Surrogate endpoints in oncology approval trials

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Disclosure

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Left Ventricular Ejection Fraction May Not Be Useful As an End Point of Thrombolytic Therapy Comparative Trials

Robert M. Califf, MD, Lynn Harrelson-Woodlief, MS, and Eric J. Topol, MD

In the era of comparative and adjunctive trials in reperfusion therapy, the need to develop alternative end points for mortality reduction is clear. Left ventricular ejection fraction, which has been commonly used as a surrogate, is problematic due to missing values, technically inadequate studies, and lack of correlation with mortality results in controlled reperfusion trials performed to date. In this paper, we present a composite clinical end point that includes, in order, severity of adverse outcome death, hemorrhagic stroke, nonhemorrhagic stroke, poor ejection fraction (<30%), reinfarction, heart failure, and pulmonary edema. Such a composite index may be useful to detect true therapeutic benefit in reperfusion trials without necessitating greater than 20–30,000 patient enrollment. (*Circulation* 1990;82:1847–1853)

TABLE 1. Problems With Using Ejection Fraction As the Primary End Point in Reperfusion Trials

Missing Values
Patients who die (3–13%)
Failure to obtain study (5–20%)
Technically inadequate study (10–20%)
Pathophysiology
Lack of correlation of mortality with ejection fraction
Lack of correlation of ejection fraction with time from symptom onset
Volumes relate more closely to mortality
Compensatory noninfarct zone hyperkinesis
Little change over 6 months
Clinical
Other end points (reinfarction, recurrent ischemia, stroke, and cost) are important

Outcomes and endpoints in cancer trials: bridging the divide

Michelle K Wilson, Deborah Collyar, Diana T Chingos, Michael Friedlander, Tony W Ho, Katherine Karakasis, Stan Kaye, Mahesh K B Parmar, Matthew R Sydes, Ian F Tannock, Amit M Oza

Cancer is not one disease. Outcomes and endpoints in trials should incorporate the therapeutic modality and cancer type because these factors affect clinician and patient expectations. In this Review, we discuss how to: define the importance of endpoints; make endpoints understandable to patients; improve the use of patient-reported outcomes; advance endpoints to parallel changes in trial design and therapeutic interventions; and integrate these improvements into trials and practice. Endpoints need to reflect benefit to patients, and show that changes in tumour size either in absolute terms (response and progression) or relative to control (progression) are clinically relevant. Improvements in trial design should be accompanied by improvements in available endpoints. Stakeholders need to come together to determine the best approach for research that ensures accountability and optimises the use of available resources.

Lancet Oncol 2015; 16: e43–52

University of Toronto Princess Margaret Cancer Centre, Toronto, ON, Canada (M K Wilson FRACP, Prof I F Tannock PhD, Prof A M Oza FRCP, K Karakasis MSc); **Patient Advocates In Research, Danville, CA, USA** (D Collyar BSc); **The Norsen**

Who decides what is important?

Clinicians, patients, regulatory agencies, and industry are all stakeholders who have an interest in the determination of which endpoints are of clinical relevance. Regulatory agencies carry the burden of responsibility for making the ultimate decision about drug approval. Integral to this decision is the balance between a comprehensive review of safety and efficacy

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K Karakasis MSc); Patient Advocates In Research, Danville, CA, USA

Table 1. Comparison of different clinical endpoints

Serial No	Endpoint	Definition	Unique feature
1.	Overall survival	Time from randomization to death.	The 'gold standard' primary clinical endpoint.
2.	Progression-free survival	Time from randomization to disease progression or death, whichever comes first.	Used to assess therapies targeting advanced or metastatic malignancies.
3.	Time to progression	Time from randomization to disease progression.	Only uses time to progression and does not include time to death.
4.	Event-Free Survival	Time from randomization to disease progression, discontinuation of treatment for any reason, or death.	Used to evaluate highly toxic treatments.
5.	Disease-free survival	Time from randomization to disease recurrence.	Used to assess adjunctive and curative therapies.
6.	Time to Treatment Failure	Time from initiation of chemotherapy to premature discontinuation of treatment.	Used with other endpoints to assess reasons for discontinuing treatment.
7.	Time to Next Treatment	Time from initiation of treatment to beginning the next line of therapy.	Used as a meaningful endpoint for patients with low grade, incurable malignancies.
8.	Duration of Clinical Benefit	Time from randomization to progression or death in patients who had a complete or partial response or a stable disease for over 24 weeks.	Used in settings where disease stabilization is meaningful.
9.	Duration of Response	Time from randomization to progression or death in patients who had a complete or partial response.	Used to assess therapies for durable response.
10.	Objective Response Rate	Proportion of patients with partial or complete response to therapy.	Used to assess neoadjuvant therapies.
11.	Complete Response	Lack of detectable evidence of tumor.	Included as a major goal of multiple myeloma treatment.
12.	Pathological Complete Response	Lack of residual invasive cancer in resected breast tissue or regional lymph nodes.	Used in accelerated approval for neoadjuvant therapies targeting breast cancer.
13.	Disease Control Rate	Percentage of patients with complete response, partial response, or stable disease as a result of their therapy.	Used to assess the tumorstatic efficacy of a therapy.
14.	Clinical Benefit Rate	Percentage of patients with complete response, partial response, or at least months of stable disease as a result of their therapy.	Used to capture tumorstatic efficacy of a therapy and stable dise
15.	Health-Related Quality of Life	Assessment of patient quality of life with respect to health status.	Used
16.	Milestone survival	Survival probability at a prespecified time point.	Used to evaluate a cross-section of OS data.

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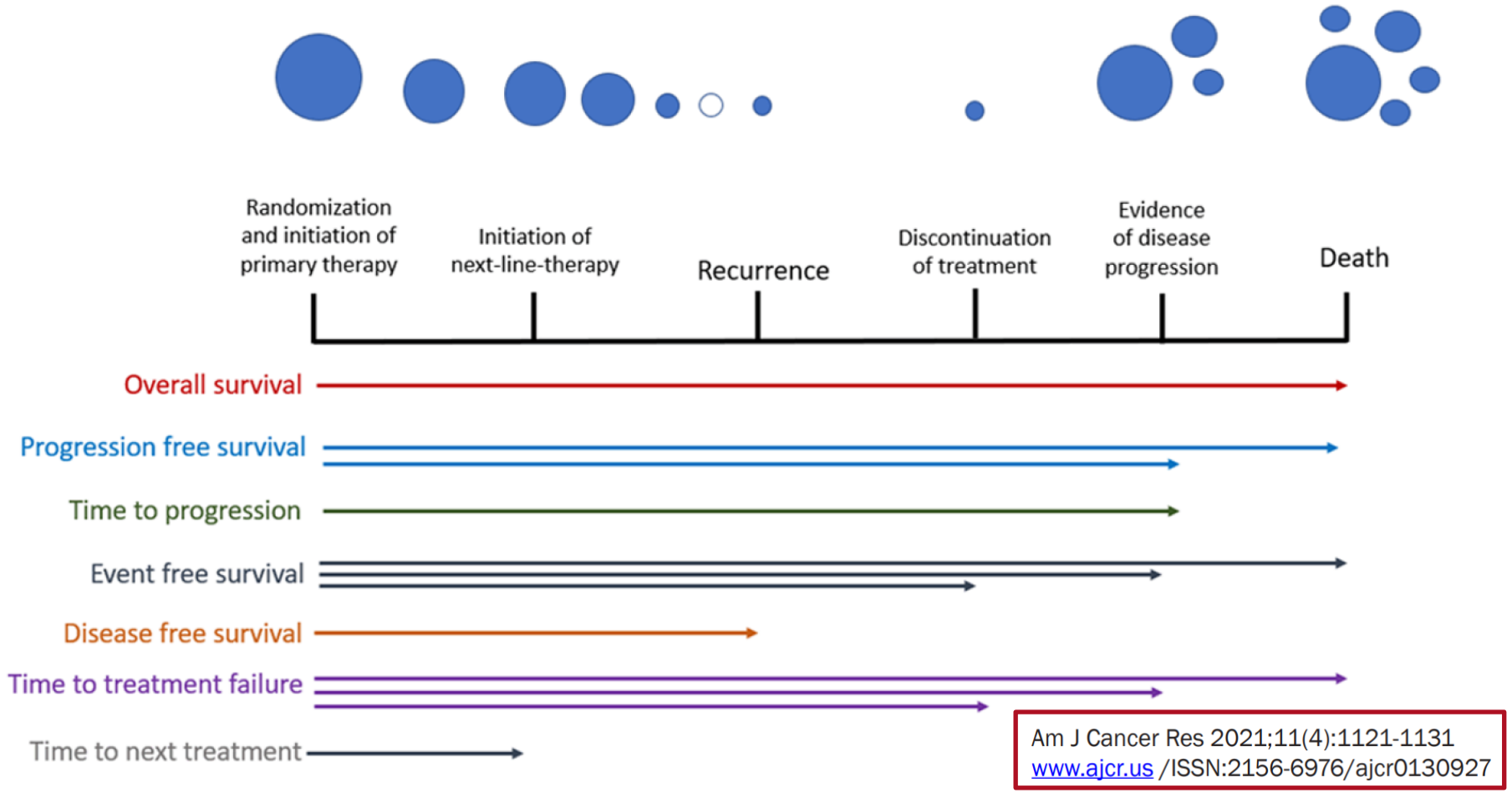

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Figure 1. Illustration of various endpoints with relationship to hypothetical tumor size on a time scale.

Table 2. Advantages and Disadvantages of Important Cancer Approval Endpoints

Endpoint	Advantages	Disadvantages
Overall Survival	• Easily and precisely measured • Generally based on objective and quantitative assessment	• May be affected by switch-over of control to treatment or subsequent therapies • Needs longer follow-up • Includes noncancer deaths
Objective Response Rate	• Generally assessed earlier and with smaller sample size compared with survival studies • Effect on tumor attributable to drug(s), not natural history • Generally based on objective and quantitative assessment	• Definitions vary among studies • Frequent radiological or other assessments • May not always correlate with survival
Progression-Free Survival or Time to Progression	• Generally assessed earlier and with smaller sample size compared with survival studies • Measurement of stable disease included • Generally based on objective and quantitative assessment	• Potentially subject to assessment bias, particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Balanced timing of assessments among treatment arms is critical • May not always correlate with survival

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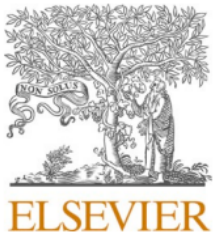
Lung Cancer 170 (2022) 122–132



Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Correlations between objective response rate and survival-based endpoints in first-line advanced non-small cell lung Cancer: A systematic review and meta-analysis

Sarah Goring [a,*], Nebibe Varol [b], Nathalie Waser [c], Evan Popoff [a], Greta Lozano-Ortega [a], Adam Lee [b], Yong Yuan [d], Laura Eccles [d], Phuong Tran [d], John R. Penrod [d]

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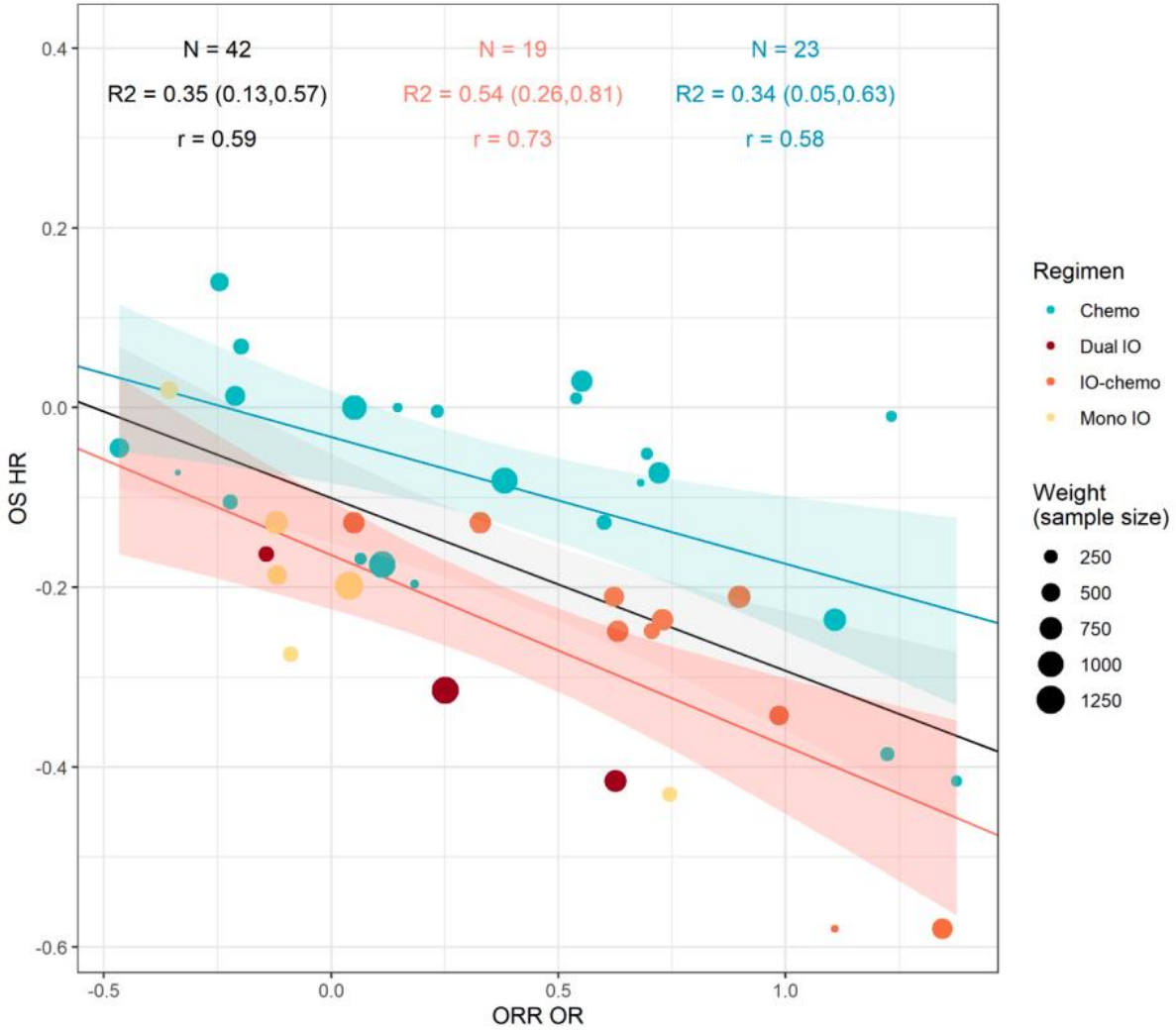

Fig. 2. Trial-level analysis of correlation between OS and ORR (overall and stratified by drug class comparison). *Abbreviations: HR = hazard ratio; IO = immunotherapy; OR = odds ratio; ORR = objective response rate; OS = overall survival; RCT = randomized controlled trial, Black line = weighted regression of all RCTs together; turquoise line = chemotherapy doublet-based RCTs; red line = immunotherapy-based versus chemotherapy doublet-based RCTs. Note: OS HR values less than 1 represent a benefit for the intervention vs. control arm; ORR OR values greater than 1 represent a benefit for the intervention vs. control arm.*

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Review

Relationship between Progression-free Survival and Overall Survival in Randomized Clinical Trials of Targeted and Biologic Agents in Oncology

Lisa M Hess[1]✉, Alan Brnabic[2], Oksana Mason[1], Pablo Lee[1], Scott Barker[1]

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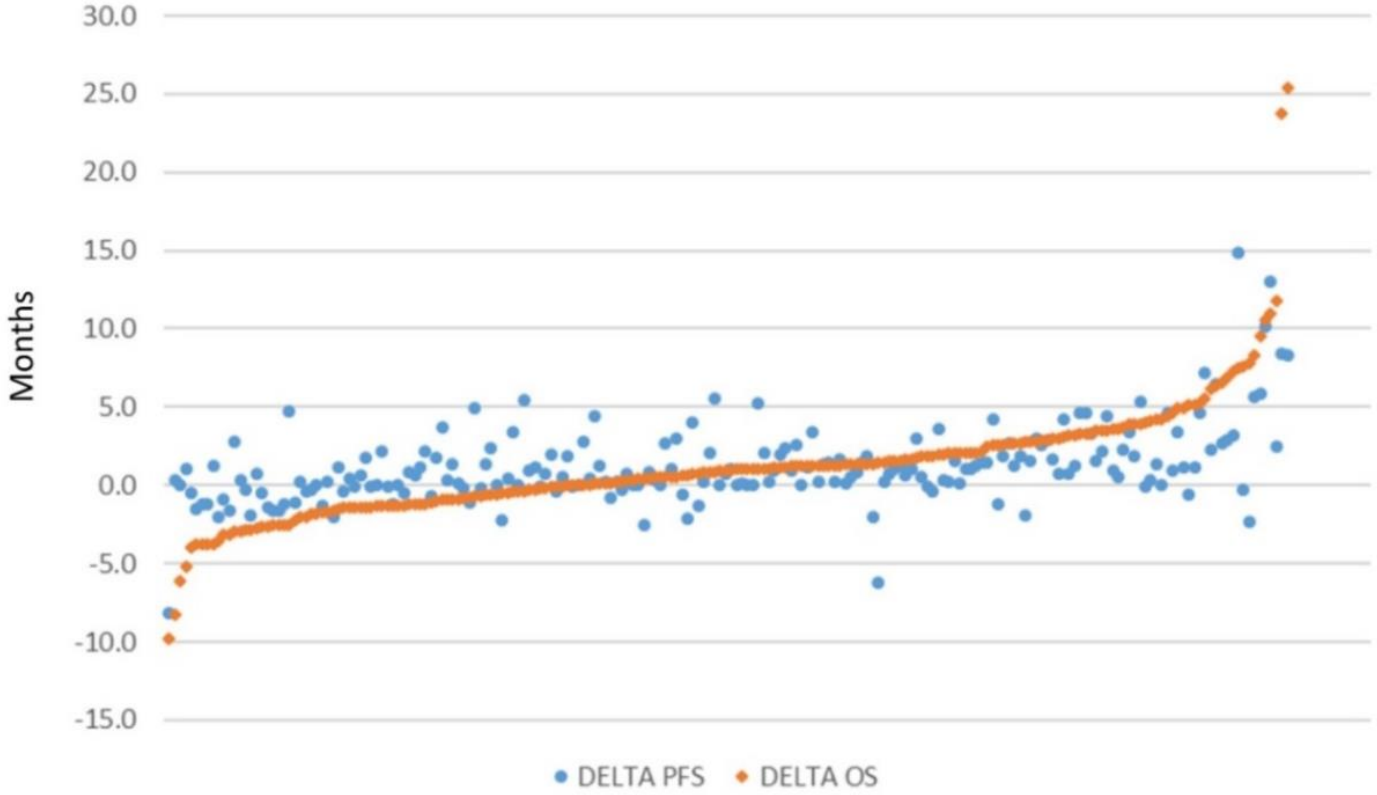


Figure 2. Scatterplot of difference in median months of overall survival (OS) and median progression-free survival (PFS), respectively, between treatment arms (n=206)

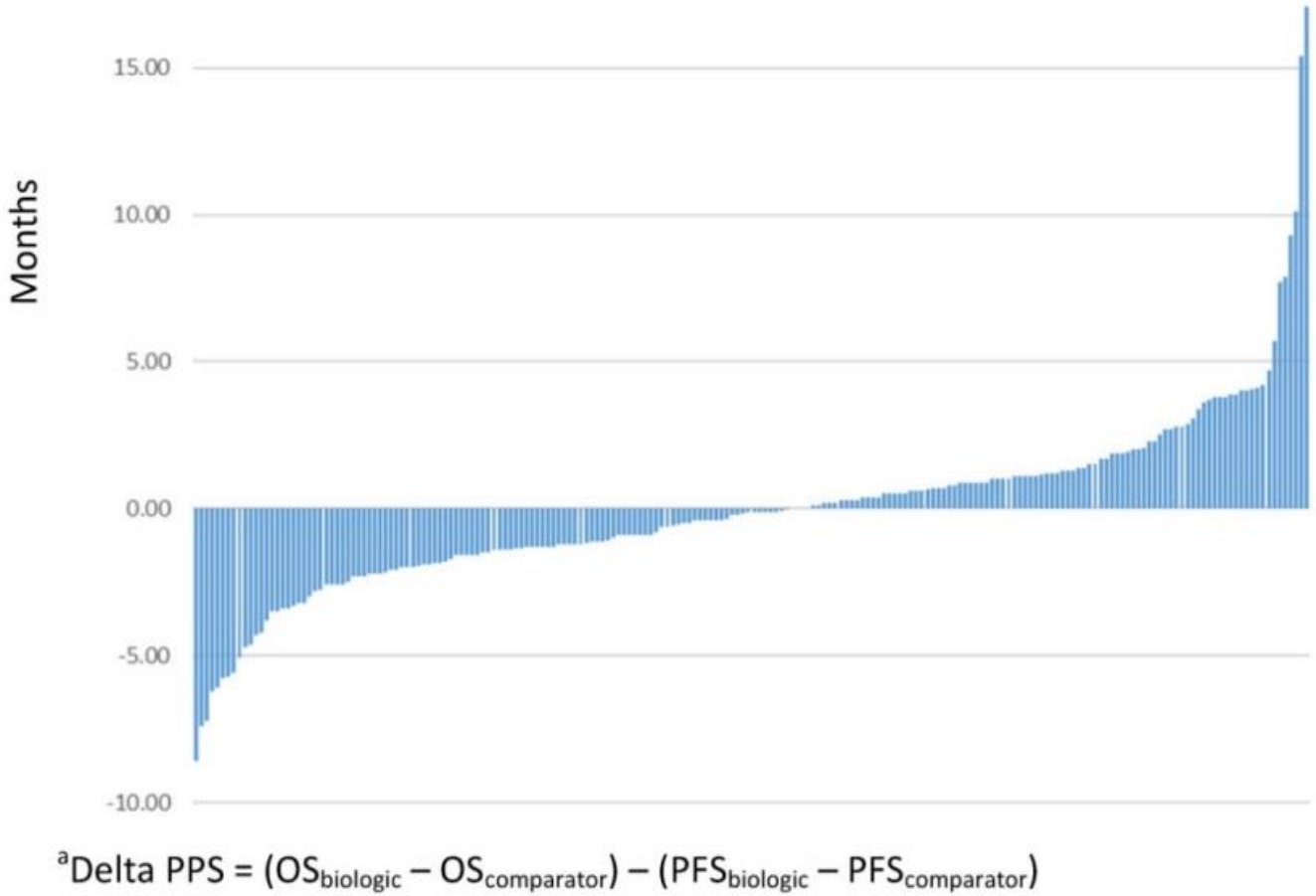
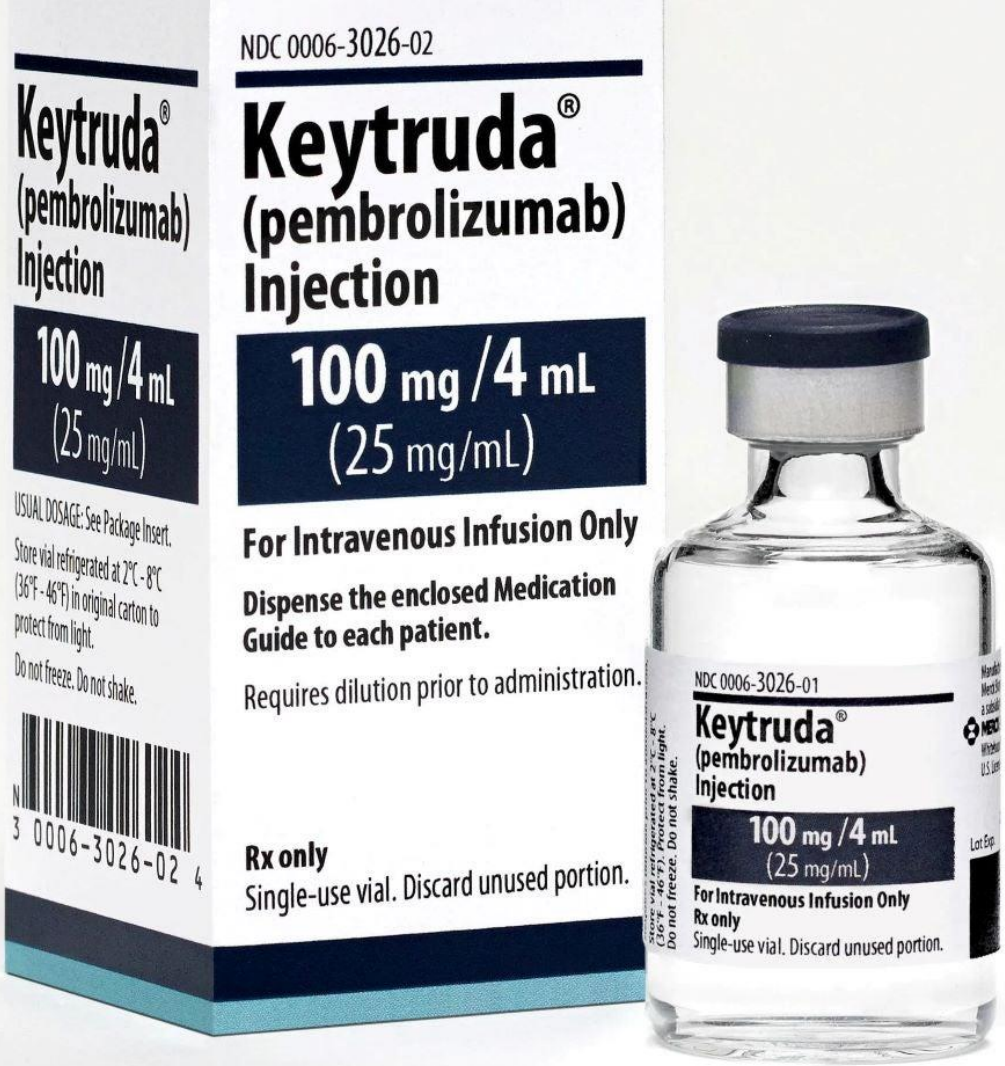


Figure 3. Delta post-progression survival (PPS) between biologic/targeted and non-biologic/targeted comparator[a] (N=206)


NDC 0006-3026-02
Keytruda®
(pembrolizumab)
Injection
100 mg /4 mL
(25 mg/mL)
USUAL DOSAGE: See Package Insert.
Store vial refrigerated at 2°C - 8°C (36°F - 46°F) in original carton to protect from light.
Do not freeze. Do not shake.
3 0006-3026-02 4
Keytruda®
(pembrolizumab)
Injection
100 mg /4 mL
(25 mg/mL)
For Intravenous Infusion Only
Dispense the enclosed Medication Guide to each patient.
Requires dilution prior to administration.
Rx only
Single-use vial. Discard unused portion.
NDC 0006-3026-01
Keytruda®
(pembrolizumab)
Injection
100 mg /4 mL
(25 mg/mL)
For Intravenous Infusion Only
Rx only
Single-use vial. Discard unused portion.

Melanoma (skin cancer)

Keytruda can delay worsening of melanoma and improve survival. Results from a study of 540 previously

Non-small cell lung cancer (NSCLC)

Keytruda is also effective in delaying worsening of the disease and improving survival in patients with NSCLC that tested positive for the PD-L1 protein.

Hodgkin lymphoma

Keytruda partially or completely clears cancer cells in classical Hodgkin lymphoma that has not improved or had returned after previous treatment.

Urothelial cancer

Keytruda improves survival of patients with urothelial cancer. A study looked at 542 patients previously

Head and neck cancer

Keytruda is also effective in improving survival of patients with head and neck squamous cell carcinoma

Kidney cancer

In a study of 861 patients with renal cell carcinoma, patients given Keytruda in combination with an already authorised medicine for renal cell carcinoma, axitinib, lived for around 15 months without their disease getting worse, compared with 11 months for patients who received treatment with another renal cell carcinoma medicine, sunitinib. Keytruda is also effective in improving survival of patients with renal cell carcinoma. At 18 months, 81% of the patients given the combination were alive, compared with 71% in the sunitinib group.