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

Roberto Ferrara*, ¹Giuseppe Lo Russo, ¹Elena Jachetti, ¹Giuseppina Calareso, ¹Claudia Proto, ¹Arsela Prelaj, ¹Giulia Galli, ²Diego Signorelli, ¹Marta Brambilla, ¹Alessandro De Toma, ¹Mario Occhipinti, ¹Sara Manglaviti, ¹Giulia Apollonio, ¹Laura Mazzeo, ¹Monica Ganzinelli, ¹Antonia Martinetti, ¹Filippo De Braud, ³Marina Garassino, ¹Mario Paolo Colombo, ¹Sabina Sangaletti. ¹Istituto Nazionale dei Tumori di Milano, Milano, Italy; ²Ospedale Niguarda, Milan, Italy; ³University of Chicago, Chicago, USA

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

CD10- LDNs dynamic variation upon treatment

Abstract 15 Figure 2 Neutrophils dynamic variation upon treatment (5 patients with high baseline CD10- LDNs and PD/SD to chemo-ICI vs 4 patients with HPD upon single-agent ICI)

Abstract 15 Figure 3 Mature (CD10+) and immature (CD10-) LDNs in coculture with T-cells from a healthy donor differently influence CD8 and CD4 T-cells survival, proliferation, IFN-gamma production and expression of a senescent (CD28- CD57+) phenotype.

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

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 (PMBCs). 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

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 $\geq 43.5\%$ (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- γ production (figure 3). Cisplatin treatment significantly increased necrotic cell death among CD10- LDNs compared to CD10+ LDNs (figure 4).

Abstract 15 Table 1 Patients characteristics in the single-agent ICI and PCT+ICI cohorts

	Single-agent ICI	PCT + ICI
Patients Characteristic	N=46 (%)	N=17 (%)
Age		
≥ 70 years	21 (46%)	6 (35%)
< 70 years	25 (54%)	11 (65%)
Sex		
Male	29 (63%)	11 (65%)
Female	17 (37%)	6 (35%)
Histology		
Adenocarcinoma	32 (69%)	15 (88%)
Squamous	8 (17%)	0 (0%)
NSCLC-Other	6 (13%)	2 (12%)
Smoking status		
Never	4 (9%)	3 (18%)
Former	25 (54%)	8 (47%)
Current	17 (37%)	6 (35%)
N° met sites ICI baseline		
0-2	34 (74%)	10 (59%)
> 2	12 (26%)	7 (41%)
Performance status		
0-1	40 (87%)	16 (94%)
≥ 2	6 (13%)	1 (6%)
PD-L1 IHC (dako 22c3)		
< 1	2 (4%)	7 (41%)
1-49%	31 (67%)	8 (47%)
≥ 50%	13 (28%)	1 (6%)
Unknown	0 (0%)	1 (6%)
Molecular Status		
KRAS mut	12 (26%)	4 (23%)
Wild type*	25 (55%)	6 (36%)
Targetable §	2 (4%)	4 (23%)
Unknown	7 (15%)	3 (18%)

*wild type for EGFR, ALK, ROS1, § 2 MET ex 14 mutation, 1 BRAF V600E mutation, 1 ALK fusion, 2 EGFR mutations

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.

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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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