FIRST-LINE PLATINUM-BASED CHEMOTHERAPY COMBINED WITH PD-1/PD-L1 INHIBITORS (ICI) PREVENTS HYPERPROGRESSION IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS BY REDUCING CIRCULATING IMMATURE NEUTROPHILS

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Background Hyperprogression (HPD) has been described in 14–26% of NSCLC patients upon single-agent ICI1 and has not been reported upon ICI and platinum-based chemotherapy (PCT) combinations. Both high circulating neutrophils2 and senescent T-cells3 correlated with HPD, however the exact neutrophils-T-cells interplay and the role of specific neutrophils subsets in driving HPD is unknown.

Abstract 15 Figure 1 Patterns of response, progression and hyperprogression to single-agent ICI and correlation with mature (CD10+) or immature (CD10-) LDNs' subtypes

Methods NSCLC patients treated with 1st line ICI as single-agent or in combination with PCT were assessed for HPD and circulating neutrophils' phenotype. HPD required 3 assessment (2 before ICI, 1 upon ICI) and was defined as delta tumor growth rate (TGR) (TGR upon ICI - TGR before ICI) >50% and/or TGR ratio (TGR upon ICI/TGR before ICI) ≥2. Circulating low density neutrophils (LDNs) subtypes were assessed by flow cytometry on peripheral blood mononuclear cells (PBMCs). LDNs were defined as CD66b+CD15+ cells among CD11b+ PBMCs. Immature subtypes were defined as CD10-LDNs. T-cells were isolated from healthy donors and cocultured with patients' LDNs to characterize the neutrophils-T-cells interplay. LDNs subtypes were isolated from patients and treated in-vitro with cisplatin to assess cell death.

Results 46 NSCLC patients were treated with single-agent ICI and 17 with PCT+ICI (table 1). In the ICI single-agent cohort, PD and HPD occurred in 21 (41%) and 4 (9%) patients. Before ICI start, HPD patients had significantly higher median% of circulating immature CD10- LDNs neutrophils [43.5 (min 29.5; max 82.6) vs 10.3 (min 0.1; max 29.5)].

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7-Aminoactinomycin D: cell death marker

Abstract 15 Figure 4 Cisplatin in-vitro treatment at different concentration (1 uM and 5 uM) increases necrotic (7AAD expression) cell death preferentially of immature (CD10-) rather than mature (CD10+) LDNs.
79.4), p=0.01] compared to PD patients (figure 1). In the ICI-PCT cohort no HPD was reported. 5 patients had baseline CD10- LDNs ≥ 43.5% (median% of CD10- LDNs in HPD patients upon single-agent ICI), 2 of them had stable disease and 3 PD upon ICI-PCT. In these 5 patients, CD10- LDNs significantly decreased during ICI-PCT compared to what observed in HPD patients upon single-agent ICI [median variation -43.4 (min -67.6, max -31.6) vs +6.9 (min -33, max +44), p= 0.03] (figure 2). After 7 days of coculture with T-cells, immature CD10- LDNs significantly reduced T-cells survival and promoted a T-cell senescent phenotype (CD28 loss, CD57 gain) impairing T-cells proliferation and increasing IFN-gamma production (figure 3). Cisplatin treatment significantly increased necrotic cell death among CD10- LDNs compared to CD10+ LDNs (figure 4).

Conclusions Higher baseline immature CD10- LDNs impair T-cell survival and promote T-cell senescence being a circulating biomarker of HPD upon single-agent ICI. The addition of PCT prevents HPD by inducing immature neutrophils cell death.

REFERENCES

Ethics Approval Patients blood was obtained after signature of informed consent and within an observational prospective study (INT 22_15) approved by local Institutional Ethical Committee.

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