POSITIVE OR NEGATIVE?

PD-L1 STATUS FROM THE PERSPECTIVE OF DOCTORS TREATING NON-SMALL CELL LUNG CANCER

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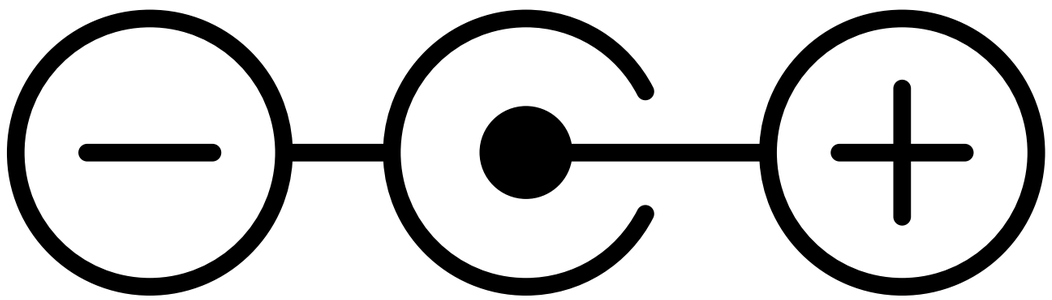
Introduction

The treatment landscape of non-small cell lung cancer (NSCLC) has changed substantially with the emergence of immunotherapy treatments. The approval in March 2015 of the first immunotherapy, nivolumab, a PD-1 inhibitor, for the treatment of patients with metastatic NSCLC[1] paved the way for approvals of other immunotherapies in lung cancer. For example, since the October 2016 FDA approval of pembrolizumab as first line treatment for advanced NSCLC patients whose tumours have high PD-L1 expressions (Tumour Proportion Score, TPS ≥50%), it has now become the frontline standard of care for such patients. Additional approvals of therapies for patients with TPS ≥1% have followed, as clinical efficacy demonstrated inhibition on tumour cells with lowered PD-L1 expressions.

Besides the change in the treatment paradigm, immunotherapy treatments have also reshaped the biomarker testing landscape, with PD-L1 testing being rapidly adopted and becoming part of the diagnostic requirement to select the most appropriate treatment. In other words, with the evolution of PD-L1 approvals also comes the need for physicians to familiarise themselves with the changed PD-L1 expression requirement.

In this article, we use Ipsos' Global Oncology Monitor data to highlight the possibility that physician interpretation of PD-L1 expression may not always be clear cut and how this may be affecting the resulting treatment choice.

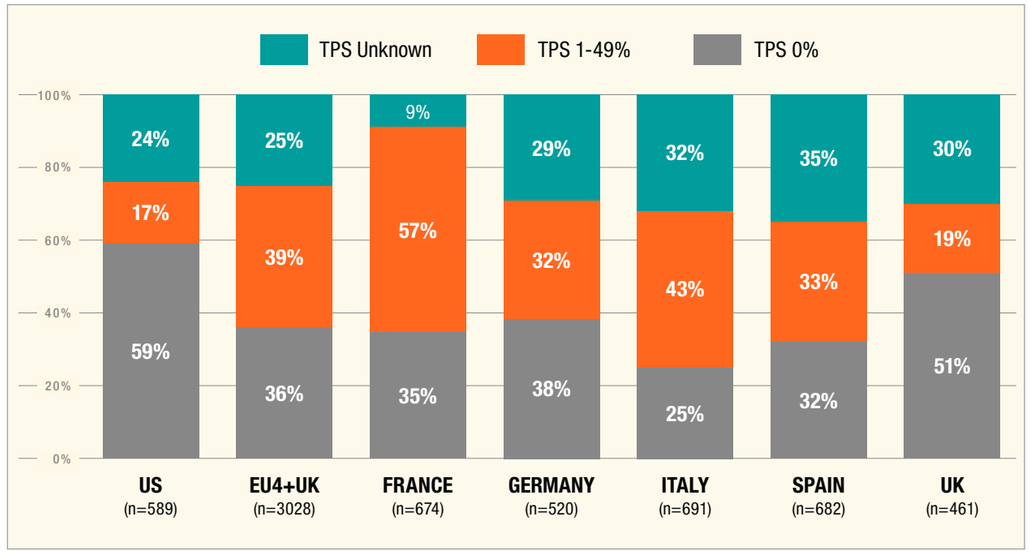


A grey area: how are physicians defining PD-L1 negative?

Patient chart data collected from the Ipsos Oncology Monitor shows high levels of testing for PD-L1 expression: 91% of reported first line metastatic NSCLC patients in our US data cohort and 93% in our EU4+UK cohort were tested for PD-L1 expression, underlining how these results have become a key piece of information in a physician's decision process for the most appropriate frontline treatment for their patients. It is when we delve further into the labelling of PD-L1 positive or negative that things may not be as easily distinguished as one would think.

PD-L1 expression is divided into three levels: no PD-L1 expression, PD-L1 expression and high PD-L1 expression, based on a TPS of 0%, 1-49% and ≥50%, respectively[2]; PD-L1 expression may also be referred to as PD-L1-negative or positive. Our data go on to show that, of first line patients who were tested for the biomarker, 35% in the US and 40% in EU4+UK were categorised by doctors as PD-L1-negative. At the same time, the proportion of patients with TPS 0% was only 22% in the US and 15% in EU4+UK. This suggests there is a subset of patients that, despite showing PD-L1 staining, are considered PD-L1-negative by their doctor. Looking specifically at those considered PD-L1-negative, 17% in US and 39% in EU4+UK had TPS 1-49%.

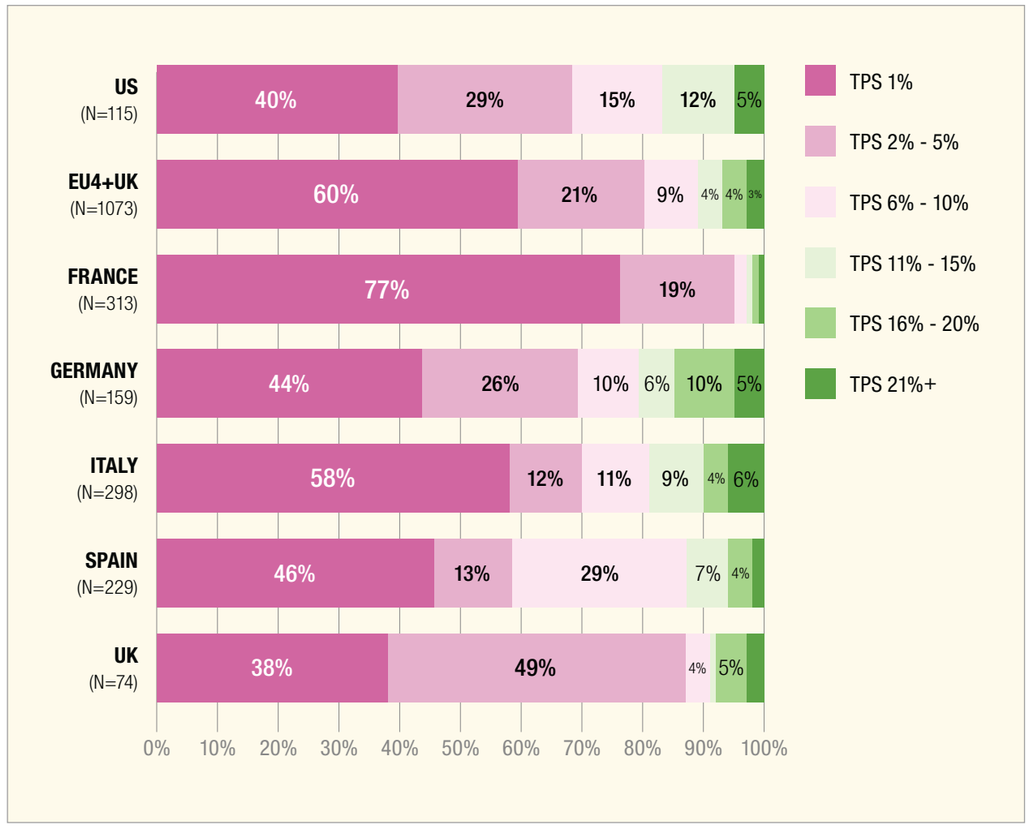
Figure 1: Recorded TPS range of reported first line PD-L1 negative stage IIIb-IV NSCLC patients



Source: Ipsos Oncology Monitor (Jan 2022-Dec 2022, with 63,703 (total) cancer patients reported by cancer treating physicians in US and 105,433 (total) in EU4+UK, data collected online. Participating doctors were primary treaters and saw a minimum number of patients per month).

Together with PD-L1 negative patients for which a TPS score was not reported (possibly due to labs reporting test results simply as 'positive' or 'negative'), we can start picturing a very fragmented space in which the actual TPS score used to define a negative patient ranged from 1% to 49%, with the majority having a range of 1%-15% (US) and 1%-20% (EU4+UK). Our data also records market-specific nuances; for example, the reported French patient cohort deemed negative are more likely to be recorded as TPS 1% compared to the UK market.

Figure 2: Recorded TPS of reported first line PD-L1-negative stage IIIb-IV NSCLC patients with TPS 1-49%



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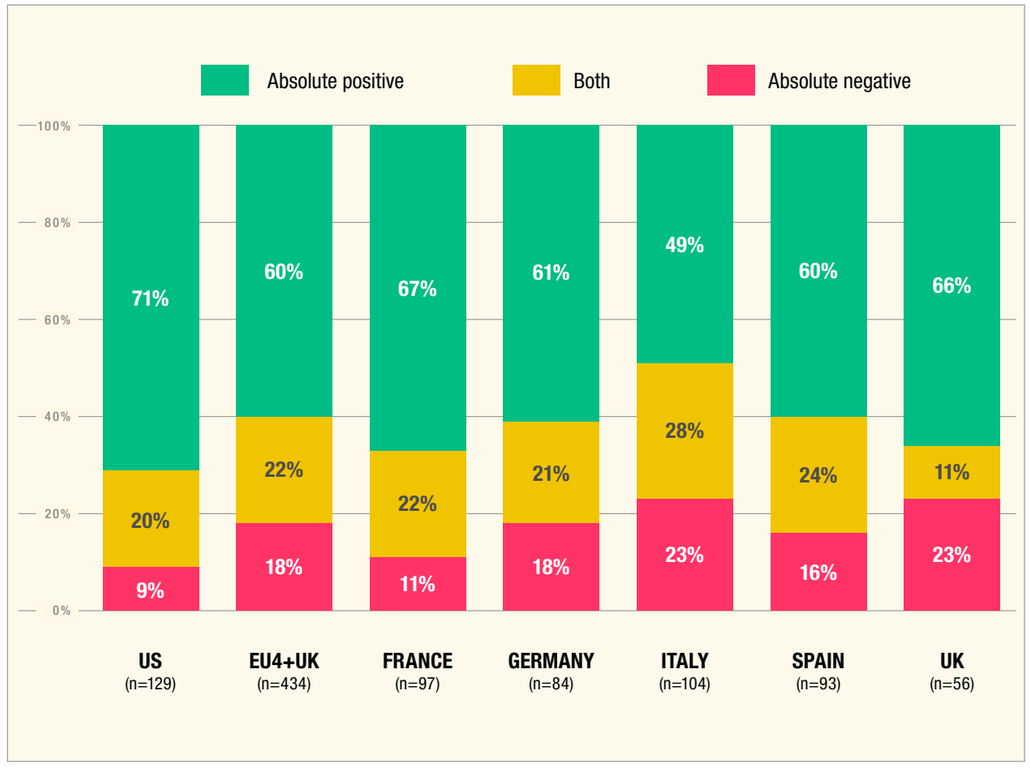
When looking specifically at the sampled physician level, our data show that 20% and 22% of the physicians in the US and EU4+UK, respectively, classified a patient with a TPS of between 1-49% as both positive and negative. Interestingly, these oncologists reported at least 75% of their patients being tested for PD-L1, suggesting that the PD-L1 negative classification was not due to a lack of experience. There is not a simple answer as to why we are observing such a degree of variation in defining PD-L1 positive and negative patients, but we believe it is an effect of both biomarker result thresholds shifting over time, and PD-(L)1 product labels changing since their initial approval.

Figure 3: Distribution of doctors submitting first line stage IIIb-IV NSCLC forms of patients who are PD-L1 tested and have TPS 1-49%

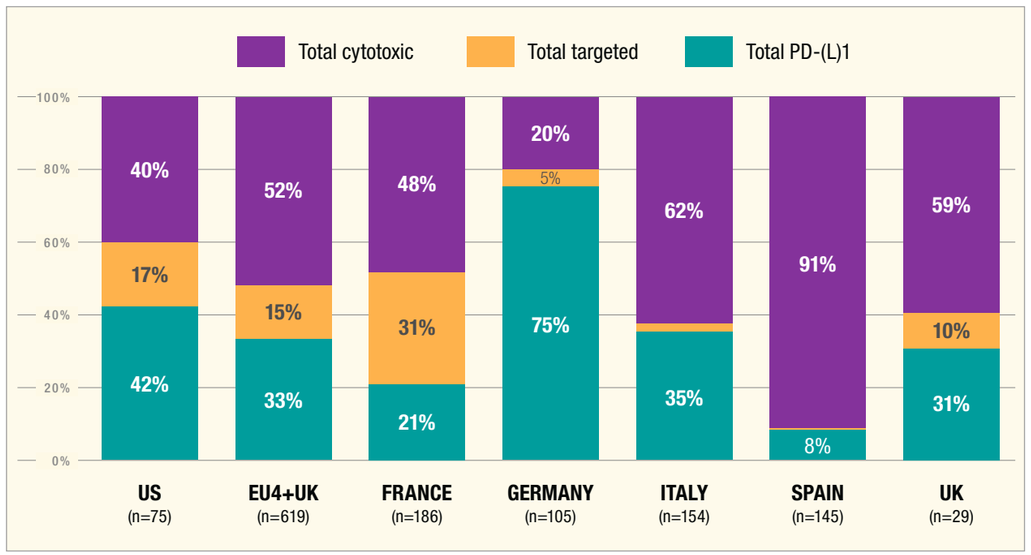


Source: Ipsos Oncology Monitor (Jan 2022-Dec 2022, with 938 (total) treating doctors in US and 1,649 (total) in EU4+UK, data collected online. Participating doctors were primary treaters and saw a minimum number of patients per month).

What impact does this have on treatment choice?

Efficacy and safety of PD-(L)1 inhibitors in first line NSCLC has been widely documented and our 2022 data reflects a high proportion of reported 'low expressor' patients (i.e., those with TPS 1%-49%) receiving PD-(L)1 inhibitors versus traditional chemotherapy. Interestingly, however, we have also observed variations in treatment choices between regions for first line patients who were classified as PD-L1-negative with TPS 1-49%. In the US, PD-(L)1 and cytotoxic treatments were almost equally used in this group of patients. In France, Italy, Spain, and UK, however, around half or more of reported patients received cytotoxic treatments: paclitaxel-based regimens were more common in France and Spain, while larger proportions of non-paclitaxel and non-pemetrexed-based cytotoxic regimens were used in Italy and UK cohorts. In Germany, 75% of patients were treated with PD-(L)1 inhibitors, the highest of all regions analysed. Comparatively, when TPS 1-49% was considered as PD-L1-positive within the reported patient cohort, first line treatments were largely comprised of pembrolizumab combinations – this is true of all regions reviewed. Thus, we see how sampled physicians that consider a patient PD-L1 negative, despite a staining between 1%-49%, are more likely to prescribe a traditional chemotherapy-based regimen (with the exception of our German cohort).

Figure 4: First line treatment distribution among reported stage IIIb-IV NSCLC patients considered PD-L1-negative and with TPS 1-49%



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Conclusion

Despite expression variability during a patient's disease and treatment journey, PD-L1 has become one of the most important decision-making tools available for physicians when deciding on an optimal treatment approach for their NSCLC patients, especially upfront therapy. However, as our data show, the decision-making can be further complicated by different thresholds that physicians may adopt for low expressor patients. As highlighted earlier, we hypothesize that these differences could be a consequence of the evolution and changes in the approvals of PD-(L)1 inhibitors, especially in NSCLC, but it is also possible that the different scoring methodologies used in different companion diagnostic tests, such as TPS for the PD-L1 IHC 22C3 pharmDx assay and immune cell staining for the PD-L1 SP263 assay, may also have contributed to this fluidity in interpretation.

These observations suggest the importance of understanding that treating physicians may have varying benchmarks in mind when labelling PD-L1 status as positive or negative, which in turn can cause variation in their treatment approach. We believe it is crucial that these nuances be considered when collecting PD-L1 status related information, for example in market research questionnaire development, performance tracking, and in detailing and messaging materials; understanding these nuances will help optimise data collection and data analysis, and also help ensure clear and consistent conversations between pharmaceutical company representations and oncologists. Additionally, we recommend that rather than using PD-L1 status and TPS information separately, they should instead be considered in combination to allow for the most comprehensive insights when analysing data of this nature.

References

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2. PD-L1 IHC 22C3 pharmDx Interpretation Manual – NSCLC. Agilent Dako. [ONLINE] Download at: https://www.agilent.com/cs/library/usermanuals/public/29288_22C3-ihc-pharmdx-nsclc-interpretation-manual_ce-ivd.pdf [Accessed 7 June 2023].

About the Research

The Ipsos Global Oncology Monitor is a physician-reported syndicated patient record database, capturing prescribing of anti-cancer and supportive care agents. Participating physicians are screened for specialty, level of seniority and number of drug-treated cancer patients seen per study wave and must be the primary decision-maker for their patients. Each wave, participants provide demographic information and de-identified information on a predefined quota of oncology patients (across solid and liquid tumours) seen in consultation, retrospectively. Sample sizes and fieldwork dates for the data shared in this article are provided beneath the relevant chart. The Global Oncology Monitor is validated with market sizing studies to ensure that the size and representativeness of the physician sample reflects the wider population of relevant treating physicians.

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