

## CLINICOPATHOLOGICAL AND MOLECULAR PREDICTIVE FACTORS OF SURVIVAL IN NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH FIRST-LINE IMMUNOTHERAPY WITH OR WITHOUT CHEMOTHERAPY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Alessandro Di Federico\*, Francesco Gelsomino, Andrea De Giglio, Francesca Sperandi, Barbara Melotti, Andrea Ardizzone. *IRCCS Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy*

**Background** The majority of advanced non-small cell lung cancer (NSCLC) patients derives modest benefit from immunotherapy (IO) alone. For some of them, adding chemotherapy (CT) may significantly improve the outcomes, but the reliability of PD-L1 expression as the only biomarker to identify patients that might need concomitant CT is unsatisfactory.<sup>1,2</sup>

**Methods** A systematic research of articles using PubMed/MEDLINE, and the Cochrane Database of Systematic Reviews and Central Register of Controlled Trials was performed, last updated April 11th, 2022. Abstract from main oncology congresses were also searched, including ASCO 2022. Eligible studies were randomized controlled clinical trials (RCT) investigating IO, alone or combined with CT, versus CT alone in previously untreated advanced NSCLC patients. The objective was to detect clinicopathological and molecular predictive factors of survival (progression-free survival and overall survival). Study characteristics and outcome estimates (hazard ratio and 95% CI) were extracted. Random-effects meta-analyses were performed to investigate IO alone versus CT, and IO plus CT versus CT. Random-effects meta-regression analyses were performed to provide a comparison of IO alone versus IO plus CT.

**Results** a total of 14367 patients with advanced NSCLC in 25 RCT was included (table 1).<sup>3-48</sup> Squamous histology, male gender, current/former smoker status, PD-L1 expression  $\geq 50\%$ , and high TMB correlated with improved survival with IO alone compared to CT. Conversely, female gender, absence of smoking history, negative PD-L1 expression, and low TMB correlated with unsatisfactory outcomes with IO alone versus CT (figure 1), but not with IO plus CT versus CT (figure 2). IO plus CT improved survival versus IO alone in female patients [HR for PFS: 1.65, 95% CI, 1.25-2.18,  $p=0.0004$ ; HR for OS: 1.31, 95% CI, 1.01-1.71,  $p=0.044$ ], never smokers [HR for PFS: 3.59, 95% CI, 1.62-7.94,  $p=0.0016$ ; HR for OS: 1.28, 95% CI, 0.95-1.72,  $p=0.10$ ], in those having a PD-L1 expression  $\geq 1\%$  [HR for PFS: 1.88, 95% CI, 1.55-2.28,  $p<0.0001$ ; HR for OS: 1.28, 95% CI, 1.11-1.48,  $p=0.0007$ ] or a low TMB [HR for PFS: 2.08, 95% CI, 1.61-2.70,  $p<0.0001$ ; HR for OS: 1.43, 95% CI, 1.12-1.82,  $p=0.004$ ], and in patients with central nervous system metastasis [HR for PFS: 1.51, 95% CI, 1.01-2.25,  $p=0.045$ ; HR for OS: 1.32, 95% CI, 0.85-2.06,  $p=0.22$ ] (figure 3).

**Conclusions** Certain clinicopathological and molecular features may add predictive value to PD-L1 expression in the selection of the most appropriate first-line treatment for advanced NSCLC patients.

### REFERENCES

- Di Federico A, De Giglio A, Parisi C, Gelsomino F, Ardizzone A. PD-1/PD-L1 inhibitor monotherapy or in combination with chemotherapy as upfront treatment for advanced NSCLC with PD-L1 expression  $\geq 50\%$ : Selecting the best strategy. *Crit Rev Oncol Hematol*. 2021;160. doi:10.1016/j.critrevonc.2021.103302
- Gelsomino F, Facchinetti F, Sisi M, Zielli T, Tiseo M, Ardizzone A. PD-L1  $\geq 50\%$  lung cancer refractory to PD-1 inhibition: the role of salvage chemo-immunotherapy combination. *Immunotherapy*. 2021 Apr;13(5):363-369. doi: 10.2217/imt-2020-0280. Epub 2021 Feb 3. PMID: 33533279.

- Ren S, Chen J, Xu X, et al. Camrelizumab Plus Carboplatin and Paclitaxel as First-Line Treatment for Advanced Squamous NSCLC (Camel-Sq): A Phase 3 Trial. *J Thorac Oncol*. 2022;17(4):544-557. doi:10.1016/j.jtho.2021.11.018
- Carbone DP, Reck M, Paz-Ares L, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017;376(25):2415-2426. doi:10.1056/NEJMoa1613493/SUPPL\_FILE/NEJMoa1613493\_DISCLOSURES.PDF
- Borghaei H, Pluzanski A, Caro RB, et al. Abstract CT221: Nivolumab (NIVO) + ipilimumab (IPI) as first-line (1L) treatment for patients with advanced non-small cell lung cancer (NSCLC) with brain metastases: Results from CheckMate 227. *Cancer Res*. 2020;80(16\_Supplement):CT221-CT221. doi:10.1158/1538-7445.AM2020-CT221
- Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. *N Engl J Med*. 2019;381(21):2020-2031. doi:10.1056/NEJMoa1910231/SUPPL\_FILE/NEJMoa1910231\_DATA-SHARING.PDF
- Paz-Ares LG, Ramalingam SS, Ciuleanu TE, et al. First-Line Nivolumab Plus Ipilimumab in Advanced NSCLC: 4-Year Outcomes From the Randomized, Open-Label, Phase 3 CheckMate 227 Part 1 Trial. *J Thorac Oncol*. 2022;17(2):289-308. doi:10.1016/j.jtho.2021.09.010
- Hellmann MD, Ciuleanu T-E, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N Engl J Med*. 2018;378(22):2093-2104. doi:10.1056/NEJMoa1801946/SUPPL\_FILE/NEJMoa1801946\_DISCLOSURES.PDF
- Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):198-211. doi:10.1016/S1470-2045(20)30641-0
- Reck M, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update. *ESMO Open*. 2021;6(5). doi:10.1016/j.esmoop.2021.100273/ATTACHMENT/6DA1AD81-B43A-4503-BA0B-7BFA0079C4AE/MMC2.PDF
- Paz-Ares L, Ciuleanu T-E, Cobo M, et al. 980 First-line nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles chemotherapy (chemo) vs 4 cycles chemo in advanced non-small cell lung cancer (aNSCLC): Association of blood and tissue tumor mutational burden (TMB) with efficacy in CheckMate 9LA. *J Thorac Oncol*. 2021;16(4):S750-S751. doi:10.1016/S1556-0864(21)01940-7
- Sezer A, Kilickap S, Gümüş M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. *Lancet*. 2021;397(10274):592-604. doi:10.1016/S0140-6736(21)00228-2
- Gogishvili M, Melkadze T, Makhharadze T, et al. LBA51 EMPOWER-Lung 3: Cemiplimab in combination with platinum doublet chemotherapy for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC). *Ann Oncol*. 2021;32:S1328. doi:10.1016/j.annonc.2021.08.2130
- Zhou C, Wang Z, Sun Y, et al. Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302): interim and final analyses of a double-blind, randomised, phase 3 clinical trial. *Lancet Oncol*. 2022;23(2):220-233. doi:10.1016/S1470-2045(21)00650-1
- Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol*. 2016;17(11):1497-1508. doi:10.1016/S1470-2045(16)30498-3
- Awad MM, Gadgeel SM, Borghaei H, et al. Long-Term Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC. *J Thorac Oncol*. 2021;16(1):162-168. doi:10.1016/j.jtho.2020.09.015
- Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;378(22):2078-2092. doi:10.1056/NEJMoa1801005/SUPPL\_FILE/NEJMoa1801005\_DISCLOSURES.PDF
- Rodríguez-Abreu D, Powell SF, Hochmair MJ, et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. *Ann Oncol*. 2021;32(7):881-895. doi:10.1016/j.annonc.2021.04.008
- Gadgeel SM, Rodríguez-Abreu D, Felip E, et al. Abstract LB-397: Pembrolizumab plus pemetrexed and platinum vs placebo plus pemetrexed and platinum as first-line therapy for metastatic nonsquamous NSCLC: analysis of KEYNOTE-189 by STK11 and KEAP1 status. *Cancer Res*. 2020;80(16\_Supplement):LB-397. doi:10.1158/1538-7445.AM2020-LB-397
- Gadgeel S, Rodríguez-Abreu D, Felip E, et al. KRAS mutational status and efficacy in KEYNOTE-189: Pembrolizumab (pembro) plus chemotherapy (chemo) vs placebo plus chemo as first-line therapy for metastatic non-squamous NSCLC. *Ann Oncol*. 2019;30:xi64-xi65. doi:10.1093/annonc/mdz453.002
- Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2018;379(21):2040-2051. doi:10.1056/NEJMoa1810865/SUPPL\_FILE/NEJMoa1810865\_DATA-SHARING.PDF