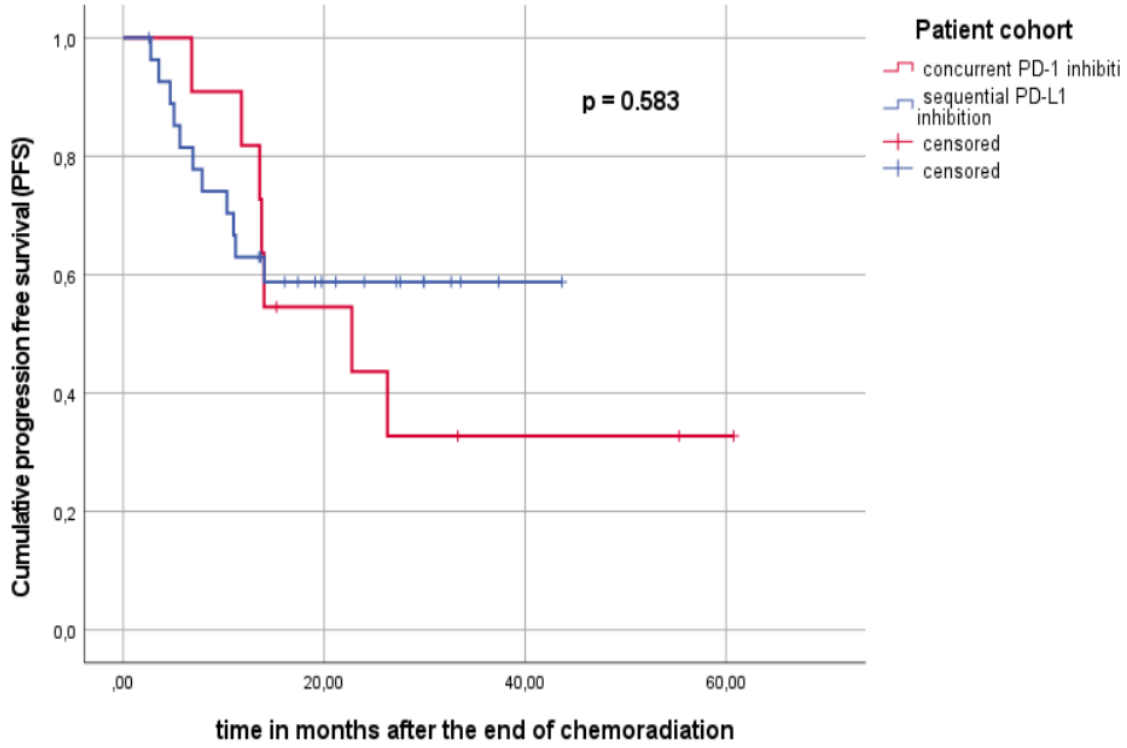


Figure II: Kaplan-Meier curves for progression free survival according to concurrent versus sequential checkpoint inhibition

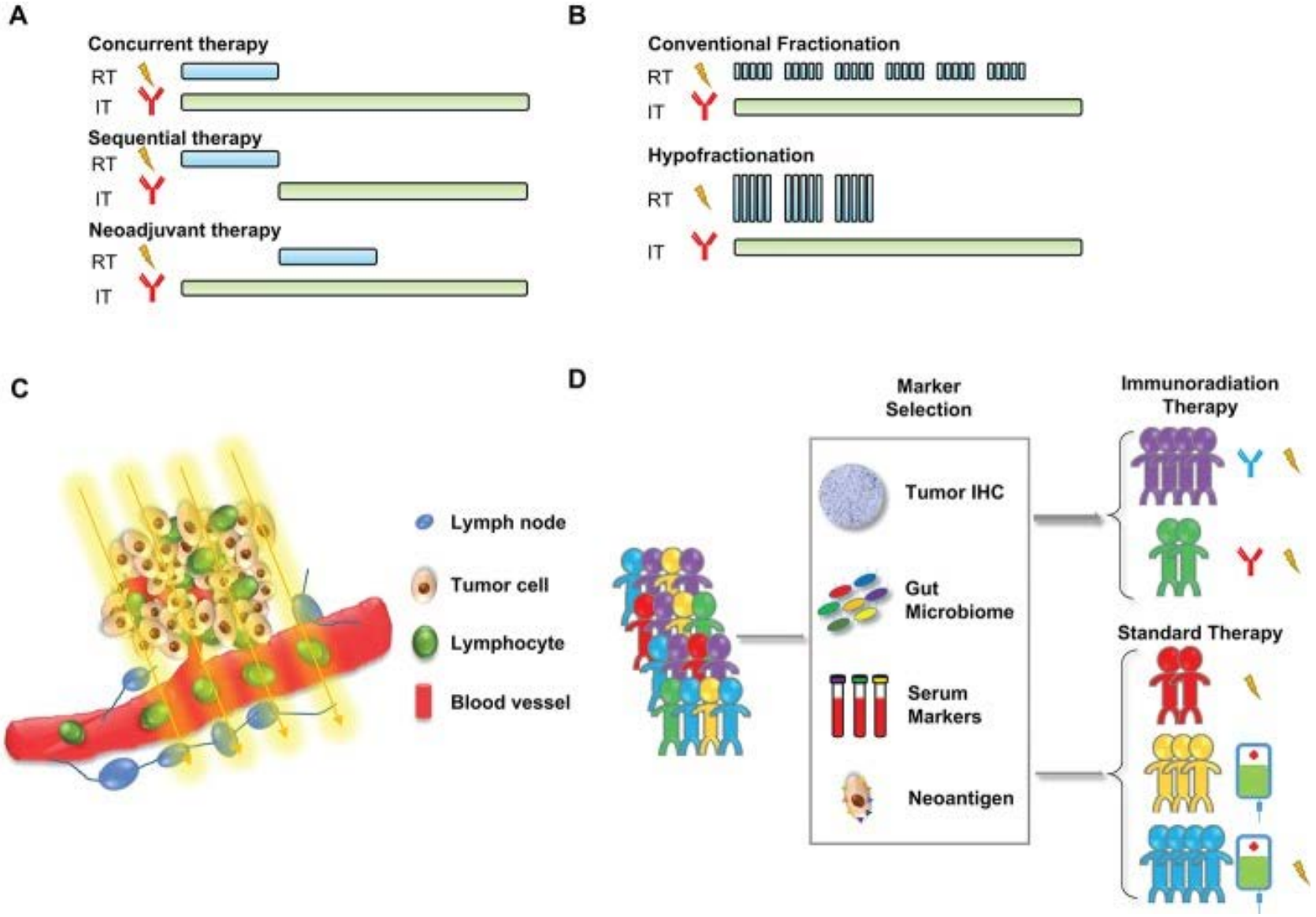
Safety Profile

- In the SIM-I cohort, 18.2% of patients showed grade III radiogenic pneumonitis and in the SEQ-I cohort 14.3% (p=0.765). Grade 4 and 5 toxicities did not occur.

Conclusion

- Simultaneous as well as sequential immune checkpoint inhibition for CRT in patients with unresectable stage III NSCLC show a favorable side effect profile and promising results.

- Concurrent immune checkpoint inhibition did not show improved prognosis (PFS, OS) compared to sequential immunotherapy and was associated with a non-significant increase in grade III pneumonitis.



(A) Treatment timing

(B) Radiation dosing

(C) Reduction of the radiation-induced toxicity of circulating and tumor-infiltrated lymphocytes.

(D) Selection of immunoradiation therapy or standard therapy for patients based on predictive biomarkers.

Current challenges in combining radiotherapy with immunotherapy

Wang Y, Deng W, Li N, Neri S, Sharma A, Jiang W, Lin SH. Combining immunotherapy and radiotherapy for cancer treatment: current challenges and future directions. Frontiers in pharmacology. 2018 Mar 5;9:185.

Could immunotherapy be a radiation sensitizer?

- No clear evidence, but yes.. It is a possibility..
- P53, which is a radiation response regulator, it also modulates PDL1 expression.
- Immune checkpoint blockade may influence the tumor microenvironment by regulating cytokine secretion and by remodeling tumor vasculature.

Wang Y, Deng W, Li N, Neri S, Sharma A, Jiang W, Lin SH. Combining immunotherapy and radiotherapy for cancer treatment: current challenges and future directions. Frontiers in pharmacology. 2018 Mar 5;9:185.

Thank You