Adjuvant treatment in stage III melanoma patients: effects on disease relapse and prognosis. A Real world studio/data.

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Background. Stage III melanoma management has changed in the last years. Lymphadenectomy (LA) is no more indicated after a positive sentinel node biopsy (SNB)[1,2], and adjuvant (adj) therapy with anti-PD-1 agents[3,4] or BRAF/MEK inhibitors[5] has become part of the standard treatment of these patients in all guidelines. However, studies on the real-world effectiveness and toxicity are scarce. In this retrospective analysis we evaluated the outcomes of the adj-treatment in the standard clinical practice.

Methods. In this retrospective study, we analyzed resected stage III melanoma patients (resected stage IV patients have been excluded), who received adj-treatment with anti-PD-1 immunotherapy (IT) or target therapy (TT).
The primary endpoints were 3-years overall survival (OS), relapse-free survival (RFS) and distant metastasis-free survival (DMFS); safety evaluation is ongoing.

Results

PATIENT CARACTERISTICS	SNB (n=96)	SNB + LA (n=54)	LA (n=20)
Age, years	54 (46-66)	51 (43-64)	53 (48-61)
Males	58 (60.4 %)	30 (55.6 %)	15 (75.0 %)
Mutation			
BRAF-mutated	69 (73.4 %)	37 (68.5 %)	14 (70.0 %)
NRAS-mutated	1 (1.1 %)	2 (3.7 %)	0 (0.0 %)
BRAF-Wild-type	24 (25.5 %)	15 (27.8 %)	6 (30.0 %)
Stage			
IIIA	32 (33.3 %)	12 (22.2 %)	0 (0.0 %)
IIIB	19 (19.8 %)	10 (18.5 %)	3 (15.0 %)
IIIC	43 (44.8 %)	31 (57.4 %)	15 (75.0 %)
IIID	2 (2.1 %)	1 (1.9 %)	2 (10.0 %)
PS ECOG			
0	92 (95.8 %)	52 (96.3 %)	18 (90.0 %)
1	2 (2.1 %)	2 (3.7 %)	2 (10.0 %)
2	2 (2.1 %)	0 (0.0 %)	0 (0.0 %)
Adjuvant therapy			
Anti-PD1 (IT)	34 (35.4 %)	31 (57.4 %)	8 (40.0 %)
Anti-BRAF/MEK (TT)	62 (64.6 %)	23 (42.6 %)	12 (60.0 %)

Table 1. *Patient characteristics of the population under study.*

LA does not improve the prognosis of patients with loco-regional positive lymph-nodes, treated with adjuvant therapy: at a median follow-up of 3 years there was no statistically significant difference between patients who did not undergo LA and those who underwent LA after SNB in term of OS (89% vs 83%, p=0.60), RFS (57% vs 54%, p=0.40) and DMFS (82% vs 86%, p=0.20).

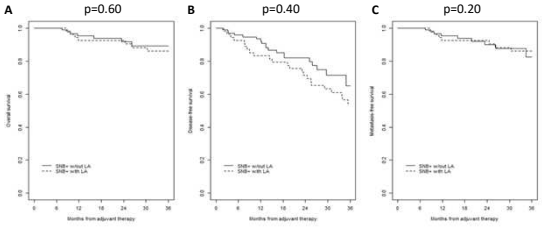
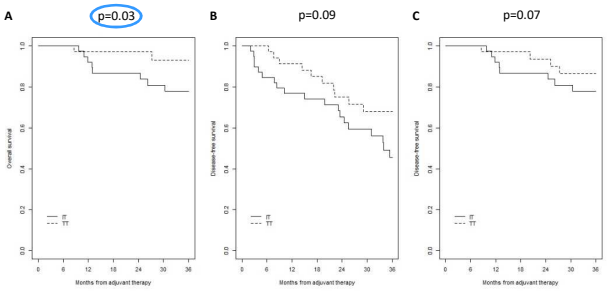


Figure 1. *Overall survival (A), relapse-free survival (B) and metastasis-free survival (C): comparison between who did not undergo LA after positive SNB and patients who underwent LA after positive SNB.*

All 170 patients received adj-treatment: IT (73 pts) or TT (97 pts).



While the difference between the use of IT *vs* TT was not statistically significant in subjects who did not undergo LA after SNB term of OS (83% *vs* 92%, p=0.60), RFS (45% *vs* 68%, p=0.40) and DMFS (83% *vs* 80%, p=0.60), **in the group that underwent LA (n=74), TT showed a 3y-OS of 77% *vs* 93% of IT (p=0.03);** at variance, no statistically significant association was documented for RFS (45% *vs* 67%, p=0.09) and DMFS (77% *vs* 86%, p=0.07).

Figure 2. *Overall survival (A), disease-free survival (B) and metastasis-free survival (C) in patients who underwent LA: comparison between those who received IT and those who received TT.*

An exploratory analysis of **IT *vs* TT outcomes**, according to AJCC 8th ed. stage subgroups, highlighted **3y-RFS of 48% vs 85% (p=0.01) in stage IIIA** and 55% *vs* 76% (p=0.10) in stage IIIB while it was 51% *vs* 43% (p=0.90) in stage IIIC.

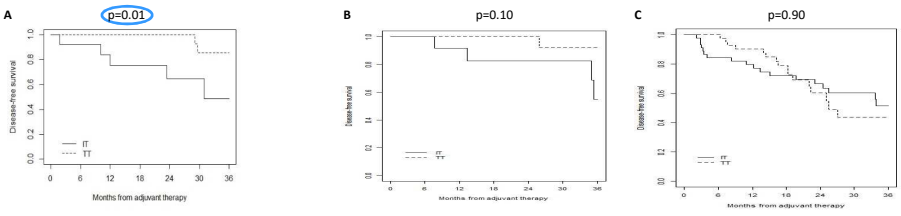


Figure 3. *Relapse-free survival in stage IIIA (panel A), IIIB (panel B) and IIIC (panel C) -patients: comparison between IT vs TT outcomes.*

Conclusions. We confirmed that **LA does not improve the prognosis of stage III patients treated with adjuvant therapy**.
Our preliminary data support that **TT effectiveness in no lower than IT** in this setting, above all in early stages where the cost-effectiveness, also due to long-term toxicities, should be carefully taken into account. However, a larger sample size and a longer follow-up are needed. Safety evaluation and discontinuation rate are under evaluation.

References: **1.** Leiter *et al.* (2016) *The Lancet. Oncology*, *17*(6), 757–767. **2.** Faries *et al.* (2017) *The New England journal of medicine*, *376*(23), 2211–2222. **3.** Eggermont *et al.* (2018) *The New England journal of medicine*, *378*(19), 1789–1801. **4.** Weber *et al.* (2017) *The New England journal of medicine*, *377*(19), 1824–1835. **5.** Long *et al.* (2017) *The New England journal of medicine*, *377*(19), 1813–1823.