CO142

Systematic review of real-world evidence on overall survival in first-line advanced/metastatic cancer patients before and after the approval of anti-PD-(L)1 therapy

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Background

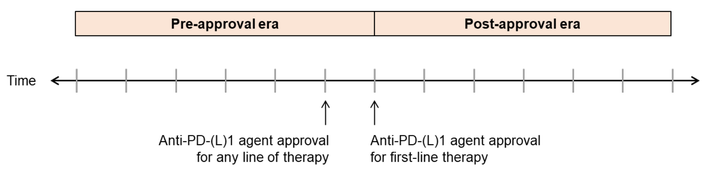
The development and regulatory approval of immune checkpoint inhibitors (ICIs), including anti-programmed death (ligand) 1 (anti-PD-(L)1) agents, has dramatically changed the way cancer is treated in clinical practice.[1,2] As the regulatory approval of cancer treatments is largely based on the findings of randomized controlled trials, it is unclear how treatment efficacy as measured in these trials translates to real-world settings.

To elucidate the degree of improvements in outcomes that anti-PD-(L)1 therapy has brought to cancer patients in clinical practice, there is a need to understand available real-world evidence on the overall survival (OS) of patients who, based on their clinical presentation, would currently be eligible for treatment with an anti-PD-(L)1 agent but were treated with conventional care before the regulatory approval of anti-PD-(L)1 therapy and of patients treated with anti-PD-(L)1 agents after their approval.

Methods

A systematic review was conducted to identify observational studies reporting OS for previously untreated patients with advanced/metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), or melanoma in the anti-PD-(L)1 therapy pre- and post-approval eras. For each tumor type, the pre-approval era was defined as a period beginning 5 years before the first approval of an anti-PD-(L)1 agent by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA) for any line of therapy and ending the year before the first approval of an anti-PD-(L)1 agent for first-line (1L) therapy, and the post-approval era was defined as a period beginning the year of first approval of an anti-PD-(L)1 agent for 1L therapy to the search date (**Figure 1**). Studies were identified through MEDLINE and Embase searches on July 10, 2023.

Figure 1. Timeline for defining pre- and post-approval eras



Two independent reviewers conducted title/abstract screening and full-text screening to select studies meeting the PICOTS eligibility criteria (Table 1) and performed data extraction conforming to a predefined structure described in the study protocol. Any conflicts between reviewers were reconciled by reaching consensus or involving a third reviewer.

Table 1. Study selection criteria

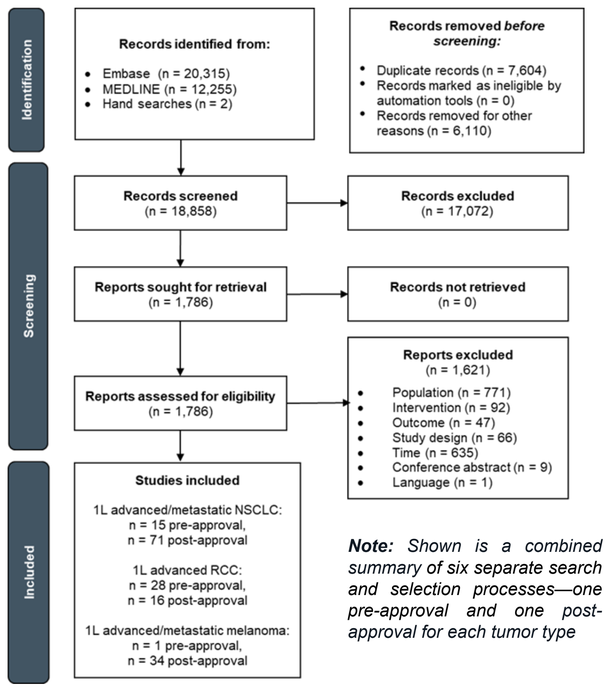
Population	• **NSCLC:** Adult (≥18 years) patients with locally advanced/stage III (but not candidates for surgical resection or definitive chemoradiation), metastatic, or recurrent NSCLC with no EGFR or ALK aberrations or patients with metastatic squamous NSCLC regardless of EGFR/ALK status who received no prior systemic therapy • **RCC:** Adult (≥18 years) patients with advanced RCC who received no prior systemic therapy • **Melanoma:** Adult and pediatric (≥12 years) patients with advanced, unresectable, or metastatic melanoma (with or without BRAF V600 mutation) who received no prior systemic therapy	
Interventions	**Pre-approval era:** Any non-ICI pharmacological treatment **Post-approval era:** Any of the following anti-PD-(L)1 agents delivered alone or in combination with other pharmacological treatments • **NSCLC**: Atezolizumab, cemiplimab, durvalumab, nivolumab, or pembrolizumab • **RCC**: Avelumab, nivolumab, or pembrolizumab • **Melanoma**: Atezolizumab, nivolumab, or pembrolizumab	
Comparators	No restrictions	
Outcomes	Overall survival	
Time	**Pre-approval era**: • **NSCLC**: 2010-2015 • **RCC**: 2010-2017 • **Melanoma**: 2009-2013	**Post-approval era:** • **NSCLC**: 2016-2023 • **RCC**: 2018-2023 • **Melanoma**: 2014-2023
Study design	Observational studies	
Language	English language	

Abbreviations: *ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-(L)1, programmed death (ligand)-1; RCC, renal cell carcinoma*

Results

The study search and screening process is depicted in Figure 2.

Figure 2. PRISMA flow diagram

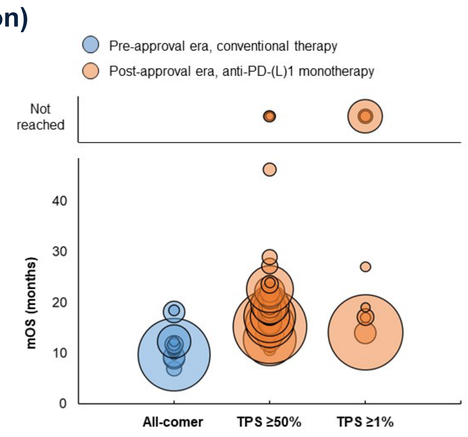


Note: *Shown is a combined summary of six separate search and selection processes—one pre-approval and one post-approval for each tumor type*

Advanced/metastatic NSCLC

mOS tended to be longer for treatment groups of patients with a PD-L1 tumor proportion score (TPS) ≥50% (range: 10.6-46.2 months) or ≥1% (14-27 months) receiving anti-PD-(L)1 monotherapy in the post-approval era than for patients receiving conventional therapy in the pre-approval era (6.9-18.4 months) (Figure 3).

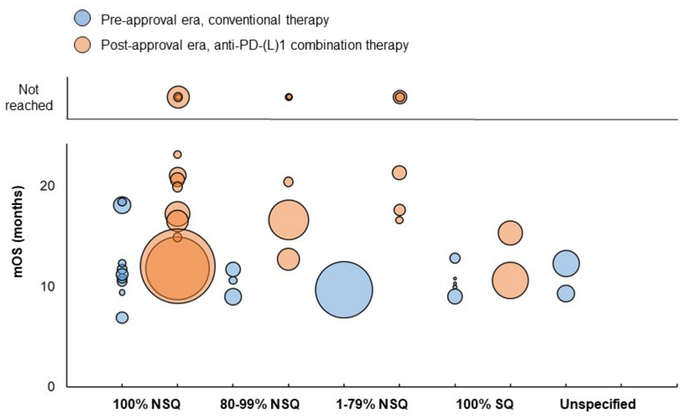
Figure 3. mOS values for advanced/metastatic NSCLC (by PD-L1 expression)



Note: *Bubble size reflects the sample size of each treatment group, which ranged from 5 to 2,166 patients. As PD-L1 expression was not of relevance to treatment decisions in the pre-approval era, pre-approval treatment groups could not be classified by PD-L1 TPS. mOS was 'not reached' (NR) for 3 'TPS ≥50%' groups; median follow-up durations were 19.9 and 26.5 months for 2 groups, respectively, and was not reported for 1 group. mOS was NR for 3 'TPS ≥1%' groups, which had median follow-up durations of 11.3, 12.5, and 14.5 months, respectively.* ***Abbreviation:*** *TPS, PD-L1 tumor proportion score.*

mOS tended to be longer for treatment groups consisting of 100% of patients with non-squamous (NSQ) tumors (range: 11.8-23.1 months), 80-99% of patients with NSQ tumors (12.7-20.7 months), or 1-79% patients with NSQ tumors (16.6-21.3 months) receiving anti-PD-(L)1 combination therapy in the post-approval era than for corresponding treatment groups of patients receiving conventional therapy in the pre-approval era (6.9-18.4, 9-11.7, and 9.67 months, respectively) (**Figure 4**).

Figure 4. mOS values for advanced/metastatic NSCLC (by tumor histology)

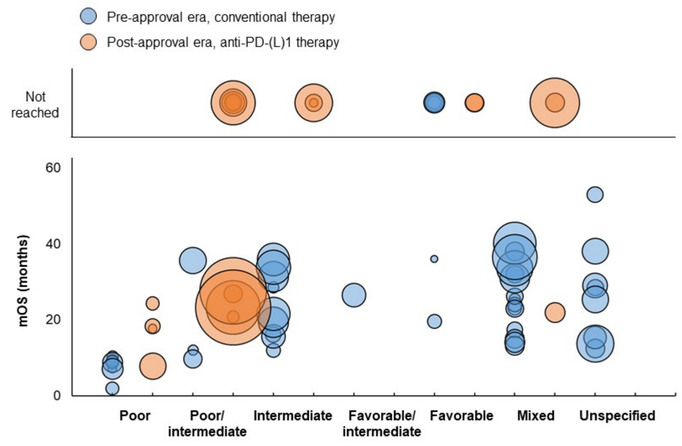


Note: *Bubble size reflects the sample size of each treatment group, which ranged from 5 to 2,488 patients. mOS was 'not reached' (NR) for 3 '100% NSQ' groups in the post-approval era, which had median follow-up durations of 5.5, 8, and 10.3 months, respectively. mOS was NR for 2 '80-99% NSQ' groups in the post-approval era, both of which had median follow-up durations of 14.8 months. mOS was NR for 2 '1-79% NSQ' groups in the post-approval era, which had median follow-up durations of 8.9 and 17.13 months, respectively. Sample size was not reported for 2 '100% SQ' groups in the pre-approval era, which had a mOS of 17 and 17.6 months respectively; these groups are not reflected in the chart.* ***Abbreviations****: NSQ, non-squamous; SQ, squamous.*

Advanced RCC

mOS tended to be longer for treatment groups of poor-risk patients (according to International mRCC Database Consortium (IMDC) or Memorial Sloan Kettering Cancer Center (MSKCC) classification) receiving anti-PD-(L)1 therapy in the post-approval era (range: 7.8-24.3 months) than for poor-risk patients receiving conventional therapy in the pre-approval era (2-10.3 months) (Figure 5).

Figure 5. mOS values for advanced RCC

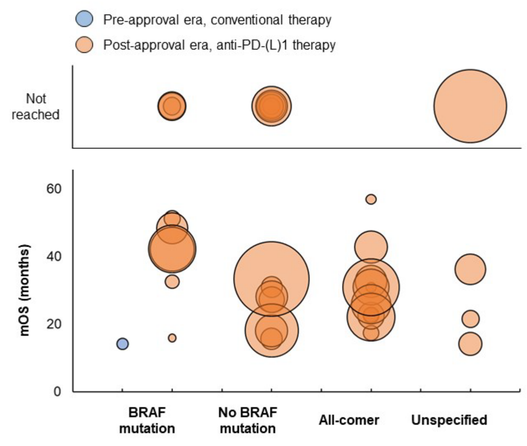


Note: *Bubble size reflects the sample size of each treatment group, which ranged from 7 to 817 patients. mOS was 'not reached' (NR) for 5 'poor/intermediate' groups in the post-approval era, for which median follow-up durations were 7.2, 12, 12.4, 13.8, and 16.1 months, respectively. mOS was NR for 3 'intermediate' groups in the post-approval era, for which median follow-up durations were 8.96, 12.2, and 24 months, respectively. mOS was NR for 4 'favorable' treatment groups in the pre-approval era; median follow-up durations were 23 and 46.1 months for 2 groups, respectively, and was not reported for 2 groups. mOS was NR for 2 'favorable' groups in the post-approval era, both of which had median follow-up durations of 20 months. mOS was NR for 2 'mixed' groups in the post-approval era, for which median follow-up durations were 7 and 9.67 months, respectively.*

Advanced/metastatic melanoma

mOS tended to be longer for treatment groups of patients with BRAF mutation receiving anti-PD-(L)1 therapy in the post-approval era (range:15.9-51.2 months) than for patients with any type of BRAF mutation receiving conventional therapy in the pre-approval era (14.2 months) (Figure 6).

Figure 6. mOS values for advanced/metastatic melanoma



Note: *Bubble size reflects the sample size of each treatment group, which ranged from 7 to 1,174 patients. mOS was 'not reached' (NR) for 3 'BRAF mutation' groups in the post-approval era; median follow-up durations were 11.3 and 23.2 months for 2 groups, respectively, and was not reported for 1 group. mOS was NR for 6 'no BRAF mutation' groups in the post-approval era; median follow-up durations were 12.1, 14.5, and 16.5 months for 3 groups, respectively, and were not reported for 3 groups. mOS was NR for 1 'unspecified' group in the post-approval era, which had a median follow-up duration of 25 months.*

Conclusion

The results of this systematic review suggest a survival benefit for specific subpopulations of patients with advanced/metastatic NSCLC, RCC, or melanoma receiving 1L treatment with anti-PD-(L)1 therapy in real-world practice after its regulatory approval, which supports the use of anti-PD-(L)1 therapy as the standard of care in many countries.

References

1. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nat Rev Immunol.* Nov 2020;20(11):651-668. doi:10.1038/s41577-020-0306-5

2. Bagchi S, Yuan R, Engleman EG. Immune Checkpoint Inhibitors for the Treatment of Cancer: Clinical Impact and Mechanisms of Response and Resistance. *Annu Rev Pathol*. Jan 24 2021;16:223-249. doi:10.1146/annurev-pathol-042020-042741

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