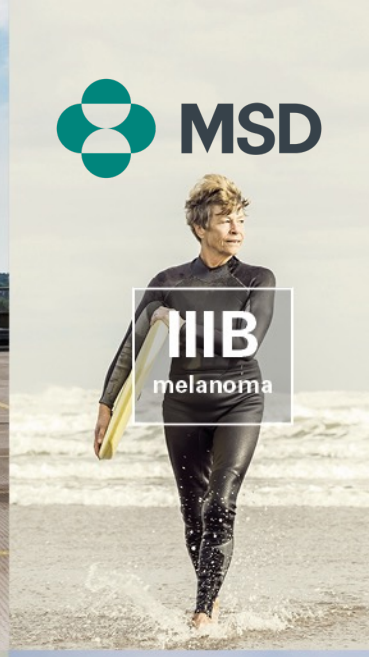
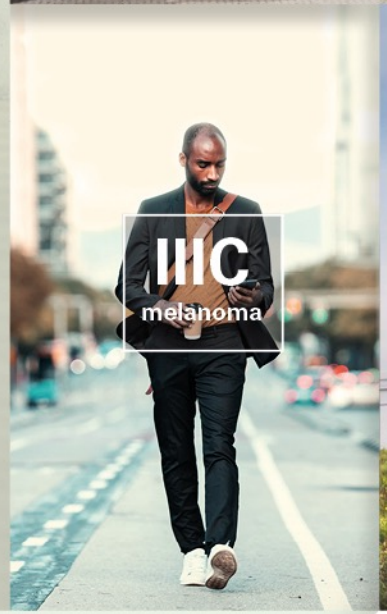
KEYTRUDA® (pembrolizumab) In The Adjuvant Treatment Of Patients with Stage III Melanoma





Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD, UK (Tel: 0208 154 8000).

These slides are provided to UK healthcare professionals as a data resource for personal education.

To ensure compliance with all relevant codes and regulations, these slides are provided in PDF format and must not be amended.

Prescribing information can be found on slide 3, and at https://www.emcpi.com/pi/33162 (Great Britain) https://www.emcpi.com/pi/ni/378 (Northern Ireland). Please refer to the full KEYTRUDA Summary of Product Characteristics and Risk Minimisation Materials for Patients before prescribing KEYTRUDA.

Images are illustrative of the range of patients diagnosed with melanoma.

Job number: GB-OOC-00755 Date of Preparation: June 2024

KEYTRUDA® (pembrolizumab)

KEYTRUDA Indications In Melanoma And Dosing[1]

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Licensed melanoma indications:[1]

- **KEYTRUDA as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma**
- **KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection**

Dosing information:[1]

- Patients with advanced melanoma should be treated with KEYTRUDA until disease progression or unacceptable toxicity
- For the adjuvant treatment of melanoma, KEYTRUDA should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to 1 year
- The recommended dose of KEYTRUDA as monotherapy in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes
- The recommended dose of KEYTRUDA as monotherapy in paediatric patients aged 12 years and older with melanoma is 2 mg/kg bodyweight (up to a maximum of 200 mg), every 3 weeks administered as an intravenous infusion over 30 minutes
- A link to the prescribing information for KEYTRUDA can be found at the top of each slide in this presentation
  - Refer to the Summary of Product Characteristics and Risk Minimisation materials available on the EMC website before prescribing, in order to help reduce the risks associated with KEYTRUDA
- For any queries, please contact your local MSD contact at msdukoncology@msd.com

MSD does not recommend use of products outside their licensed indications, please refer to the Summary of Product Characteristics (and risk minimisation materials) available on the EMC website before prescribing.

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1. KEYTRUDA Summary of Product Characteristics. Available at: https://www.emcpi.com/pi/33162 (GB) and https://www.emcpi.com/pi/ni/378 (NI). Accessed April 2024.

Prescribing Information

GB PI | NI PI

Prescribing information can be found at:

https://www.emcpi.com/pi/33162 (Great Britain)

https://www.emcpi.com/pi/ni/378 (Northern Ireland)

Pooled safety data of KEYTRUDA across all indications and AE management can be found in the Summary of Product Characteristics.

Please refer to the full KEYTRUDA Summary of Product Characteristics and Risk Minimisation Materials for Patients before prescribing KEYTRUDA.

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to MSD, UK (Tel: 0208 154 8000).

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KEYTRUDA: Bringing Immunotherapy to Your Eligible Patients With Stage IIB–IV Melanoma

Images are illustrative of the range of patients diagnosed with melanoma.

Licensed melanoma indications:[1]

- KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection
- KEYTRUDA as monotherapy is indicated for the treatment of adults or adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma

1. KEYTRUDA Summary of Product Characteristics. Available at: https://www.emcpi.com/pi/33162 (GB) and https://www.emcpi.com/pi/ni/378 (NI). Accessed April 2024.

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Click On The Icons Below To Explore KEYTRUDA In Stage III Melanoma

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Do we know the associated risks for patients with resected Stage III melanoma?

How can KEYTRUDA support patients with Stage III melanoma in the adjuvant setting?

- KEYNOTE-054

Using KEYTRUDA

GB PI | NI PI **Click on this icon to access KEYTRUDA prescribing information**

Click on this icon to return to this page

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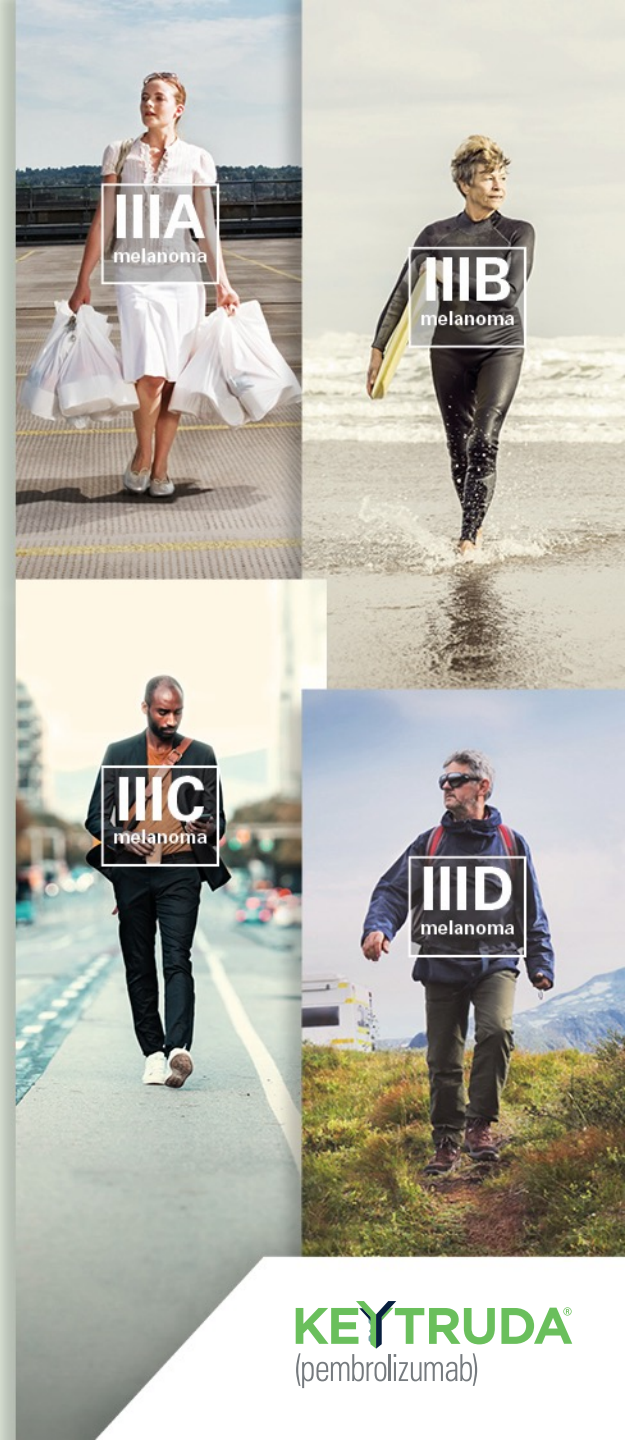
Do We Know The Associated Risks For Patients With Resected Stage III Melanoma?

Background
- Stages of melanoma
- 5- and 10-year survival rates

Relapse rates and distant metastasis rates

Time to relapse



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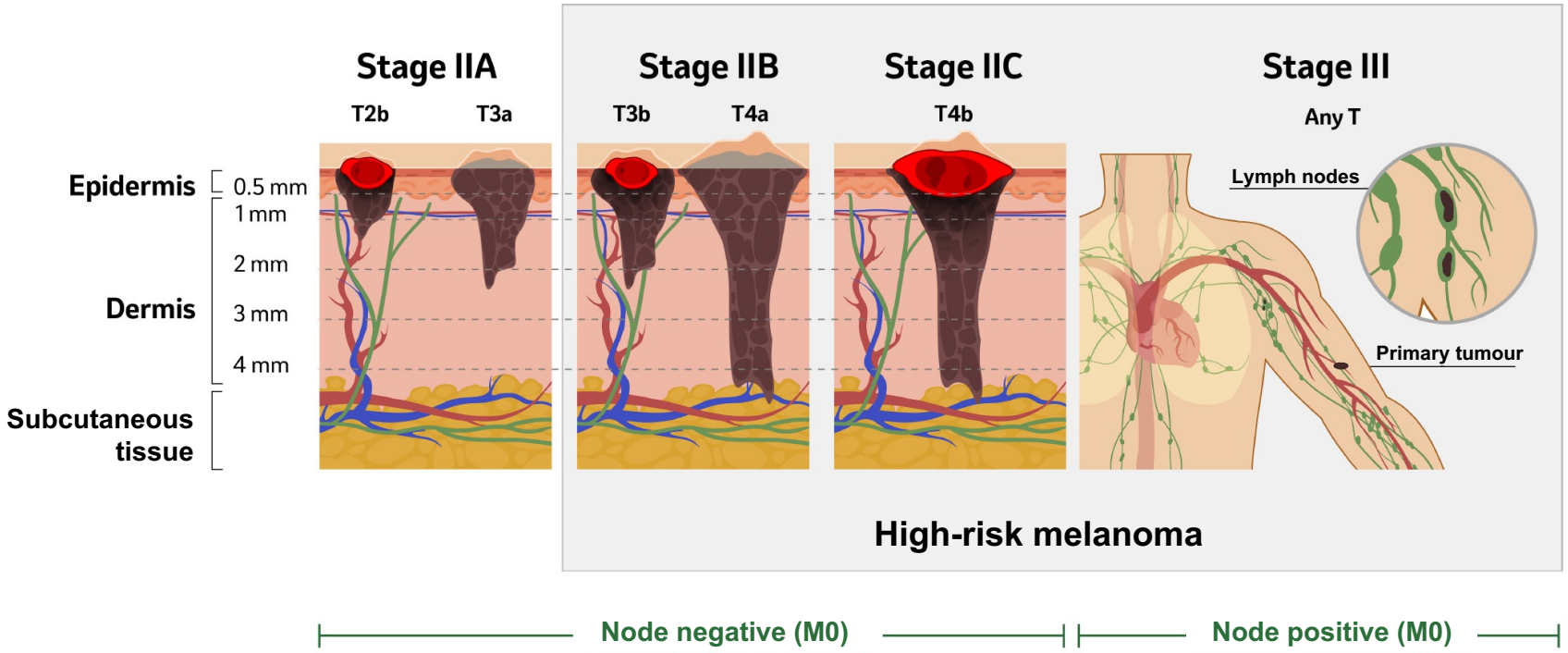
Patients With Melanoma Stage IIB Or Higher Are At Risk Of Recurrence Following Resection*[1–3]

Based on the AJCC 8th edition clinical staging criteria for melanoma[4]

Stages of melanoma*†[4]



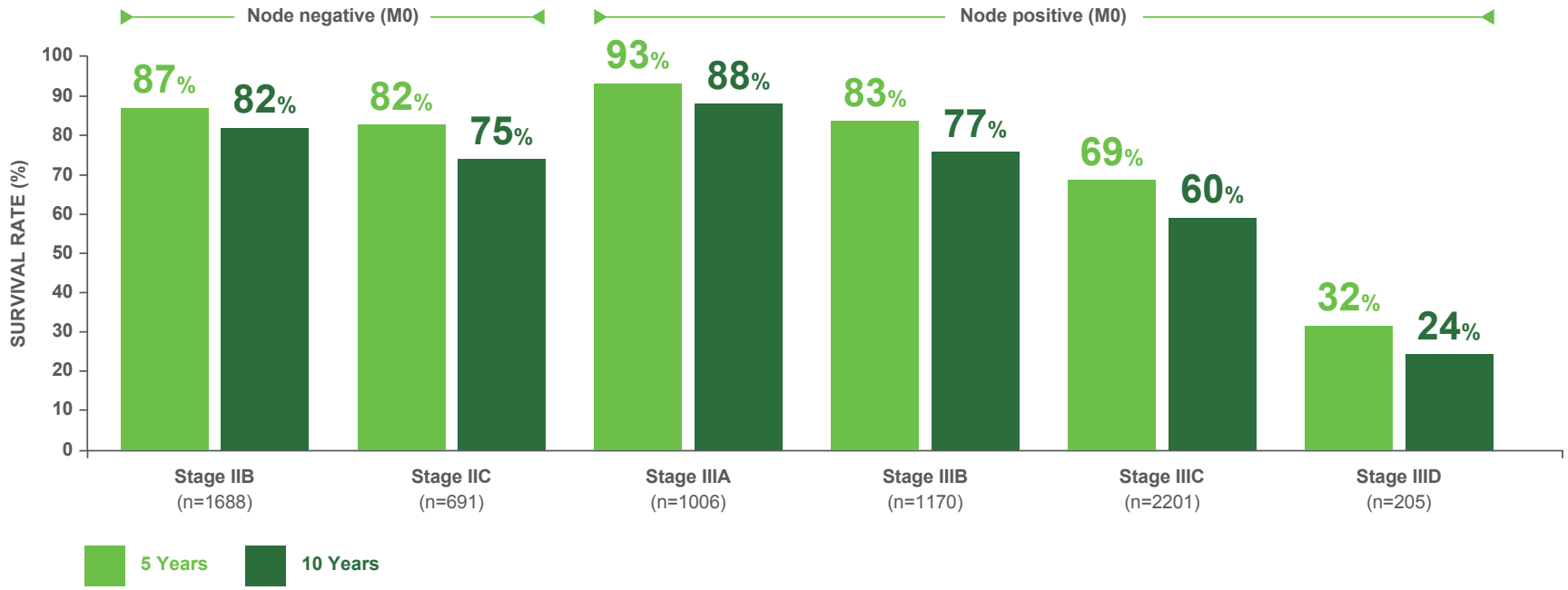
Adapted from Gershenwald JE, *et al.* 2017.[4]

*Stage IV melanoma that is resectable is also high risk but is not discussed here.
†Based on the AJCC 8th edition clinical staging criteria for melanoma.[4]
AJCC, American Joint Committee on Cancer.

1. Mohr P, *et al. Melanoma Manag* 2019;6:MMT33; **2.** Yushak M, *et al. Am Soc Clin Oncol Educ Book* 2019;39:e207–e211; **3.** Lee AY, *et al. Ann Surg Oncol* 2017;24:939–946; **4.** Gershenwald JE, *et al. CA Cancer J Clin* 2017;67:472–492.

Melanoma-Specific Survival Rates At 5 And 10 Years According To AJCC 8th Edition Pathologic Staging Criteria For Melanoma[1]

- Survival data generated using IMDPP database, containing records of >46,000 patients with melanoma (n=43,792 qualified for analysis)
- Included patient records from 10 institutions in the US, Europe and Australia with melanoma at Stage I–III at initial diagnosis and had received treatment since 1998



Adapted from Gershenwald JE, *et al* 2017.[1]

Were you aware of the difference in survival rates across Stage III melanoma?

Data based on Kaplan-Meier estimates of melanoma-specific survival as reported by the AJCC melanoma expert panel.[1]
AJCC, American Joint Committee on Cancer; IMDPP, International Melanoma Database and Discovery Platform.

1. Gershenwald JE, *et al. CA Cancer J Clin* 2017;67:472–492.

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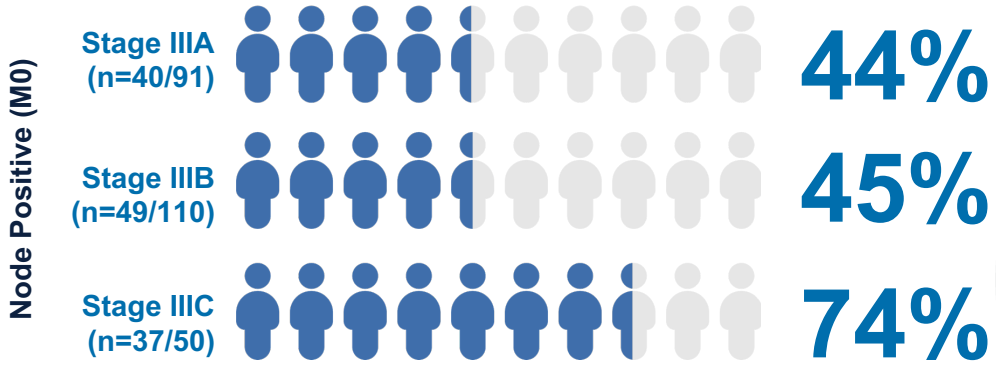
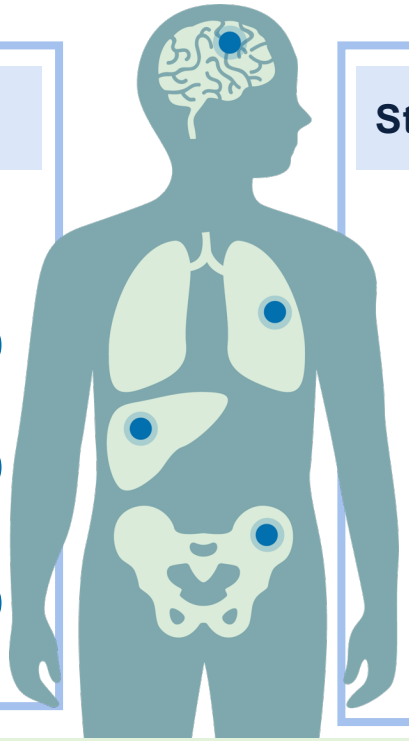
Relapse Rates In Patients With Stage III Melanoma Are 44%, 45% And 74% For Stages IIIA, IIIB And IIIC, Respectively[1]

A retrospective chart review of 251 patients from 2011–2016 with Stage III resected melanoma (AJCC 7th ed.) followed by watch-and-wait. Patients included in this study were from North America, South America and Europe.

Median follow-up was 3.1 years.[2] Relapse-free survival (RFS) was measured from the date of initial surgery for Stage III melanoma to the earliest among the date of first relapse (event), date of death (event) or end of follow-up (i.e. end of care for the patient or date of data collection; censoring) among patients with known information on time of relapse/death.

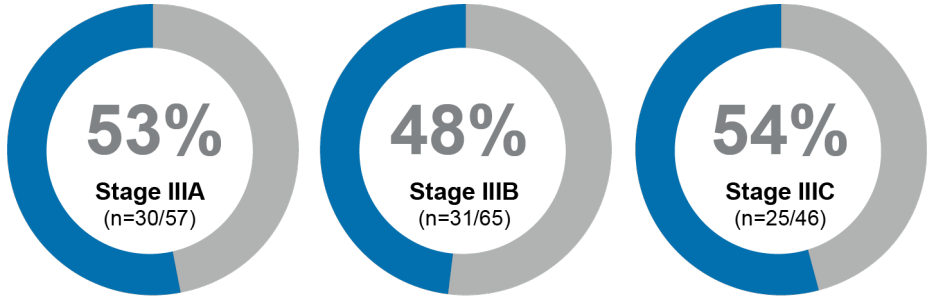
Stage III relapse rates in patients who received watch-and-wait post-surgery[1]





Stage III who relapsed with distant metastasis[1]

Percentage of patients who relapsed with unresectable or distant metastasis as first relapse*



*The remainder of patients experienced a locoregional relapse or a secondary primary melanoma relapse.

Were you aware of the rate of distant relapses across Stage III melanoma?

AJCC, American Joint Committee on Cancer.

1. Mohr P, *et al. Melanoma Manag* 2019;6:MMT33. Supplementary appendix. **2.** Mohr P, *et al. Melanoma Manag* 2019;6:MMT33.

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The Median Time To Relapse From Resection Is 5.2 Months At Stage IIIC And Less Than 1.5 Years At Stage IIIA[1,2]

A retrospective chart review of 251 patients from 2011–2016 with Stage III resected melanoma (AJCC 7th ed.) followed by watch-and-wait. Patients included in this study were from North America, South America and Europe.

Median follow-up was 3.1 years.

RFS was measured from the date of initial surgery for Stage III melanoma to the earliest among the date of first relapse (event), date of death (event) or end of follow-up (i.e. end of care for the patient or date of data collection; censoring) among patients with known information on time of relapse/death.

Stage III time to relapse[2]

Median time to relapse among patients who relapsed

Stage IIIA (n=40/91)

Stage IIIB (n=49/110)

Stage IIIC (n=37/50)

Would you treat patients with Stage IIIA melanoma differently to those with Stage IIIB melanoma?

AJCC, American Joint Committee on Cancer; RFS, relapse-free survival.

1. Mohr P, *et al. Melanoma Manag* 2019;6:MMT33; **2.** Mohr P, *et al. Melanoma Manag* 2019;6:MMT33. Supplementary appendix.

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Summary

- Patients with Stage III are at risk of relapse following resection *†[1,2]
- 5- and 10-year estimated survival rates decrease in patients with more advanced Stage III melanoma‡[3]

- Over 44% of patients with melanoma in Stages IIIA and beyond will recur*†[1]
- When patients with Stage III melanoma relapse, approximately 50% present with distant metastases*†[1]
- The median time to relapse in patients with Stage IIIA melanoma is less than 1.5 years and as low as 5.2 months in Stage IIIC patients*†[1]

Patients with Stage III melanoma could be considered at risk of disease recurrence

*According to AJCC 7th edition pathologic staging criteria for melanoma.
†A retrospective chart review of 251 patients from 2011–2016 with Stage III resected melanoma followed by watch-and-wait. Patients included in this study were from North America, South America and Europe.
‡Based on the AJCC 8th edition clinical staging criteria for melanoma.
AJCC, American Joint Committee on Cancer.
1. Mohr P, *et al. Melanoma Manag* 2019;6:MMT33; **2.** Yushak M, *et al. Am Soc Clin Oncol Educ Book* 2019;39:e207–e211; **3.** Gershenwald JE, *et al. CA Cancer J Clin* 2017;67:472–492.

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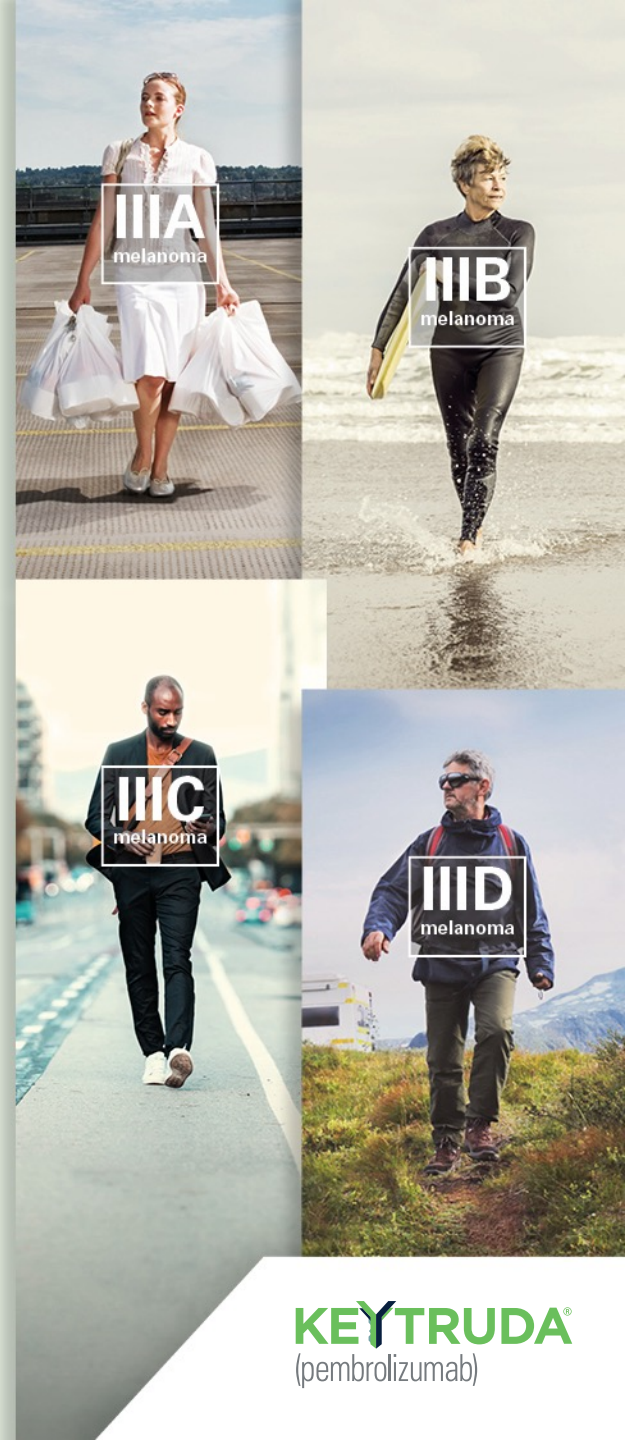
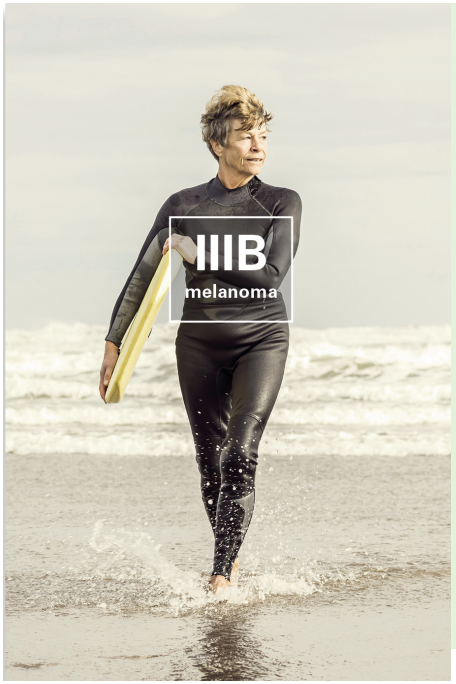
How Can KEYTRUDA Support Patients With Stage III Melanoma In The Adjuvant Setting?



Meet Suzie And Claire*, Two Patients Who Have Stage IIIA And IIIB Melanoma That Has Been Completely Resected

Name: Suzie
Age: 31
Medical history:

- Non-smoker with a fit and active lifestyle
- Saw her doctor after a new mole appeared on her thigh
- A biopsy revealed invasive melanoma and surgery was scheduled
- Underwent a wide local excision to remove the tumour (<2 mm thickness) and conducted a sentinel node biopsy
- Review confirmed that a microscopic tumour had spread to one nearby lymph node, which was removed



Name: Claire
Age: 64
Medical history:

- Retired nurse who enjoys outdoor activities
- Had ignored a mole on her calf for years until one day it was raised and bleeding
- Consulted her GP and was referred to a dermatologist who conducted a biopsy, which identified melanoma
- Sentinel node biopsy confirmed the tumour (3 mm thickness) had spread to one nearby lymph node
- The tumour was removed along with the lymph node involved

Would you consider Suzie and Claire to be at risk of disease relapse?

*Hypothetical patient cases.
GP, general practitioner.

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Meet Aaron And Tony*, Two Patients Who Have Stage IIIC And IIID Melanoma That Has Been Completely Resected

Name: Aaron
Age: 34
Medical history:

- At 25, he had a dark spot on his face removed as it was new and had an irregular shape. It was defined as Stage I melanoma
- 9 years later, he noticed an enlarged lymph node under his chin, which following a biopsy was identified as melanoma
- Investigations found the tumour had spread to two further nearby lymph nodes, which were removed

Name: Tony
Age: 58
Medical history:

- A retired builder who enjoys hiking
- His partner noticed a large mole on his back, which had grown rapidly in recent weeks and was dry and bleeding if rubbed
- The mole was biopsied and excised once identified as melanoma
- The tumour was deep (>4 mm) and ulcerated with a high mitotic rate
- Investigations identified melanoma in four nearby lymph nodes, which were removed
- No distant metastases were found

Would you consider Aaron and Tony to be at risk of disease relapse?

*Hypothetical patient cases.

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Learn How Patients With Stage III Melanoma May Benefit From KEYTRUDA Treatment

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KEYNOTE-054[1]

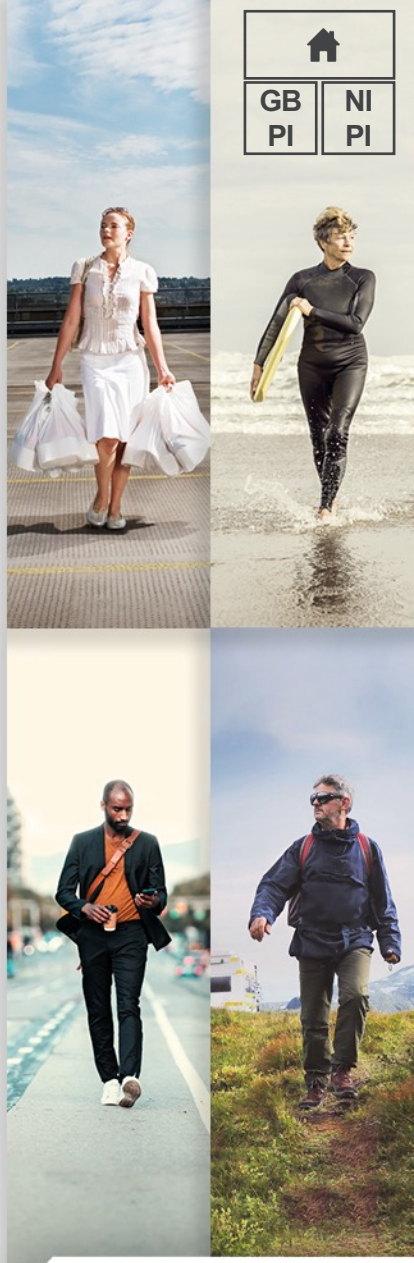
- Phase III trial of KEYTRUDA for the adjuvant treatment of patients with completely resected Stage III melanoma with lymph node involvement

Study design

Primary analysis for RFS efficacy and safety data

Primary analysis for DMFS efficacy and safety data

5-year follow-up efficacy and safety data



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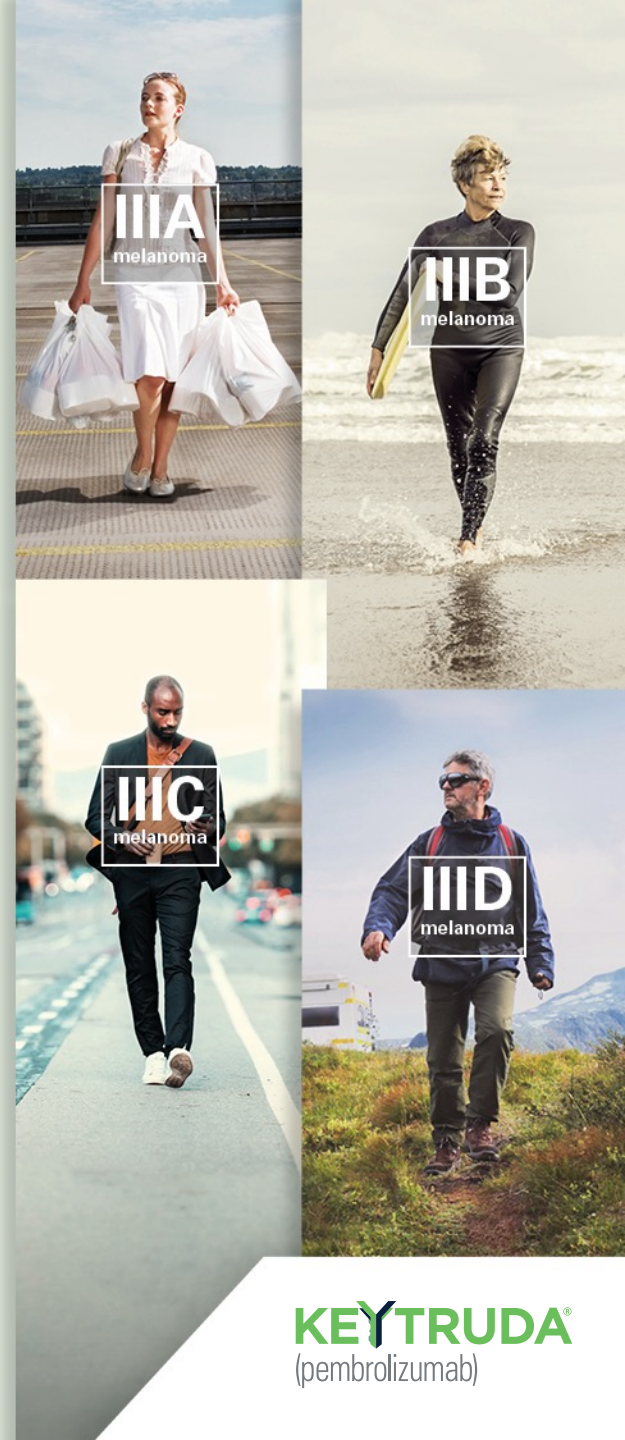
DMFS, distant metastasis-free survival; RFS, relapse-free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYNOTE-054
Study Design



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Study Design[1]

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- KEYNOTE-054 was a multicentre, randomised, double-blind, placebo-controlled Phase III trial conducted in collaboration with EORTC
- Investigated treatment with KEYTRUDA compared with placebo following complete surgical resection of Stage III melanoma, as well as an anti-PD-1 rechallenge crossover design. **Please note: Rechallenge is outside the licensed indication for KEYTRUDA**

Inclusion criteria:[1]

- High-risk, resected, Stage III cutaneous melanoma

Stratified by:*

- **Stage:** IIIA (>1 mm metastasis) vs IIIB vs IIIC 1–3 positive lymph nodes vs IIIC ≥4 positive lymph nodes
- **Region:** 17 regions, each formed by 1–3 countries

Additional eligibility criteria:[1]

- Aged ≥18 years
- No prior systemic therapy for melanoma
- No autoimmune disease or uncontrolled infections
- ECOG PS 0–1

Exclusion criteria:[2]

- Mucosal or ocular melanoma
- Prior therapy for melanoma, other than surgery or interferon for thick primary melanomas without evidence of lymph node involvement

Refer to the full protocol for the list of inclusion and exclusion criteria.[2]

Click here to view baseline patient characteristics ›

*KEYNOTE-054 enrolled patients per AJCC 7th edition. Stage IIIA melanoma according to the AJCC 8th edition identifies a patient population with a better prognosis compared to Stage IIIA according to AJCC 7th edition.[3]
AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; PD-1, programmed death protein 1.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801. Protocol; **3.** Keung EZ & Gershenwald JE. *Expert Rev Anticancer Ther* 2018;18:775–784.

Study Design[1,2]

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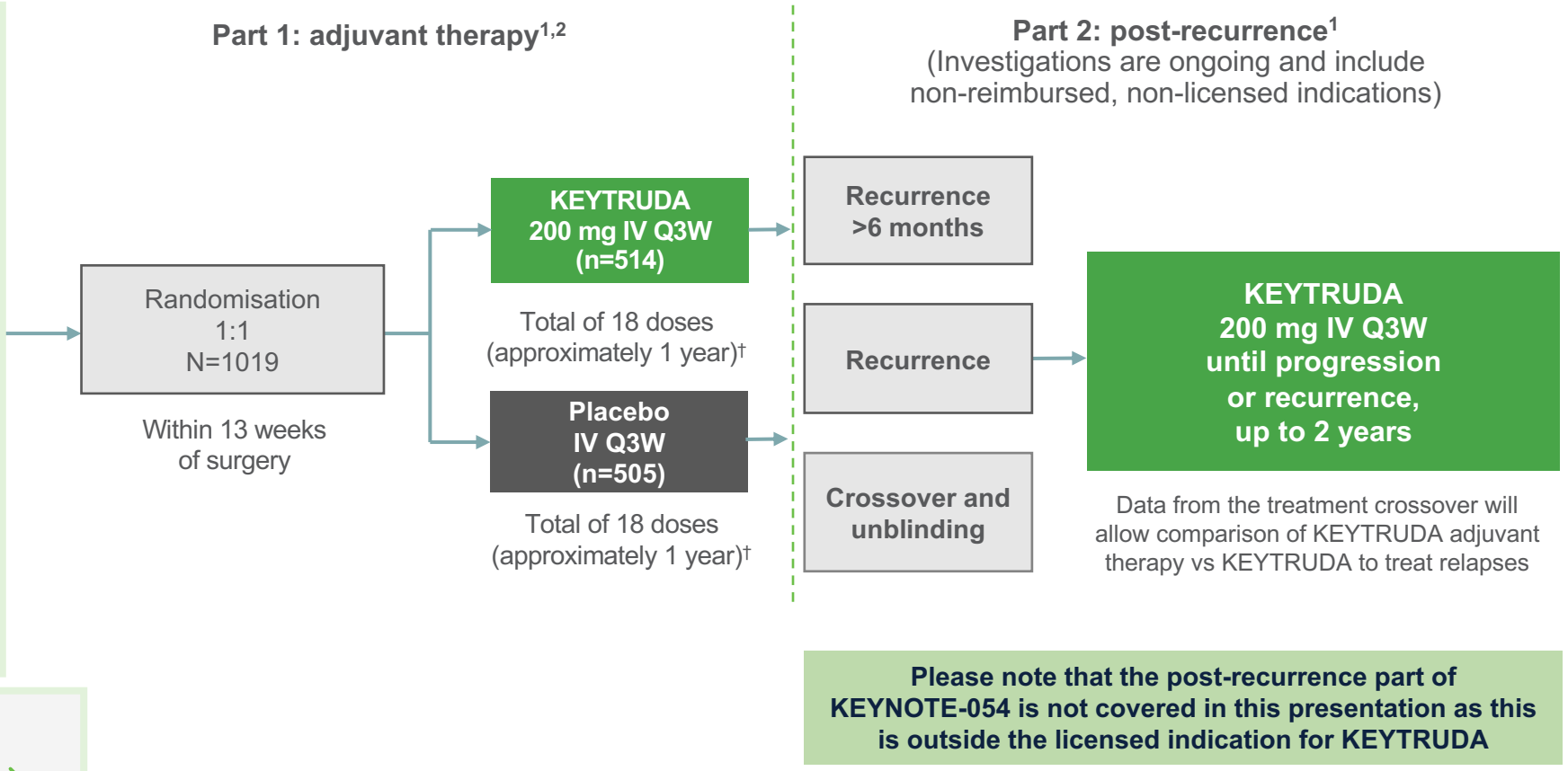
Patients with:[1,2]

- High-risk, resected, Stage III cutaneous melanoma

Stratified by:*

- **Stage:** IIIA (>1 mm metastasis) vs IIIB vs IIIC 1–3 positive lymph nodes vs IIIC ≥4 positive lymph nodes
- **Region:** 17 regions, each formed by 1–3 countries



Please note that the post-recurrence part of KEYNOTE-054 is not covered in this presentation as this is outside the licensed indication for KEYTRUDA

Click here to view baseline patient characteristics

*KEYNOTE-054 enrolled patients per AJCC 7th edition. Stage IIIA melanoma according to the AJCC 8th edition identifies a patient population with a better prognosis compared to Stage IIIA according to AJCC 7th edition.[3]
†Until recurrence or unacceptable toxic effects, a major protocol violation, or withdrawal of consent occurred.
AJCC, American Joint Committee on Cancer; IV, intravenous; Q3W, every 3 weeks.
1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801. Supplementary appendix; **3.** Keung EZ & Gershenwald JE. *Expert Rev Anticancer Ther*. 2018;18:775–784.

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Key Trial Endpoints[1]

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1

Primary efficacy outcome measure:

- Investigator-assessed, recurrence-free survival (RFS) in the whole population and in the population with PD-L1-positive tumours*

2

Secondary efficacy outcome measures

- Distant metastasis-free survival (DMFS) and overall survival (OS) in the whole population
- Adverse event profile

- At the clinical cut-off date (2 October 2017), 351 events (recurrences or deaths) had been reported in the ITT population
- The interim analysis was performed at a one-sided alpha level of 0.8% (two-sided alpha level: 1.6%)
- In December 2017, the independent data and safety monitoring committee reviewed the unblinded results and recommended the reporting of the primary endpoints and safety
- Because the results were positive in the ITT population, the interim analysis of RFS became the final analysis

RFS was defined as the time from randomisation until the date of first recurrence (local, regional or distant metastasis) or death from any cause.[1]
*PD-L1 expression was tested retrospectively by immunohistochemistry assay with the 22C3 anti-PD-L1 antibody.[1]
The primary analysis of recurrence-free survival included all the patients who underwent randomisation, according to the intent-to-treat principle. The safety profile was assessed in the group of patients who started their randomly assigned trial regimen.[1]
DMFS, distant metastasis-free survival; ITT, intent-to-treat; OS, overall survival; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival.
1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

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KEYNOTE-054: RFS And DMFS Definitions

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RFS was the primary endpoint in KEYNOTE-054[1]
DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses[2,3]

Recurrence-free survival:
The time from randomisation until the date of first recurrence (local, regional or distant metastasis) or death from any cause[1]

Distant metastasis-free survival:
The time from randomisation to the date of first distant metastasis or death from any cause[2]

DMFS, distant metastasis-free survival; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654; **3.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214.

KEYNOTE-054 Trial And EMA Approval Timeline

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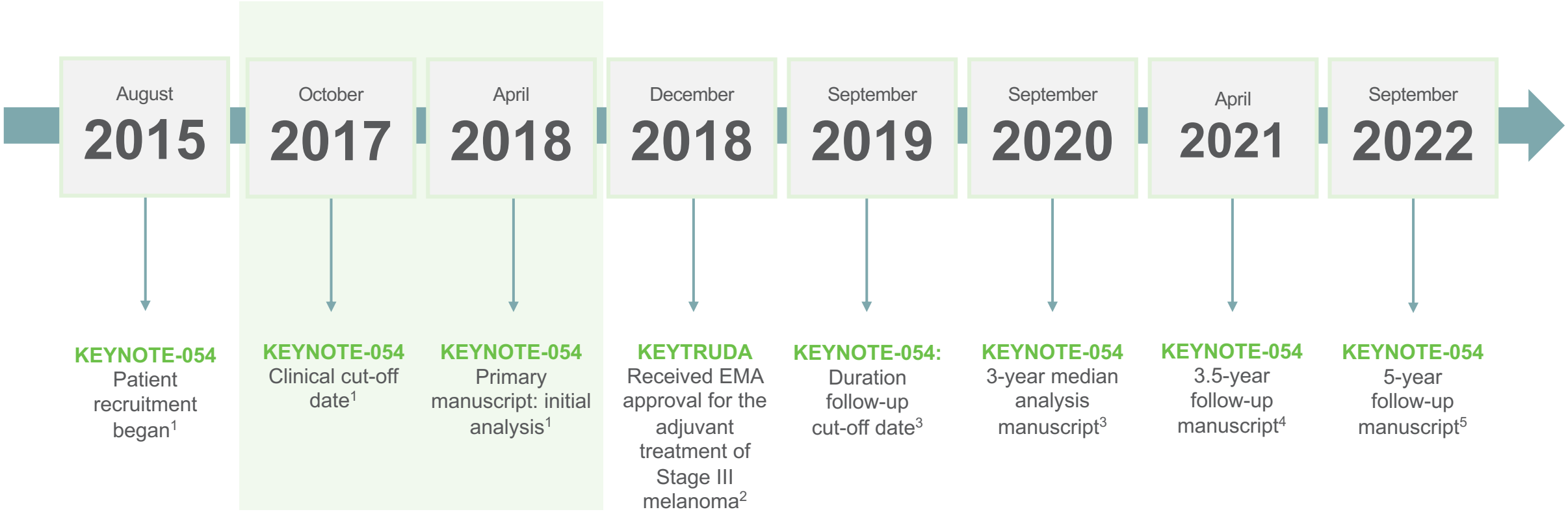

EMA, European Medicines Agency.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** KEYTRUDA. Procedural steps taken and scientific information after the authorization. Available at: https://www.ema.europa.eu/en/documents/procedural-steps-after/keytruda-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf Accessed: April 2024; **3.** Eggermont AMM, *et al. J Clin Oncol* 2020;38:3925–3936; **4.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654; **5.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214.

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Trial Analyses[1,2]

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1

Primary analysis for RFS[1]

Primary efficacy endpoint and safety

- Cut-off date (2 October 2017); median duration of follow-up: 15.1 months (KEYTRUDA monotherapy: 14.7 months; placebo: 15.4 months); 351 RFS events
- IDMC recommendation: reveal RFS results and safety; DMFS results reported in final interim analysis, study ongoing for OS

Click here to view the primary analysis for RFS data

3

Primary analysis for DMFS[2]

Primary efficacy endpoint and safety

- Cut-off date (3 April 2020); median duration of follow-up: 42.3 months (KEYTRUDA monotherapy: 42.2 months; placebo: 42.5 months); 491 RFS events
- Safety remained unchanged from previous results

Click here to view the primary analysis for DMFS data

5

5-year follow-up[3]

Primary efficacy endpoint and safety

- Cut-off date (17 January 2022); median duration of follow-up: 4.9 years (KEYTRUDA monotherapy: 4.9 years; placebo: 4.9 months); 532 RFS events; 470 DMFS events
- Long-term follow-up analysis

Click here to view the 5-year follow-up data

RFS was defined as the time from randomisation until the date of first recurrence (local, regional or distant metastasis) or death from any cause.[1]

DMFS, distant metastasis-free survival; IDMC, Independent Data and Safety Monitoring Committee; OS, overall survival; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654; **3.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214.

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Patients In The Study Were Representative Of Stage III Melanoma Population*[1–4]

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AJCC 7*

Stage IIIA (with >1 mm lymph node metastasis)	Stage IIIB	Stage IIIC (1-3 positive lymph nodes)	Stage IIIC (>3 positive lymph nodes)
16% (n=160/1019)	46% (n=467/1019)	18% (n=188/1019)	20% (n=204/1019)

AJCC 8*

Stage IIIA	Stage IIIB	Stage IIIC	Stage IIID
8% (n=82/1019)	35% (n=354/1019)	50% (n=506/1019)	4% (n=38/1019)

BRAF-V600 mutation positive	*BRAF* wild-type	PD-L1 positive†
43% (n=441/1019)	44% (n=447/1019)	84% (n=853/1019)

*AJCC 7 population characteristics are based on randomisation; AJCC 8 population characteristics are based on case report forms.[2]
†PD-L1 positivity defined as staining on >1% of tumour cells according to an investigational immunohistochemistry assay.[1,2]
AJCC: American Joint Committee on Cancer; PD-L1: programmed death-ligand 1.

1. Amin MB, Edge S, Greene F, et al. eds. AJCC Cancer Staging Manual. 8th ed. Springer International Publishing. 2017. **2.** Edge SB, Byrd DR, Compton CC, et al. eds. AJCC Cancer Staging Manual. 7th ed. Springer International Publishing. 2010. **3.** Eggermont AMM, et al. N Engl J Med 2018;378:1789–1801. **4.** Eggermont AMM, et al. Eur J Cancer 2019;116:148–157.

KEYTRUDA® (pembrolizumab)

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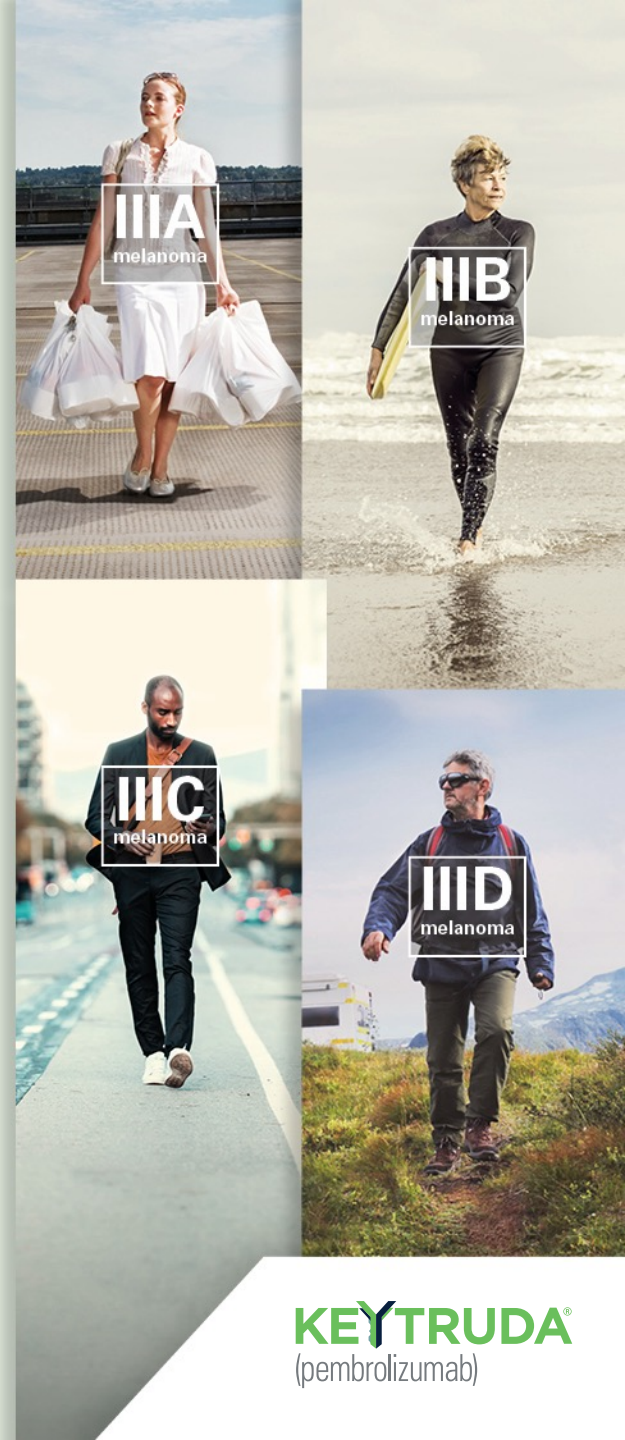
KEYNOTE-054
Efficacy Data From Primary Analysis For RFS (15.1-Month Median Follow-Up)



KEYTRUDA® (pembrolizumab)

Recurrence-Free Survival Analyses Of KEYTRUDA Vs Placebo[1,2]

Click to navigate to the section of interest

Primary endpoints

- RFS in ITT population
- RFS in PD-L1-positive patients
- RFS in Stage IIIA patients
- RFS in *BRAF*-V600E/K mutated patients
- RFS in Stage IIIB patients
- RFS in *BRAF*-WT patients
- RFS in Stage IIIC patients
- RFS in PD-L1-negative patients
- RFS according to subgroups

ITT, intent-to-treat; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival; WT, wild type.

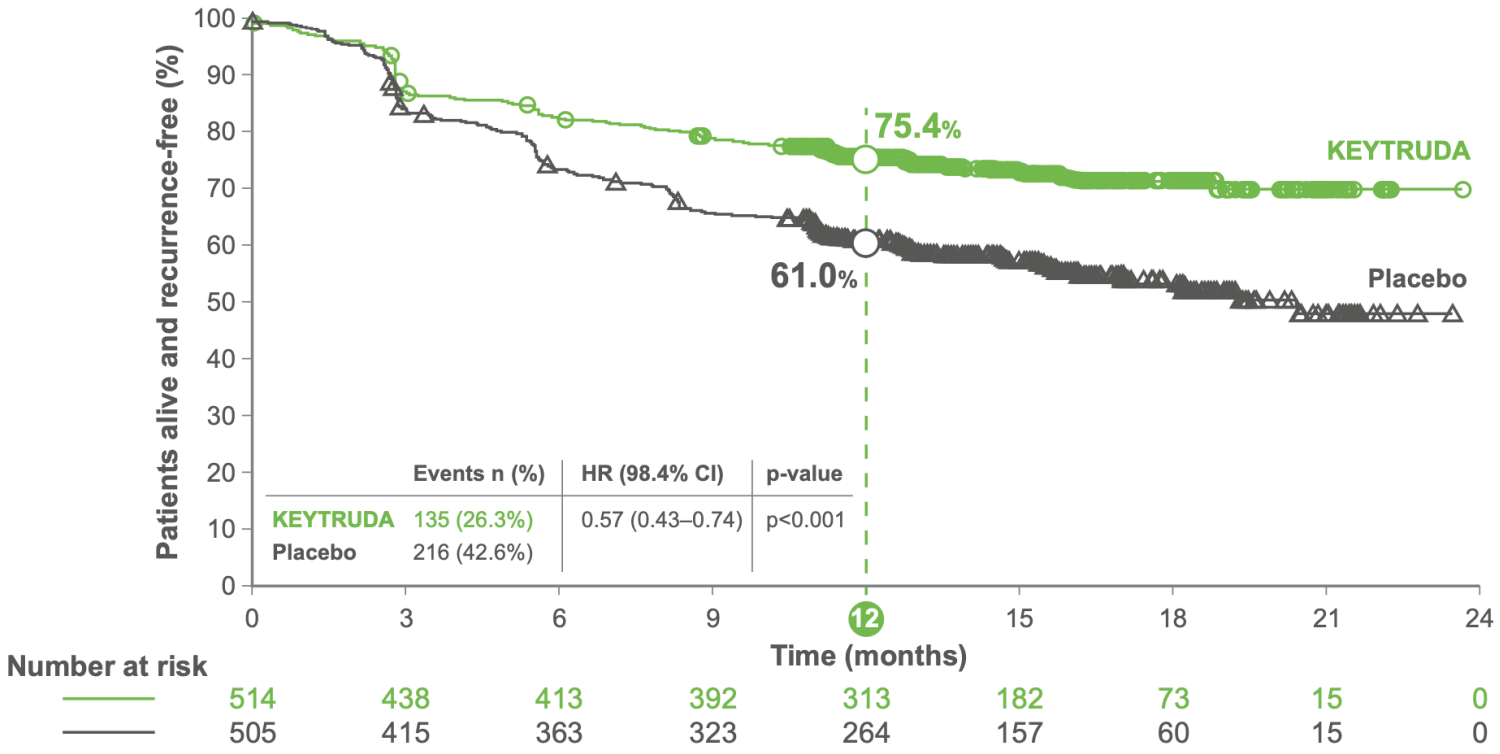
1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont A, *et al.* Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325-MG/Keynote-054 double-blinded Phase III trial. AACR Annual Meeting. 14–18 April 2018, Chicago, IL, USA. Abstract: LBA-10526.

KEYTRUDA® (pembrolizumab)

KEYTRUDA Treatment Was Associated With A Significant Improvement In RFS Vs Placebo In The Overall Population[1]

Primary endpoint: RFS in the ITT population

Median follow-up: 15.1 months[1]



HR: 0.57 demonstrated a 43% risk reduction in disease recurrence with KEYTRUDA vs placebo

Adjuvant treatment benefit was maintained beyond cessation of KEYTRUDA[1]

Adapted from Eggermont AMM, *et al.* 2018.[1]

IA1 data cut-off: 2 October 2017.[1]
Duration of treatment: Q3W for 18 doses (~1 year). Stratified by Stage given at randomisation.
CI, confidence interval; HR, hazard ratio; IA, interim analysis; ITT, intent-to-treat; Q3W, every 3 weeks; RFS, recurrence-free survival.

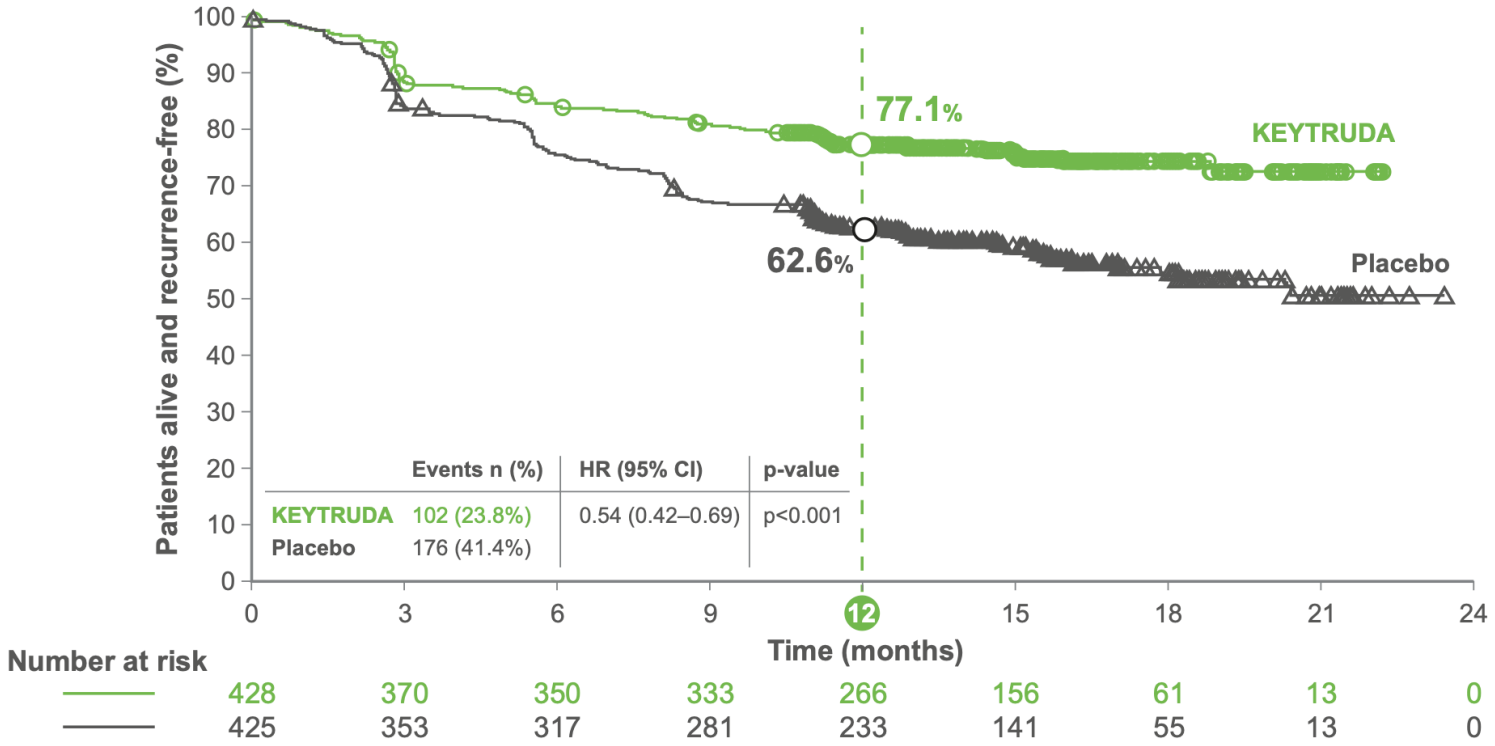
1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

PD-L1-Positive Patients Also Showed Significant Improvement In RFS With KEYTRUDA Treatment Vs Placebo[1]

RFS in the PD-L1-positive population[1,2] (primary endpoint)

Median follow-up: 15.1 months[1]



HR: 0.54 demonstrated a 46% risk reduction in disease recurrence with KEYTRUDA vs placebo

Both the PD-L1-positive and PD-L1-negative subgroups showed greater improvements in RFS with KEYTRUDA adjuvant therapy vs placebo[1]

Adapted from Eggermont AMM, *et al.* 2018.[1]

IA1 data cut-off: 2 October 2017.[1]
Duration of treatment: Q3W for 18 doses (~1 year). Stratified by Stage given at randomisation.
CI, confidence interval; HR, hazard ratio; IA, interim analysis; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont A, *et al.* Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325-MG/Keynote 054 double-blinded Phase III trial. AACR Annual Meeting. 14–18 April 2018, Chicago, IL, USA. Abstract: LBA-10526.

KEYTRUDA® (pembrolizumab)

KEYTRUDA Showed Consistent RFS Across AJCC Staging Classifications*[1]

Back to RFS data selection page

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Subgroup analysis was pre-specified but not statistically powered for comparison, therefore results should be interpreted with caution.

Median follow-up: 15.1 months[1]

Subgroup	KEYTRUDA	Placebo	HR (99% or 98.4% CI)†	p-value for interaction
	No. of events/total no.			
Tumour PD-L1 expression				0.60
Positive	102/428	176/425	0.54 (0.39–0.74)	
Negative	20/59	27/57	0.60 (0.28–1.28)	
Indeterminate	13/27	13/23	0.80 (0.29–2.19)	
Sex				0.49
Male	86/324	138/304	0.53 (0.37–0.76)	
Female	49/190	78/201	0.62 (0.39–1.00)	
Age				0.86
18 to <65 years	96/389	154/379	0.57 (0.41–0.80)	
≥65 years	39/125	62/126	0.55 (0.32–0.93)	
AJCC 2009 melanoma classification				0.69
Stage IIIA	6/77	15/76	0.38 (0.11–1.31)	
Stage IIIB	62/240	97/232	0.58 (0.38–0.88)	
Stage IIIC	67/197	104/197	0.58 (0.38–0.86)	
No. of positive lymph nodes				0.78
1	44/227	80/237	0.53 (0.33–0.86)	
2 or 3	46/177	76/166	0.52 (0.32–0.85)	
≥4	45/110	60/102	0.62 (0.37–1.03)	

Adapted from Eggermont AMM, *et al.* 2018.[1]

Click here to see RFS plots by Stage

IA1 data cut-off: 2 October 2017.[1]
Duration of treatment: Q3W for 18 doses (~1 year). Staging was performed according to AJCC 7th edition pathologic staging criteria for melanoma.[1]
The overall HR is represented by the dashed line.[1]
*Small patient sample can be a limitation. The subgroups were not analysed for statistical significance and not powered to show efficacy in individual subgroups.
†Unstratified HR. 98.4% CI covers the overall HR. 99% CI is presented for subgroup analysis.[1]
AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; IA, interim analysis; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; RFS, recurrence free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

Back to RFS data selection page

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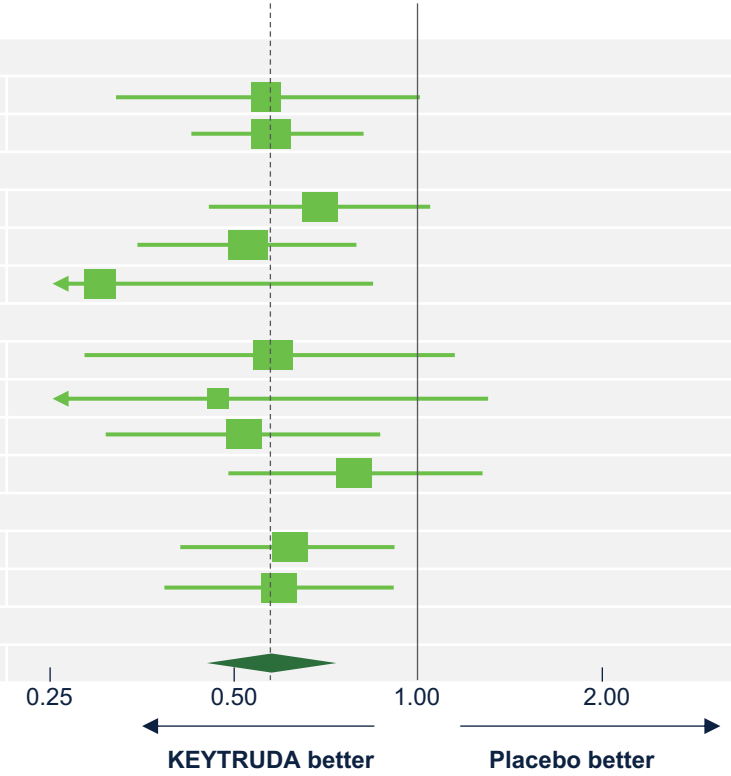
KEYTRUDA Showed Consistent RFS Regardless of *BRAF* Mutation Status*[1]

Subgroup analysis was pre-specified but not statistically powered for comparison, therefore results should be interpreted with caution.

Median follow-up: 15.1 months[1]

Subgroup	KEYTRUDA	Placebo	HR (99% or 98.4% CI)†	p-value for interaction
	No. of events/total no.			
Type of positive lymph nodes				0.86
Microscopic	35/187	50/161	0.56 (0.32–0.99)	
Macroscopic	100/327	166/344	0.59 (0.42–0.81)	
Ulceration				0.12
No	62/230	94/251	0.69 (0.45–1.05)	
Yes	64/208	101/197	0.52 (0.35–0.79)	
Not reported	9/76	21/57	0.30 (0.11–0.84)	
Lymph-mode and ulceration status				0.35
Microscopic, ulceration	25/94	31/75	0.58 (0.29–1.15)	
Microscopic, no ulceration	10/89	19/85	0.48 (0.17–1.30)	
Macroscopic, ulceration	39/114	70/122	0.51 (0.31–0.86)	
Macroscopic, no ulceration	52/141	75/166	0.79 (0.50–1.26)	
***BRAF* mutation status**				0.89
Wild type	69/233	97/214	0.61 (0.41–0.92)	
V600E mutation	54/186	94/209	0.59 (0.38–0.92)	
All patients	135/514	216/505	0.57 (0.43–0.74)	
	(26.3%)	(42.8%)		



Adapted from Eggermont AMM, *et al.* 2018.[1]

Click here to see RFS plots by *BRAF*-mutation status

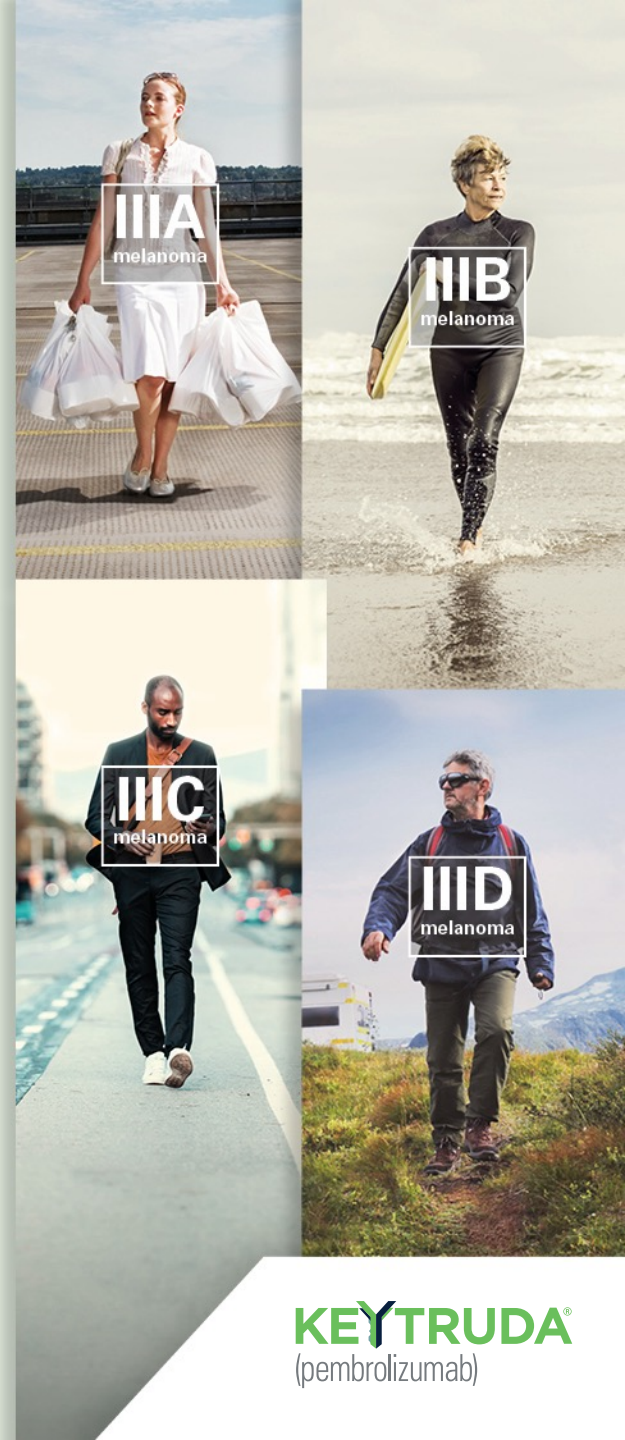
IA1 data cut-off: 2 October 2017.[1]
Duration of treatment: Q3W for 18 doses (~1 year). Stratified by Stage given at randomisation.[1]
The green diamond is centred on the overall HR (dashed line) and covers its 98.4% CI. The subgroups were not analysed for statistical significance.[1]
*Small patient sample can be a limitation. The subgroups were not analysed for statistical significance and not powered to show efficacy in individual subgroups.
†Unstratified HR. 98.4% CI covers the overall HR. 99% CI is presented for subgroup analysis.[1]
CI, confidence interval; HR, hazard ratio; IA, interim analysis; Q3W, every 3 weeks; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

KEYNOTE-054

Safety Data From Primary Analysis For RFS (15.1-Month Median Follow-Up)



Similar Proportions Of KEYTRUDA And Placebo Patients Completed Treatment[1]

	KEYTRUDA (n=514)	Placebo (n=505)
Started allocated treatment	n=509	n=502
Reasons for discontinuation, n (%)		
Normal completion (1-year)	282 (55.4)	294 (58.6)
Disease recurrence	109 (21.4)	179 (35.7)
Adverse event	70 (13.8)	11 (2.2)
Owing to an adverse event	66 (13)	8 (1.6)
Patient/investigator decision	18 (3.5)	6 (1.2)
Other malignancy	4 (0.8)	4 (0.8)
Non-compliance/other reason	7 (1.4)	1 (0.2)
Still on treatment at follow-up, n	19 (3.7)	6 (1.2)
Median (IQR) doses received per patient	18 (9–18)	18 (8–18)

Adapted from Eggermont AMM, *et al.* 2018.[1]

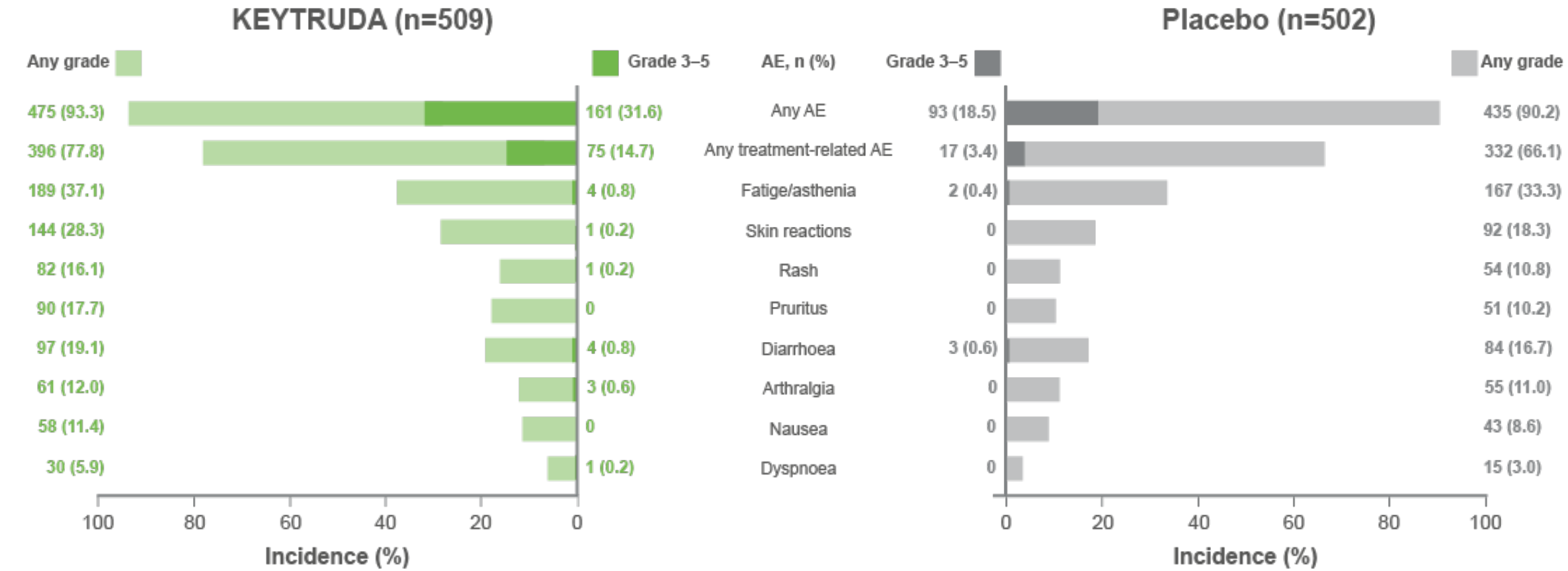
Refer to the SmPC and Risk Management Materials for further details on AEs before prescribing.

IA1 data cut-off: 2 October 2017.[1]
AE, adverse event; IA, interim analysis; IQR, interquartile range; SmPC, Summary of Product Characteristics.
1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

Grade 3–5 AEs Were More Common In Patients Receiving KEYTRUDA Than Patients Receiving Placebo[1]

AEs that occurred in at least 10% of patients or those that were considered to be medically relevant.



Adapted from Eggermont AMM, *et al.* 2018.[1]

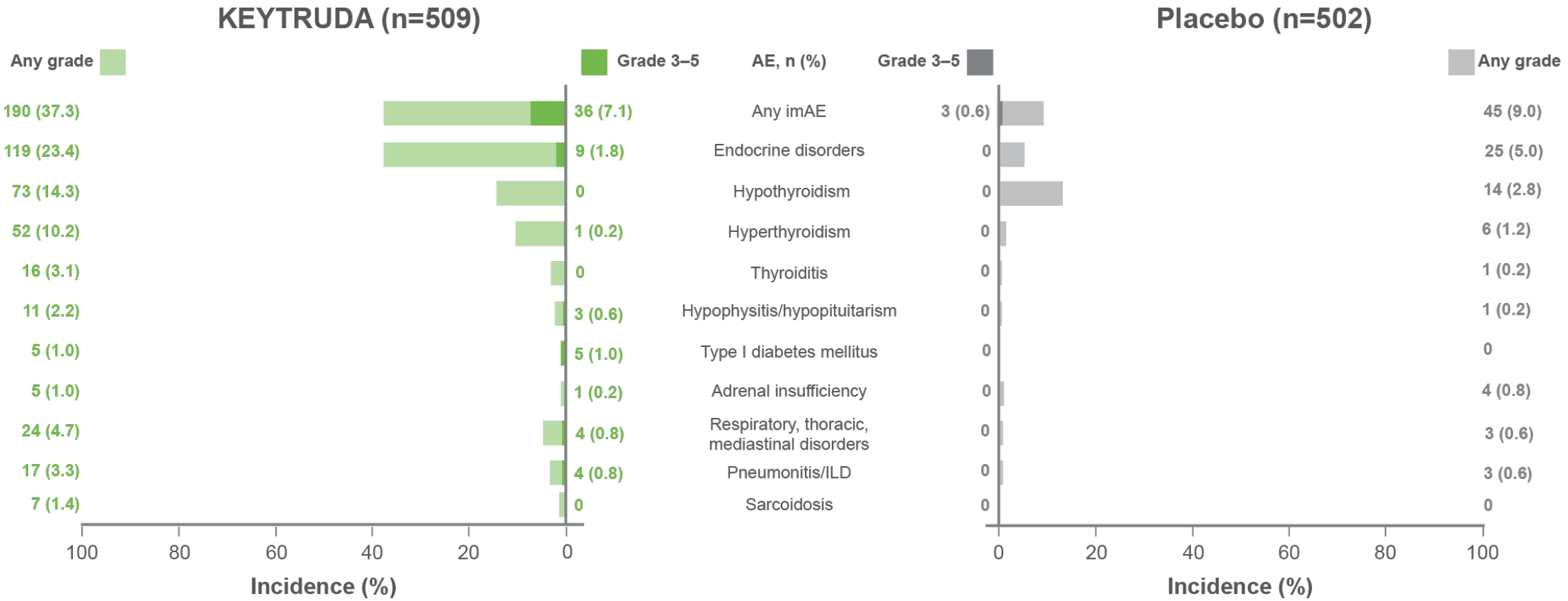
Refer to the SmPC and Risk Management Materials for further details on AEs before prescribing.

IA1 data cut-off: 2 October 2017.[1] 0.2% represents one patient.
AE, adverse event; IA, interim analysis; SmPC, Summary of Product Characteristics.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

Immune-Mediated Adverse Events Were Observed In Patients With KEYTRUDA[1] (1/2)



Adapted from Eggermont AMM, *et al.* 2018.[1]

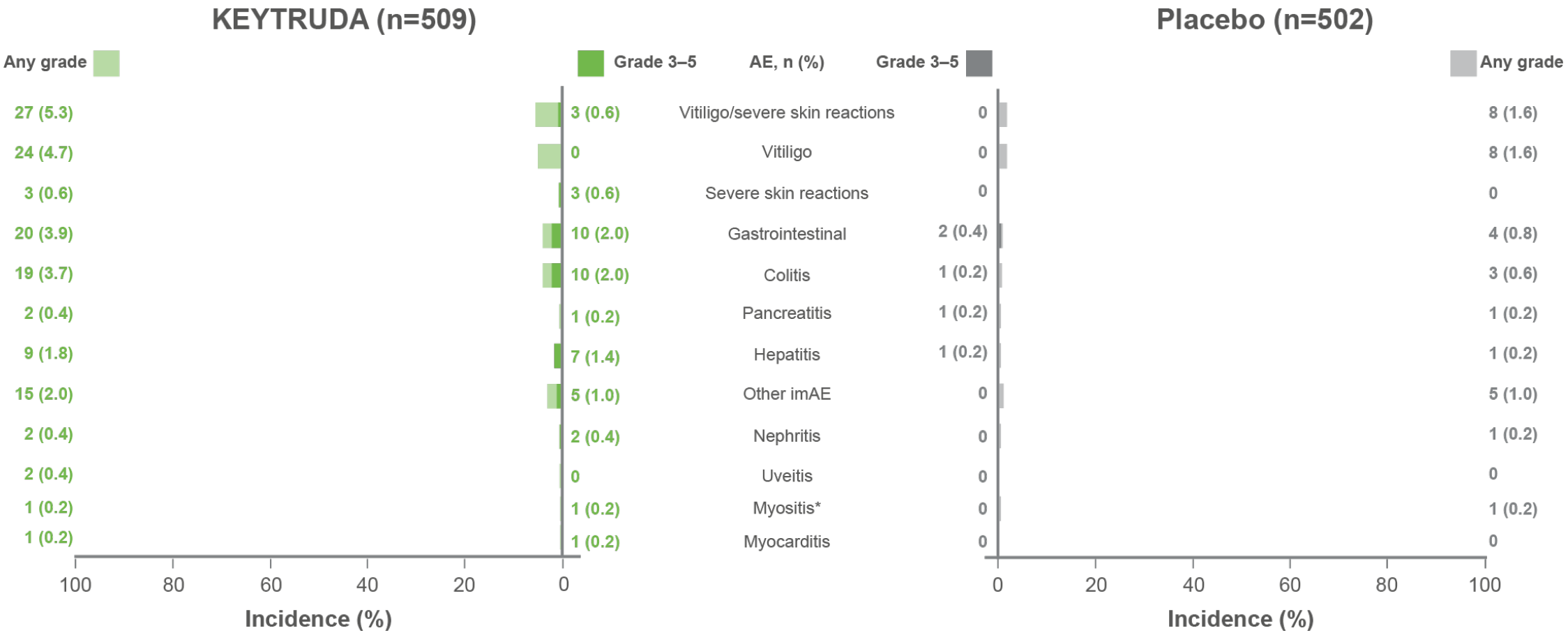
Refer to the SmPC and Risk Management Materials for further details on AEs before prescribing.

IA1 data cut-off: 2 October 2017.[1] 0.2% represents one patient.
AE, adverse event; IA, interim analysis; ILD, interstitial lung disease; imAE, immune-mediated adverse event; SmPC, Summary of Product Characteristics.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

Immune-Mediated Adverse Events Were Observed In Patients With KEYTRUDA[1] (2/2)



Adapted from Eggermont AMM, *et al.* 2018.[1]

Refer to the SmPC and Risk Management Materials for further details on AEs before prescribing.

IA1 data cut-off: 2 October 2017.[1] 0.2% represents one patient.
*There was one KEYTRUDA-related death (Grade 5) due to myositis.
AE, adverse event; IA, interim analysis; imAE, immune-mediated adverse event; SmPC, Summary of Product Characteristics.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

KEYNOTE-054: Summary Of The Primary Analysis For RFS[1,2]

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- KEYNOTE-054 study was designed in collaboration with the EORTC[1]
- KEYNOTE-054 met its primary endpoint of a significant improvement in RFS with KEYTRUDA vs placebo (a previously established standard of care: watch and wait)[1]
  - ITT overall population: HR: 0.57 (95% CI: 0.43–0.74), p<0.0001 demonstrated a 43% risk reduction in disease recurrence
  - PD-L1-positive population: HR: 0.54 (95% CI: 0.42–0.69), p<0.0001 demonstrated a 46% risk reduction in disease recurrence
- Consistent results across pre-specified subgroups with HRs favouring KEYTRUDA over placebo

- Safety profile consistent with the toxicity spectrum that has already been defined for KEYTRUDA[1,2]
  - Any grade imAEs occurred in 190 (37.3%) of patients treated with KEYTRUDA vs 45 (9.0%) with placebo
  - A total of 43 Grade 3–4 imAEs occurred in 36 (7.1%) of patients treated with KEYTRUDA
  - Endocrine disorders occurred in 23.4% of patients treated with KEYTRUDA vs 5.0% with placebo. The most common were hypothyroidism and hyperthyroidism
- Most imAEs were managed and resolved with established treatment algorithms
- Data remain blinded for OS

IA1 data cut-off: 2 October 2017.[1]
CI, confidence interval; DMFS, distant metastasis-free survival; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; IA, interim analysis; imAE, immune-mediated adverse event; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; OS; overall survival; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont A, *et al.* Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325-MG/Keynote 054 double-blinded Phase III trial. AACR Annual Meeting. 14–18 April 2018, Chicago, IL, USA. Abstract: LBA-10526.

KEYTRUDA® (pembrolizumab)

Trial Analyses[1,2]

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1

Primary analysis for RFS[1]

Primary efficacy endpoint and safety

- Cut-off date (2 October 2017); median duration of follow-up: 15.1 months (KEYTRUDA monotherapy: 14.7 months; placebo: 15.4 months); 351 RFS events
- IDMC recommendation: reveal RFS results and safety; DMFS results reported in final interim analysis, study ongoing for OS

3

Primary analysis for DMFS[2]

Primary efficacy endpoint and safety

- Cut-off date (3 April 2020); median duration of follow-up: 42.3 months (KEYTRUDA monotherapy: 42.2 months; placebo: 42.5 months); 491 RFS events
- Safety remained unchanged from previous results

Click here to view the Primary analysis for DMFS data

5

5-year follow-up[3]

Primary efficacy endpoint and safety

- Cut-off date (17 January 2022); median duration of follow-up: 4.9 years (KEYTRUDA monotherapy: 4.9 years; placebo: 4.9 months); 532 RFS events; 470 DMFS events
- Long-term follow-up analysis

Click here to view the 5-year follow-up data

RFS was defined as the time from randomisation until the date of first recurrence (local, regional or distant metastasis) or death from any cause.[1]

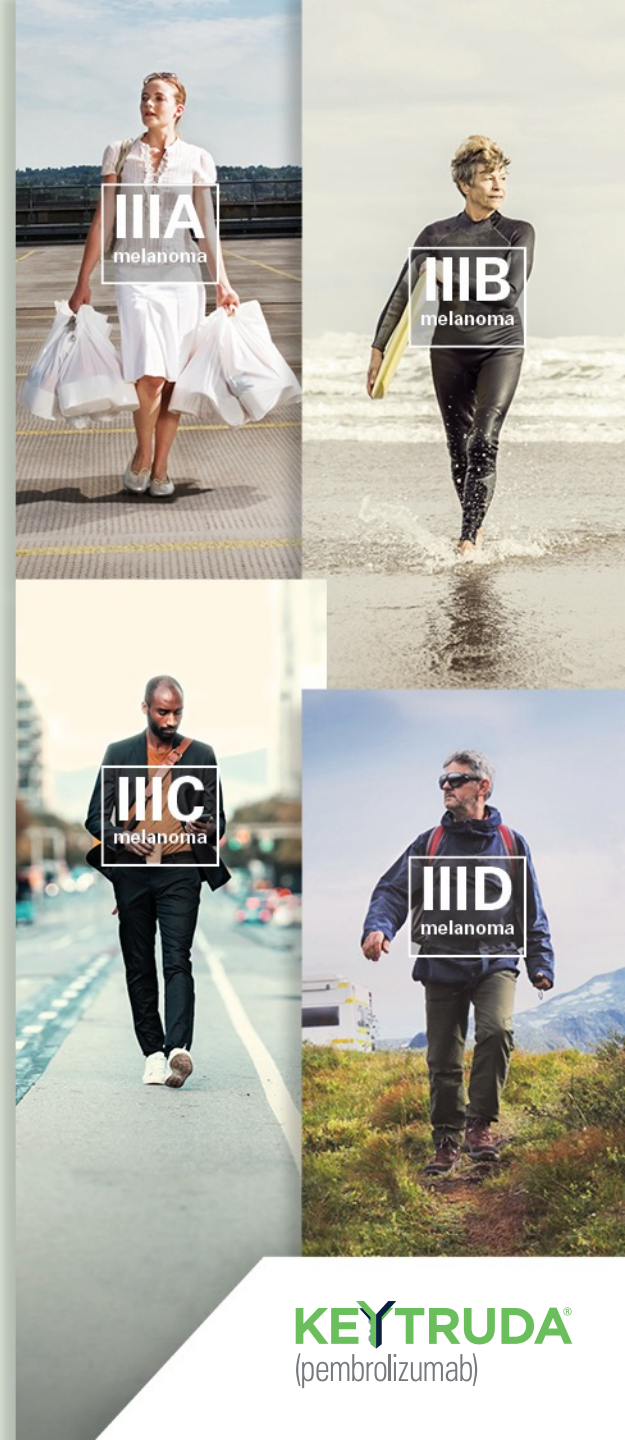
DMFS, distant metastasis-free survival; IDMC, Independent Data and Safety Monitoring Committee; OS, overall survival; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654; **3.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214.

KEYTRUDA® (pembrolizumab)

KEYNOTE-054

Efficacy Data From The Primary Analysis For DMFS (42.3-Month Median Follow-Up)

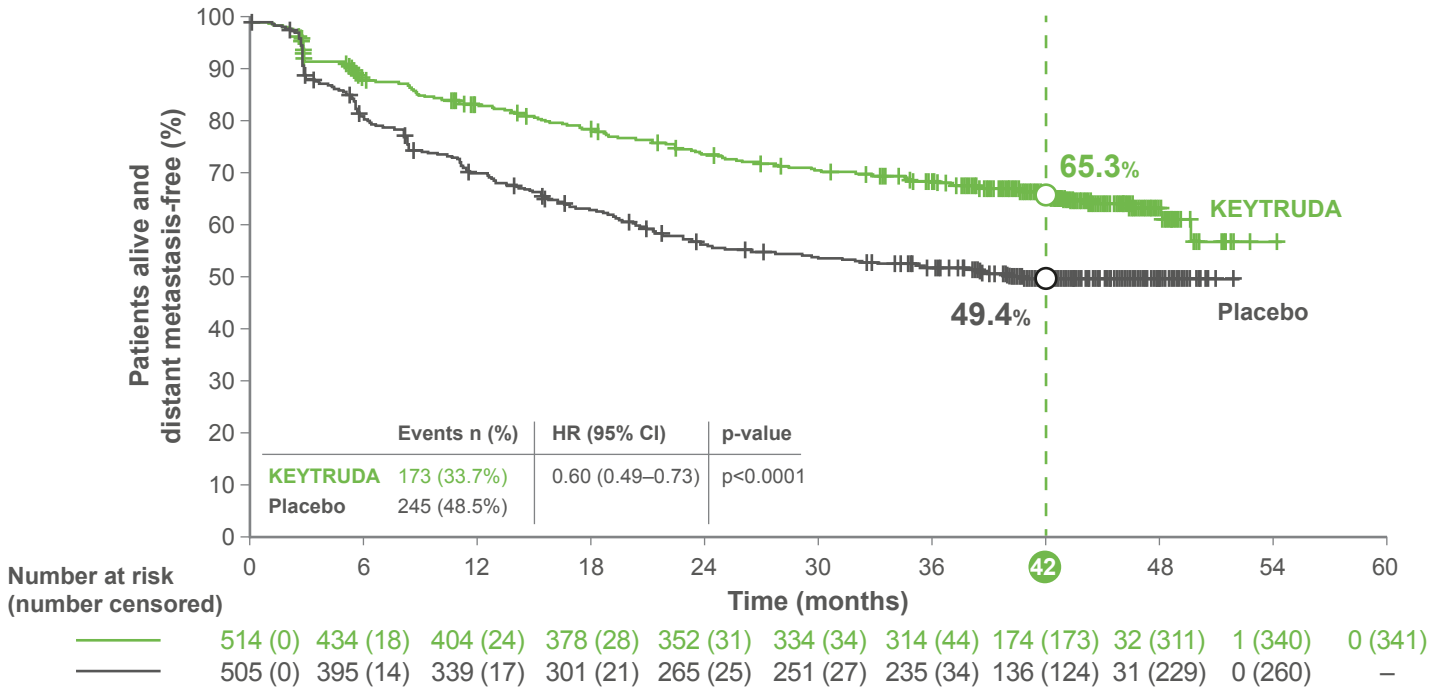


KEYNOTE-054 – Primary Analysis For DMFS

DMFS Was Significantly Higher In Patients Treated With KEYTRUDA Vs Placebo At A Median Follow-up Of 42.3 Months[1]

Secondary endpoint: DMFS in the ITT population[1]

Median follow-up: 42.3 months[1]



HR: 0.60 demonstrated a 40% risk reduction in distant metastasis with KEYTRUDA vs placebo[1]

Adapted from Eggermont AMM, *et al.* 2021.[1]

Data cut-off: 3 April 2020.[1]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month analysis.[1]
CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

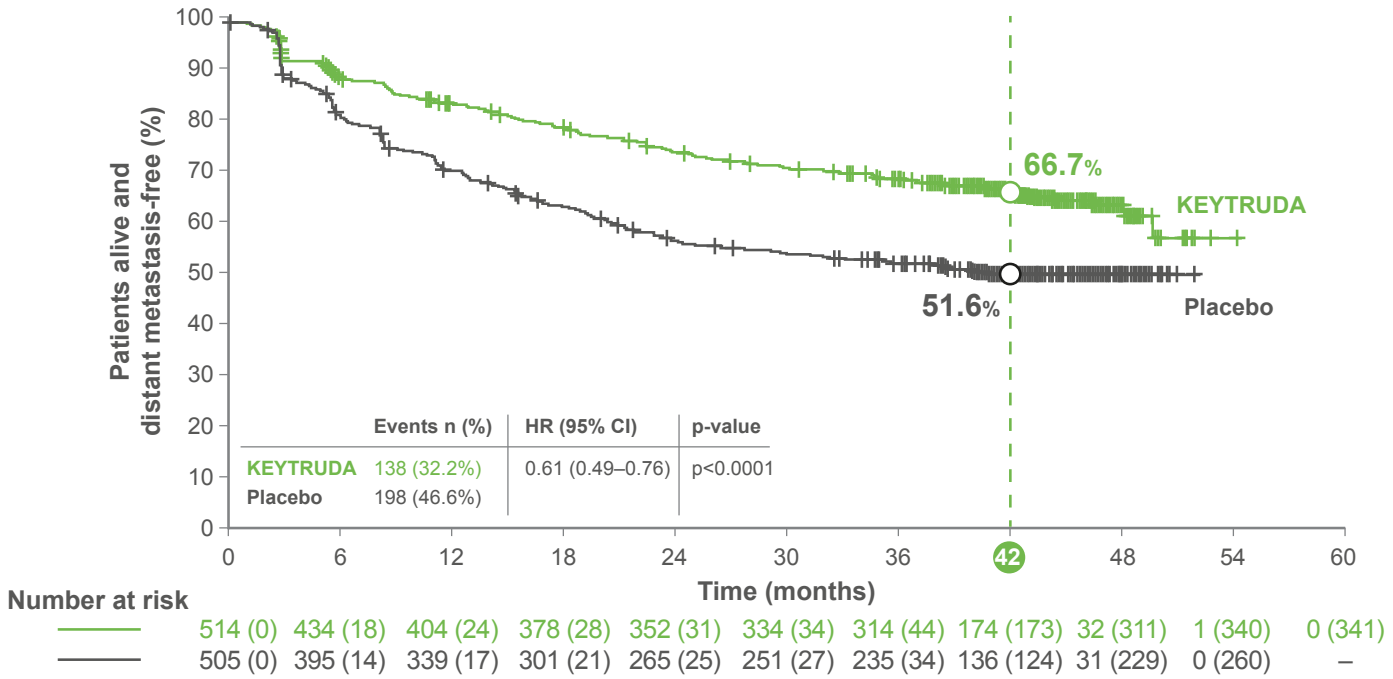
KEYTRUDA® (pembrolizumab)

KEYNOTE-054 – Primary Analysis For DMFS

Significant Increases In DMFS Were Also Seen In Patients With PD-L1-Positive Tumours Treated With KEYTRUDA Vs Placebo[1]

Secondary endpoint: DMFS in the PD-L1-positive population[1]

Median follow-up: 42.3 months[1]



HR: 0.61 demonstrated a 39% risk reduction in distant metastasis with KEYTRUDA vs placebo[1]

Adapted from Eggermont AMM, *et al.* 2021.[1]

Data cut-off: 3 April 2020.[1]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month analysis.[1]
CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

KEYTRUDA® (pembrolizumab)

Trial Analyses[1,2]

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1

Primary analysis for RFS[1]

Primary efficacy endpoint and safety

- Cut-off date (2 October 2017); median duration of follow-up: 15.1 months (KEYTRUDA monotherapy: 14.7 months; placebo: 15.4 months); 351 RFS events
- IDMC recommendation: reveal RFS results and safety; DMFS results reported in final interim analysis, study ongoing for OS

3

Primary analysis for DMFS[2]

Primary efficacy endpoint and safety

- Cut-off date (3 April 2020); median duration of follow-up: 42.3 months (KEYTRUDA monotherapy: 42.2 months; placebo: 42.5 months); 491 RFS events
- Safety remained unchanged from previous results

5

5-year follow-up[3]

Primary efficacy endpoint and safety

- Cut-off date (17 January 2022); median duration of follow-up: 4.9 years (KEYTRUDA monotherapy: 4.9 years; placebo: 4.9 months); 532 RFS events; 470 DMFS events
- Long-term follow-up analysis

Click here to view the 5-year follow-up data ›

RFS was defined as the time from randomisation until the date of first recurrence (local, regional or distant metastasis) or death from any cause.[1]

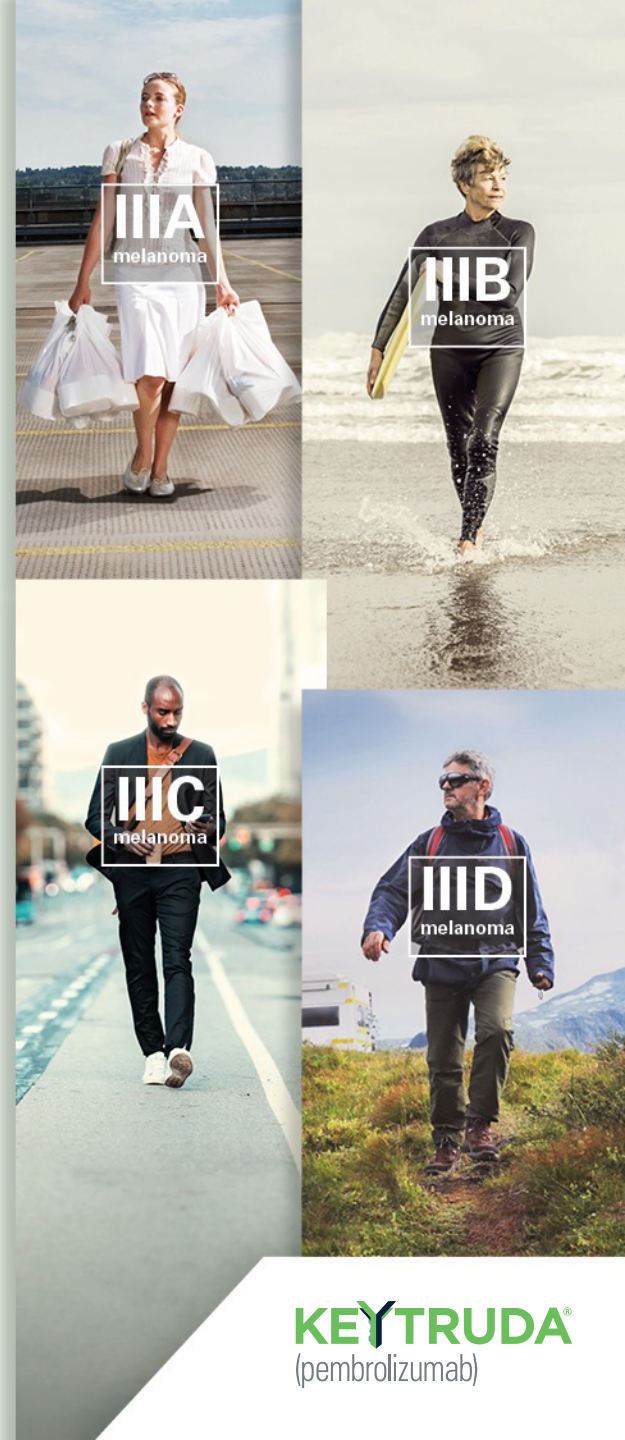
DMFS, distant metastasis-free survival; IDMC, Independent Data and Safety Monitoring Committee; OS, overall survival; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654; **3.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214.

KEYTRUDA® (pembrolizumab)

KEYNOTE-054

Efficacy Data From The 5-Year Follow-Up (4.9-Year Median Follow-Up)



RFS Analyses With KEYTRUDA Vs Placebo[1]

Click to navigate to the section of interest

Primary endpoints

- RFS in ITT population
- RFS in PD-L1-positive patients

Exploratory endpoint

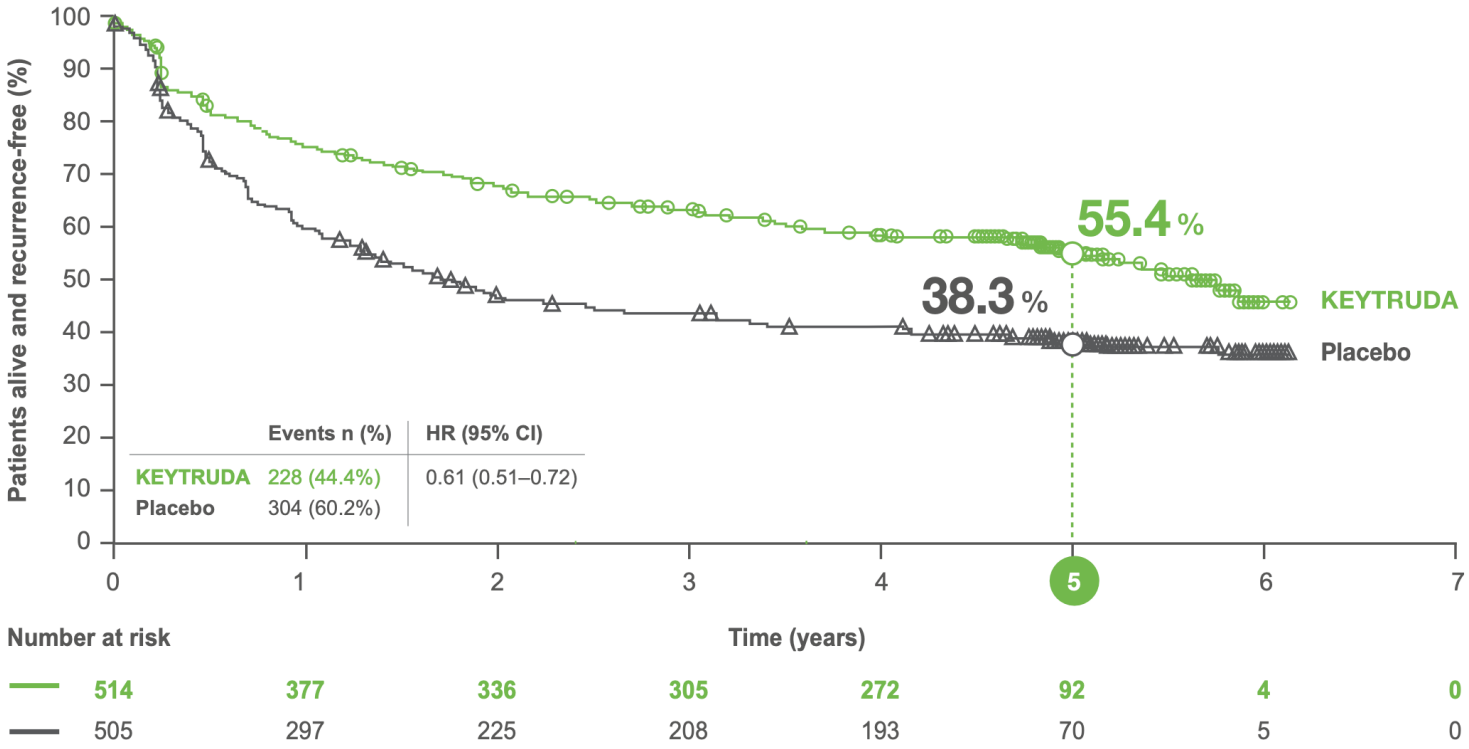
- RFS in PD-L1-negative patients

ITT, intent-to-treat; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214.

Patients Treated With KEYTRUDA Showed Higher RFS Vs Placebo At A Median Follow-Up Of 4.9 Years[1]

Exploratory long-term analysis; significance was not tested and no statistical conclusions can be drawn from this analysis*[1]
Primary endpoint: RFS in the ITT population[1]
Median follow-up: 4.9 years[1]



HR: 0.61 demonstrated a 39% reduction in disease recurrence with KEYTRUDA vs placebo[1]

Adjuvant administration of KEYTRUDA continues to provide greater RFS compared with placebo at a median 4.9 years of follow-up[1]

Adapted from Eggermont AMM, *et al.* 2022.[1]

Data cut-off: 17 January 2022.[1]
The HR and its CI were estimated using the Cox proportional hazards model stratified by Stage provided at randomisation.[1]
*Statistical significance was met in the initial analysis.[2]
CI, confidence interval; HR, hazard ratio; IA, interim analysis; ITT, intent-to-treat; RFS, recurrence-free survival.
1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. **2.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

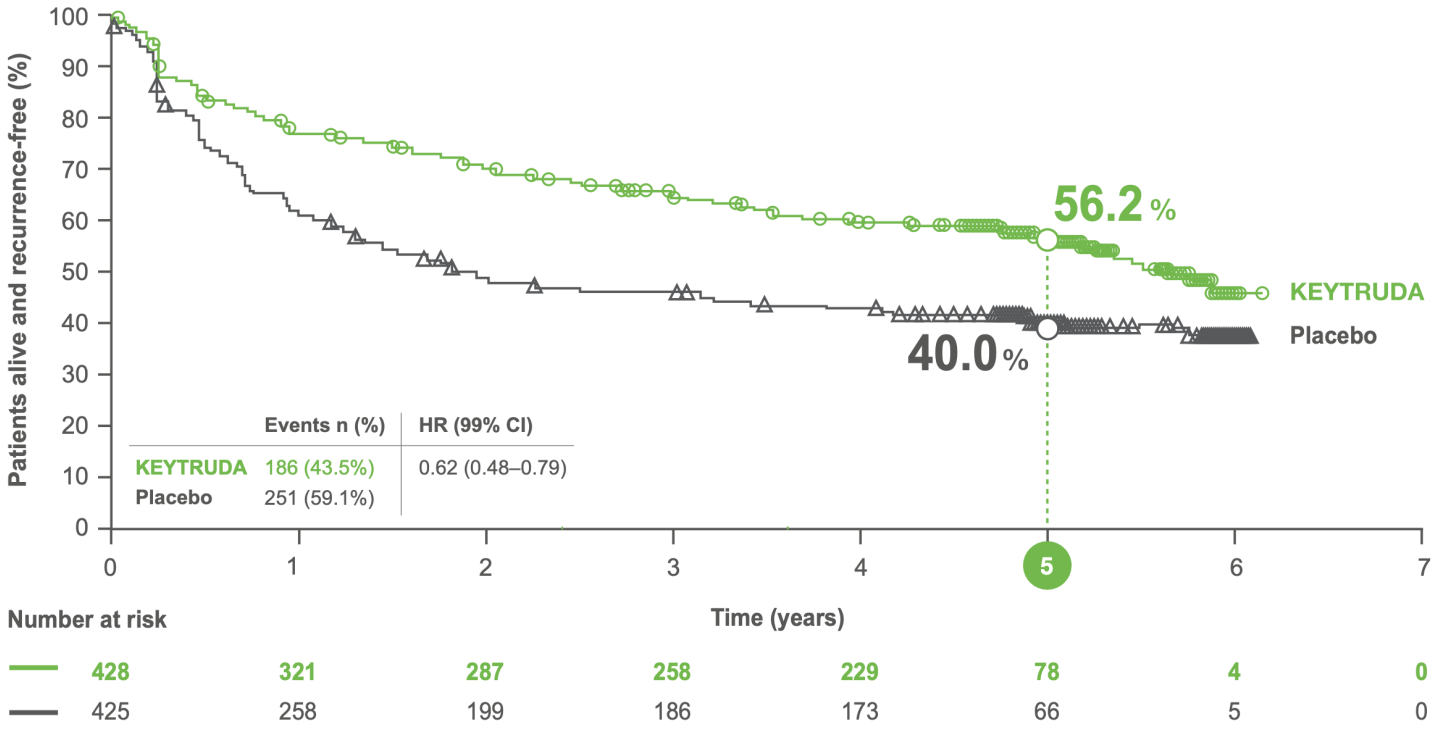
KEYNOTE-054 – 5-Year Follow-Up

KEYTRUDA Resulted In A Higher RFS In Patients With PD-L1-Positive Tumours Vs Placebo[1,2]

Exploratory long-term analysis; significance was not tested and no statistical conclusions can be drawn from this analysis*[1]

RFS in PD-L1-positive population[1]

Median follow-up: 4.9 years[1]



Adapted from Eggermont AMM, *et al.* 2022.[2]

HR: 0.62 demonstrated a 38% reduction in disease recurrence with KEYTRUDA vs placebo[1]

KEYTRUDA resulted in higher RFS in patients with PD-L1-positive and PD-L1-negative tumours vs placebo[1,2]

Data cut-off: 17 January 2022.[1]

The HR and its CI were estimated using the Cox proportional hazards model stratified by Stage provided at randomisation.[1]

*Statistical significance was met in the initial analysis.[3]

CI, confidence interval; HR, hazard ratio; IA, interim analysis; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **3.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

Distant Metastasis-Free Survival Analyses With KEYTRUDA Vs Placebo[1]

Click to navigate to the section of interest

Secondary endpoints

- DMFS in ITT population
- DMFS in PD-L1-positive patients
- DMFS in Stage IIIA patients
- DMFS in Stage IIIB patients
- DMFS in Stage IIIC patients
- DMFS in *BRAF-V600E/K* mutated patients
- DMFS in *BRAF*-WT patients
- DMFS across *BRAF* mutation subgroups
- DMFS according to subgroups

DMFS, distant metastasis-free survival; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; WT, wild type.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214.

KEYTRUDA® (pembrolizumab)

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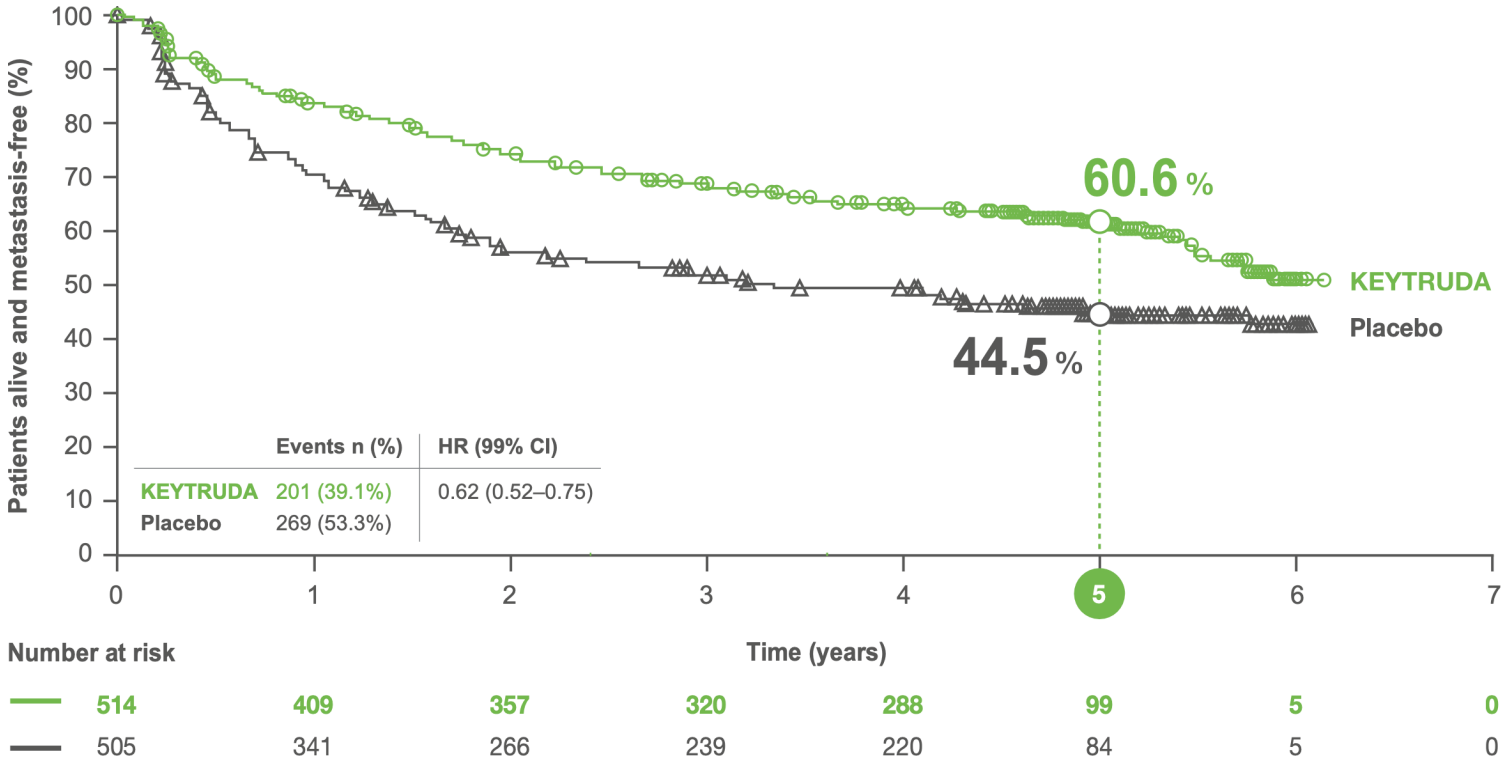
DMFS Was Higher In Patients Treated With KEYTRUDA Vs Placebo At A Median Follow-up Of 4.9 Years[1]

Subgroup analysis was pre-specified but not statistically powered for comparison.*[1]
Secondary endpoint: DMFS in the ITT population[1]
Median follow-up: 4.9 years[1]



Adapted from Eggermont AMM, *et al.* 2022.[1]

HR: 0.62 demonstrated a 38% reduction in distant metastasis with KEYTRUDA vs placebo[1]

Data cut-off: 17 January 2022.[1]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the final 42.3-month and 4.9-year analyses.[1]
*Statistical significance was met in the final analysis.[2]
CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. **2.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

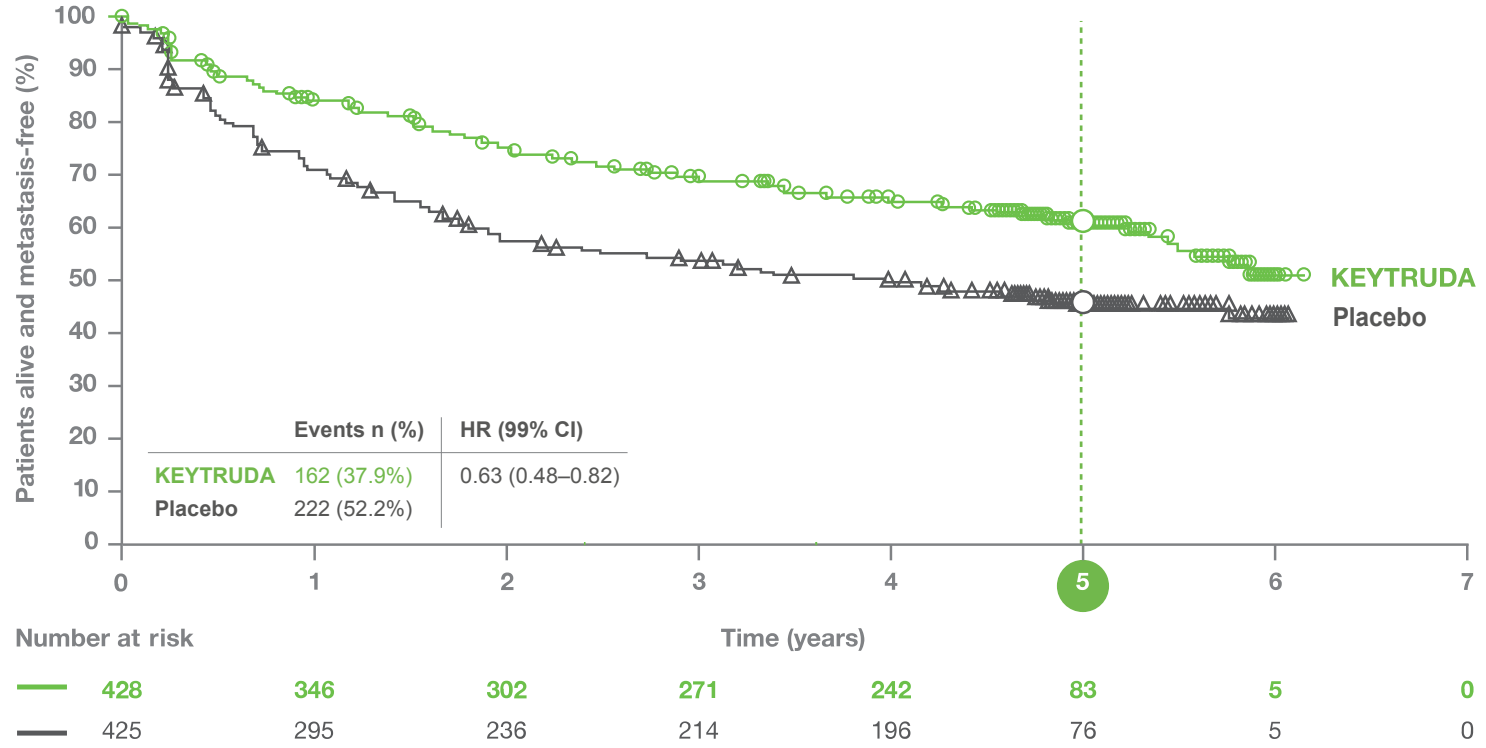
KEYTRUDA® (pembrolizumab)

KEYNOTE-054 – 5-Year Follow-Up

Increases In DMFS Were Also Seen In Patients With PD-L1-Positive Tumours Treated With KEYTRUDA Vs Placebo[1]

Exploratory long-term analysis; significance was not tested and no statistical conclusions can be drawn from this data.*[1]
Secondary endpoint: DMFS in PD-L1-positive population[1]

Median follow-up: 4.9 years[1]



Adapted from Eggermont AMM, *et al.* 2022.[2]

HR: 0.63 demonstrated a 37% reduction in distant metastasis with KEYTRUDA vs placebo[2]

Data cut-off: 17 January 2022.[1]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses.[1,3]
Staging was performed according to AJCC 7th edition pathologic staging criteria for melanoma.[1]
*The overall HR is given with 95% CI.
AJCC, American Joint Committee on Cancer; CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **3.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

KEYTRUDA® (pembrolizumab)

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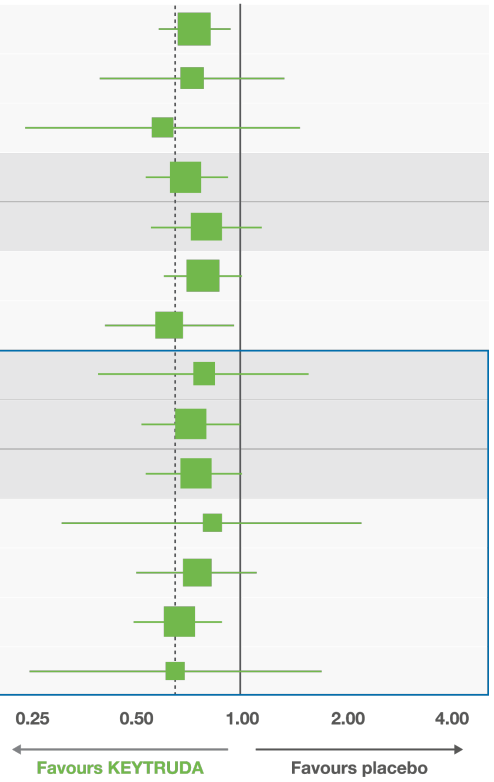
KEYTRUDA Showed Consistent DMFS Across Staging Classifications At A Median Follow-Up Of 4.9 Years[1,2]

Subgroup analysis was pre-specified but not statistically powered for comparison.*[1]
Secondary endpoint: DMFS in the ITT population according to subgroups[1]
Median follow-up: 4.9 years[2]

		KEYTRUDA (n/N)	Placebo (n/N)	HR (99% CI)*
PD-L1	Positive	162/428	222/425	0.63 (0.48–0.82)
	Negative	27/59	32/57	0.62 (0.31–1.21)
	Indeterminate	12/27	15/23	0.50 (0.18–1.36)
Sex	Male	131/324	171/304	0.59 (0.44–0.80)
	Female	70/190	98/201	0.68 (0.45–1.02)
Age, years	<65	152/389	192/379	0.67 (0.50–0.88)
	≥65	49/125	77/126	0.52 (0.32–0.83)
AJCC 7th ed.	IIIA	20/77	26/75	0.67 (0.31–1.44)
	IIIB	89/239	120/231	0.61 (0.42–0.87)
	IIIC	92/198	123/199	0.63 (0.44–0.89)
AJCC 8th ed.	IIIA	10/42	13/40	0.71 (0.24–2.10)
	IIIB	56/163	88/189	0.63 (0.41–0.98)
	IIIC	114/267	145/239	0.56 (0.40–0.77)
	IIID	10/20	14/19	0.54 (0.19–1.58)



Adapted from Eggermont AMM, *et al.* 2022.[1]

Data cut-off: 17 January 2022.[2]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses.[2,3]
*The overall HR is given with 95% CI.
AJCC, American Joint Committee on Cancer; CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **3**. Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

KEYTRUDA® (pembrolizumab)

DMFS and RFS Over The Full Study Period[1]

Median follow-up: 4.9 years[2]

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Distant metastasis-free survival status, n (%)	KEYTRUDA (n=514)	Placebo (n=505)
No event	313 (61)	236 (47)
Event	201 (39)	269 (53)
Distant metastasis*	187 (36)	264 (52)
Lymph node	65 (13)	91 (18)
Lung	68 (13)	108 (21)
Liver	40 (8)	57 (11)
Bone	21 (4)	35 (7)
Brain	29 (6)	38 (8)
Skin	14 (3)	25 (5)
Other soft tissues	28 (5)	43 (9)
Other site	24 (5)	40 (8)
Death not due to melanoma†	9 (2)	3 (<1)
Death due to melanoma, no distant metastasis reported	5 (1)	2 (<1)

Recurrence-free survival status, n (%)	KEYTRUDA (n=514)	Placebo (n=505)
No event	286 (56)	201 (40)
Event	228 (44)	304 (60)
Recurrence	228 (44)	304 (60)
Locoregional recurrence only	74 (14)	96 (19)
Distant metastasis only	133 (26)	174 (35)
Both, diagnosed within 30 days of each other	10 (2)	32 (6)
Death not due to melanoma, including unknown type of recurrence	9 (2)	2 (<1)
Death, no recurrence reported†	2 (<1)	0

Adapted from Eggermont AMM, *et al.* 2022.[1]

Data cut-off: 17 January 2022.[2]

*Distant metastasis occurring as first type of recurrence or after a locoregional recurrence; the different types of sites involved are indicated; one patient might have several sites involved.[1]

†One patient (<1%) died due to myositis in the KEYTRUDA group; all others died due to causes of death unrelated to treatment allocated by randomisation.[1]

DMFS, distant metastasis-free survival; RFS, recurrence-free survival.

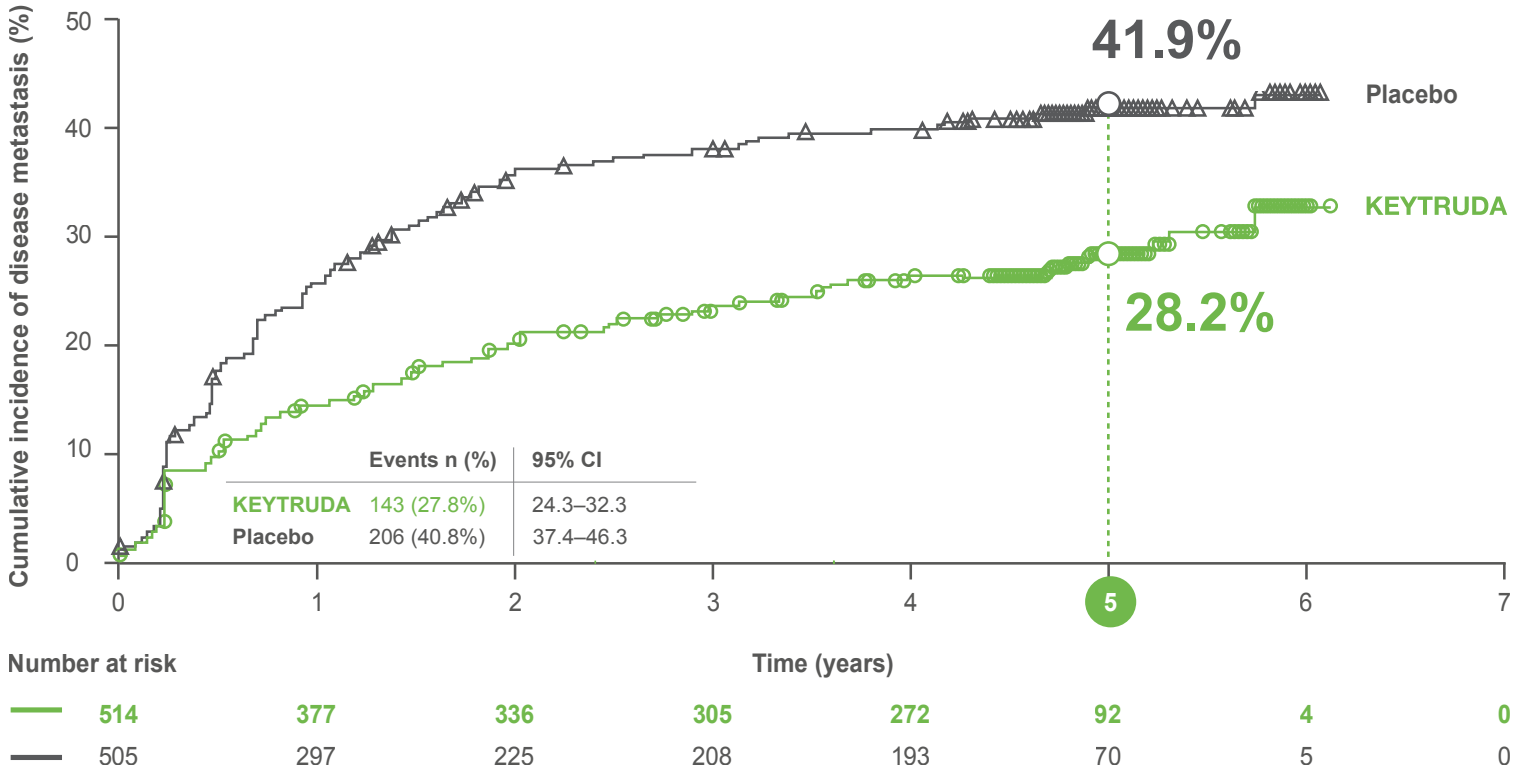
1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214.

KEYTRUDA® (pembrolizumab)

Patients Treated With Adjuvant KEYTRUDA Therapy Showed A Lower Cumulative Incidence Of Distant Metastases As First Type Of Recurrence Vs Placebo[1,2]

Cumulative incidence of distant metastases as first type of recurrence

Median follow-up: 4.9 years[2]



Adapted from Eggermont AMM, *et al.* 2022.[1,2]

The 5-year cumulative incidence of distant metastasis as first type was 28.2% and 41.9% in the KEYTRUDA and placebo groups, respectively*[2]

Data cut-off: 17 January 2022.[1]

*5-year cumulative incidence of distant metastasis as the first type of recurrence. Adjuvant KEYTRUDA group: 28.2% (95% CI: 24.3–32.3); 41.9% (95% CI: 37.4–46.3).[2]

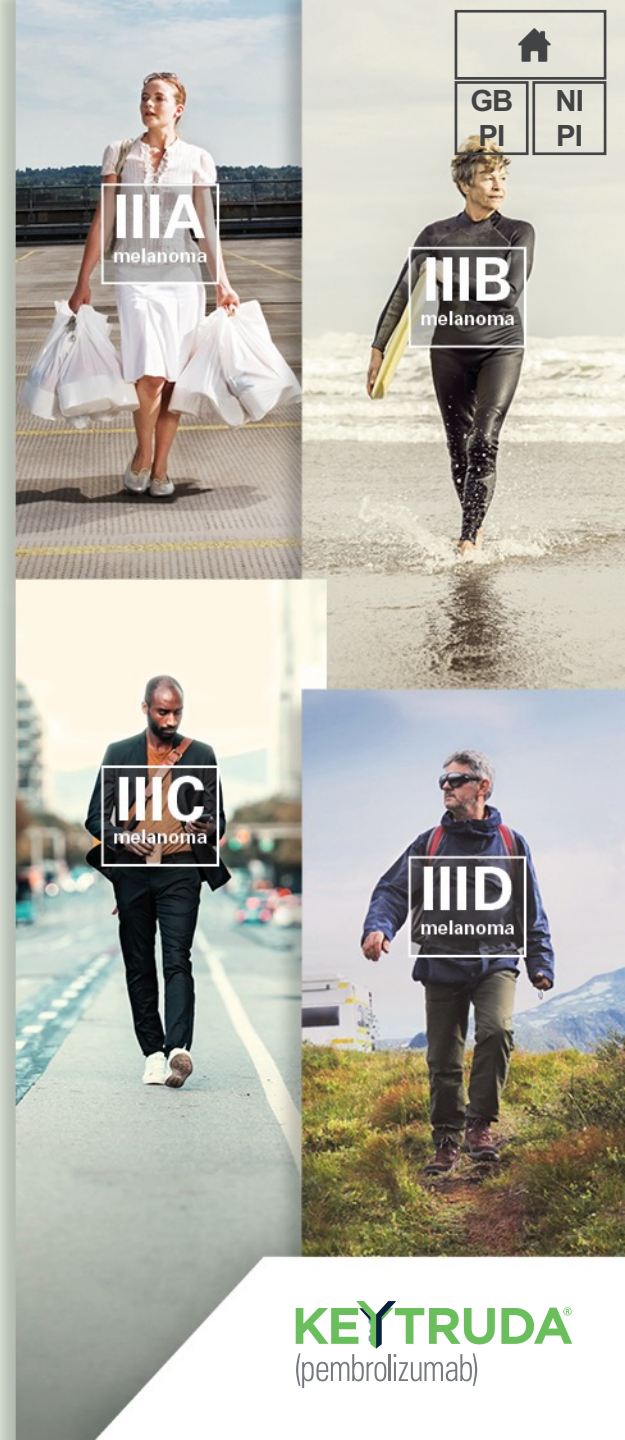
CI, confidence interval.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214.

KEYTRUDA® (pembrolizumab)

KEYNOTE-054

Safety Data From The 5-Year Follow-Up (4.9-Year Median Follow-Up)



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At The 5-Year Follow-Up, Serious Treatment-Related AEs Were Reported In Nine Patients Receiving KEYTRUDA And One Patient Receiving Placebo*[1]

Treatment-related serious AEs reported during follow-up treatment with KEYTRUDA*

Median follow-up: 4.9 years[1]

	Grade	Number of patients
AE		
Allergic oedema	3	1
Diarrhoea	3	2
Enteritis	3	1
Immune thrombocytopenia	4	1
Immune-mediated enterocolitis	4	1
Myositis	5	1
Plasmacytoma	3	1
Pneumonitis	3	1

Adapted from Eggermont AMM, *et al.* 2022.[2]

Refer to the SmPC and Risk Management Materials for further details on AEs before prescribing.

Data cut-off: 17 January 2022.[1]

*Only serious treatment-related AEs were requested to be reported during the follow-up period starting 90 days after treatment administration.[1]

AE, adverse event; SmPC, Summary of Product Characteristics.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix.

KEYTRUDA® (pembrolizumab)

Patients With Stage III Melanoma Could Benefit From KEYTRUDA Treatment Similar To Those In The KEYNOTE-054 Trial

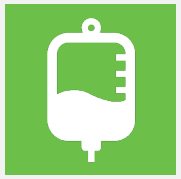
- Treatment with KEYTRUDA demonstrated **significant improvement in RFS** vs placebo (a previously established standard of care: watch and wait)[1]
  - ITT overall population: **HR: 0.57** (98.4% CI: 0.43–0.74), p<0.001 at 15.1 months median follow-up[1]
  - PD-L1-positive population: **HR: 0.54** (98.4% CI: 0.42–0.69), p<0.001 at 15.1 months median follow-up[1]
- Longer term follow-up of a median of **4.9 years** confirmed a **sustained RFS improvement of KEYTRUDA** vs placebo in the **ITT population and PD-L1-postive** population[2,3]
  - ITT overall population: **HR: 0.61 (**95% CI: 0.51–0.72), p<0.0001 at 4.9 years of follow-up[2]
  - PD-L1-positive population: **HR: 0.62** (99% CI: 0.48–0.79) at 4.9 years of follow-up[3]

- **DMFS was significantly higher** in patients treated with KEYTRUDA vs placebo at a median follow-up of 42.3 months[4] **and DMFS remained higher** in patients treated with KEYTRUDA vs placebo at a median follow-up of 4.9 years[2,3]
  - ITT overall population: **HR: 0.62** (95% CI: 0.52–0.75) at 4.9 years median follow-up[2]
  - PD-L1-positive population: **HR: 0.63** (99% CI: 0.48–0.82) at 4.9 years median follow-up[2]
  - KEYTRUDA was associated with **improvements in DMFS across Stages IIIA–C and *BRAF* mutation status vs placebo**[2,3]
- The safety profile of KEYTRUDA was consistent with previous studies in melanoma[1]

RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses.
CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival.
1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **3.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **4.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

KEYTRUDA® (pembrolizumab)

KEYTRUDA Offers Flexibility Of Dosing[1]



Administered as an IV infusion[1]

Over 30 minutes[1]

Adult patients

200 mg every **3** weeks

OR

400 mg every **6** weeks

Paediatric patients*

2 mg/kg bw every **3** weeks, up to a maximum of 200 mg

The 200 mg once every 3 weeks regimen has been assessed in Phase II and Phase III registration studies across a multitude of indications of KEYTRUDA. An exposure-response evaluation, using modelling and simulation, led to the approval of the 400 mg once every 6 weeks dosing for monotherapy and combination therapy.[1]

The recommended dose of KEYTRUDA as monotherapy in paediatric patients aged 12 years and older with melanoma is 2 mg/kg body weight (up to a maximum of 200 mg), every 3 weeks administered as an intravenous infusion over 30 minutes.[1]

What does the flexibility of dosing mean for you and your patients?

Please refer to the KEYTRUDA Summary of Product Characteristics and patient Risk Minimisation Materials before prescribing KEYTRUDA.

*Paediatric patients must be 12 years or older.

bw, bodyweight; IV, intravenous.

1. KEYTRUDA Summary of Product Characteristics. Available at: https://www.emcpi.com/pi/33162 (GB) and https://www.emcpi.com/pi/ni/378 (NI). Accessed April 2024.

KEYTRUDA® (pembrolizumab)

Find Out More About Stage III Melanoma

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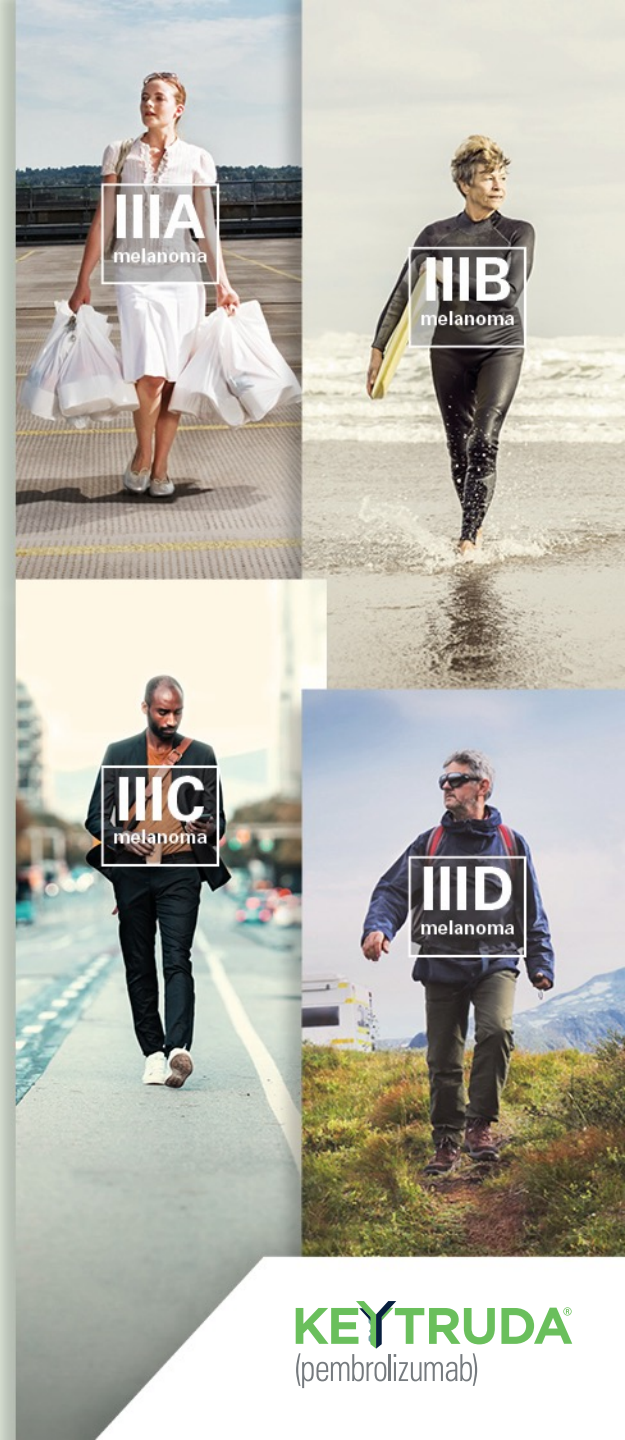
This link will take you to an MSD website within which you can give your consent to receive marketing or promotional emails from MSD about our products, services and events.

KEYTRUDA® (pembrolizumab)

KEYNOTE-054
Appendix

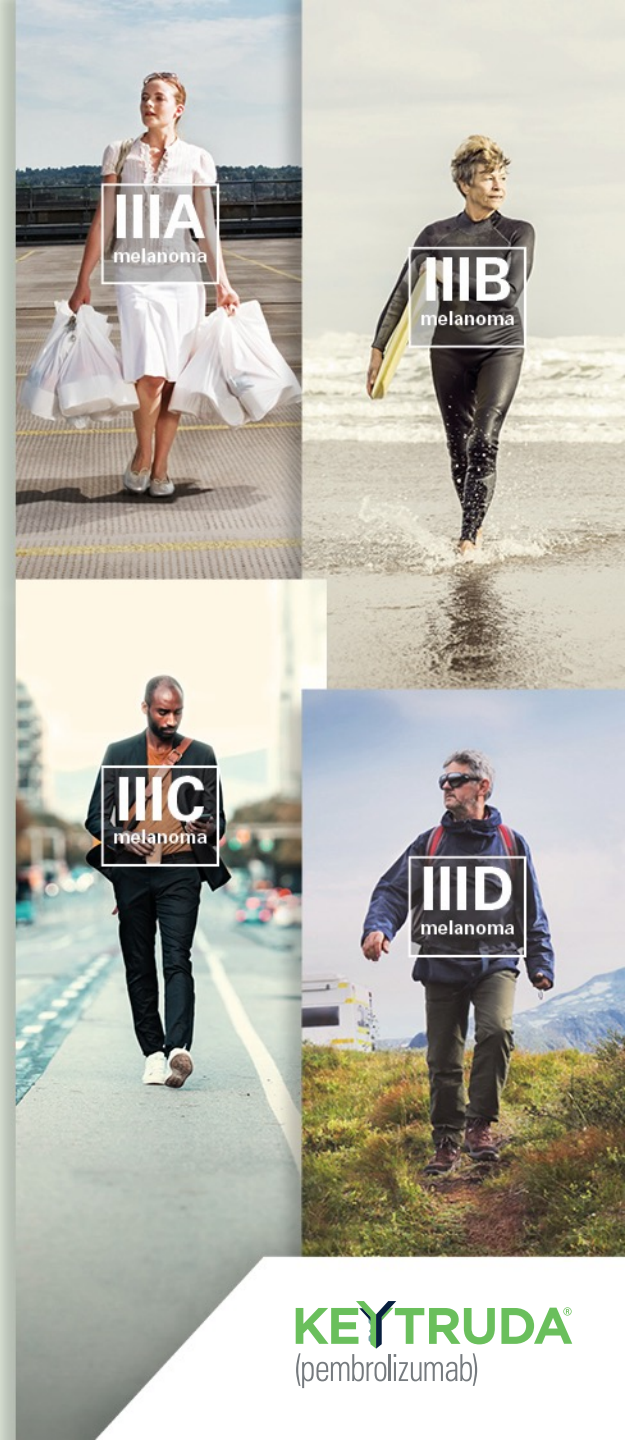


Patient Baseline Characteristics Appendix

Primary Analysis For RFS Appendix

5-Year Follow-Up Appendix

KEYNOTE-054
Baseline Patient Characteristics Appendix



Patient Baseline Characteristics (1/2)[1]

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	KEYTRUDA (n=514)	Placebo (n=505)
Median age, years	54	54
≥65 years, n (%)	125 (24)	126 (25)
Male, n (%)	324 (63)	304 (60)
Stage, n (%)*		
IIIA	80 (16)	80 (16)
IIIB	237 (46)	230 (46)
IIIC with 1–3 positive lymph nodes	95 (19)	93 (18)
IIIC with ≥4 positive lymph nodes	102 (20)	102 (20)
Ulceration, n (%)	208 (41)	197 (39)
1 vs 2–3 vs ≥4 positive lymph nodes (%)	44 vs 34 vs 21	47 vs 33 vs 20
Lymph node involvement, n (%)		
Microscopic	187 (36)	161 (32)
Macroscopic	327 (64)	344 (68)

Adapted from Eggermont AMM, *et al.* 2018.[1]

Click here to view study design

*According to AJCC 7th edition criteria.
AJCC, American Joint Committee on Cancer.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

Patient Baseline Characteristics (2/2)[1]

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	KEYTRUDA (n=514)	Placebo (n=505)
PD-L1 status, n (%)*		
Positive (MEL 2, 3, 4 or 5)	428 (83)	425 (84)
Negative (MEL 0 or 1)	59 (12)	57 (11)
Indeterminate	27 (5)	23 (5)
***BRAF* mutation status, n (%)**		
Wild type	233 (45)	214 (42)
V600E/K mutant	210 (41)	231 (46)
Other mutation	35 (7)	31 (6)
Unknown	36 (7)	29 (6)

Adapted from Eggermont AMM, *et al.* 2018.[1]

Of the 1019 patients randomised to KEYNOTE-054, ECOG PS was 0 in 94% of patients and 1 in 6% of patients.[2]

*PD-L1 expression was tested retrospectively by immunohistochemistry assay with the 22C3 anti-PD-L1 antibody. A positive score was defined as PD-L1 expression in ≥1% of tumour and tumour-associated immune cells relative to all viable tumour cells.[1]

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801; **2.** KEYTRUDA Summary of Product Characteristics. Available at: https://www.emcpi.com/pi/33162 (GB) and https://www.emcpi.com/pi/ni/378 (NI). Accessed April 2024.

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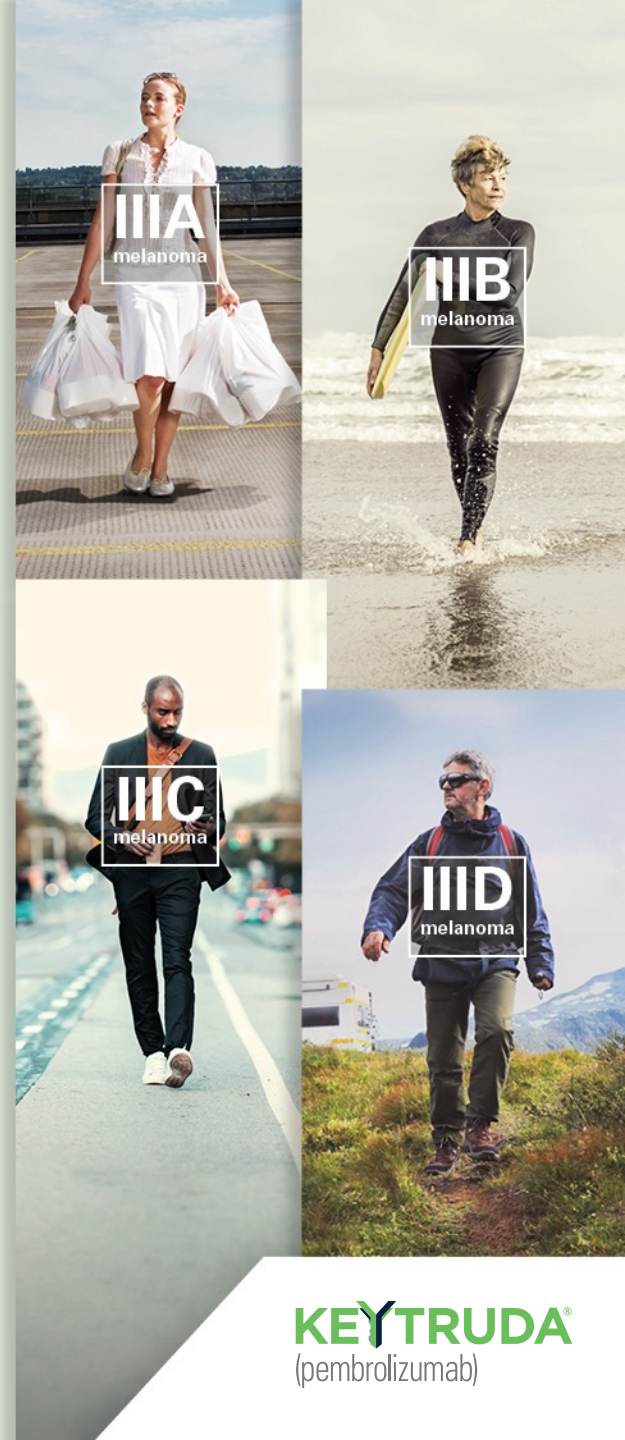
KEYTRUDA® (pembrolizumab)

KEYNOTE-054

Primary Analysis For RFS Appendix (15.1-Month Median Follow-Up)



Cumulative Incidence Of Distant Metastases As First Type Of Recurrence In Patients With Stage III Melanoma Receiving KEYTRUDA Or Placebo[1]

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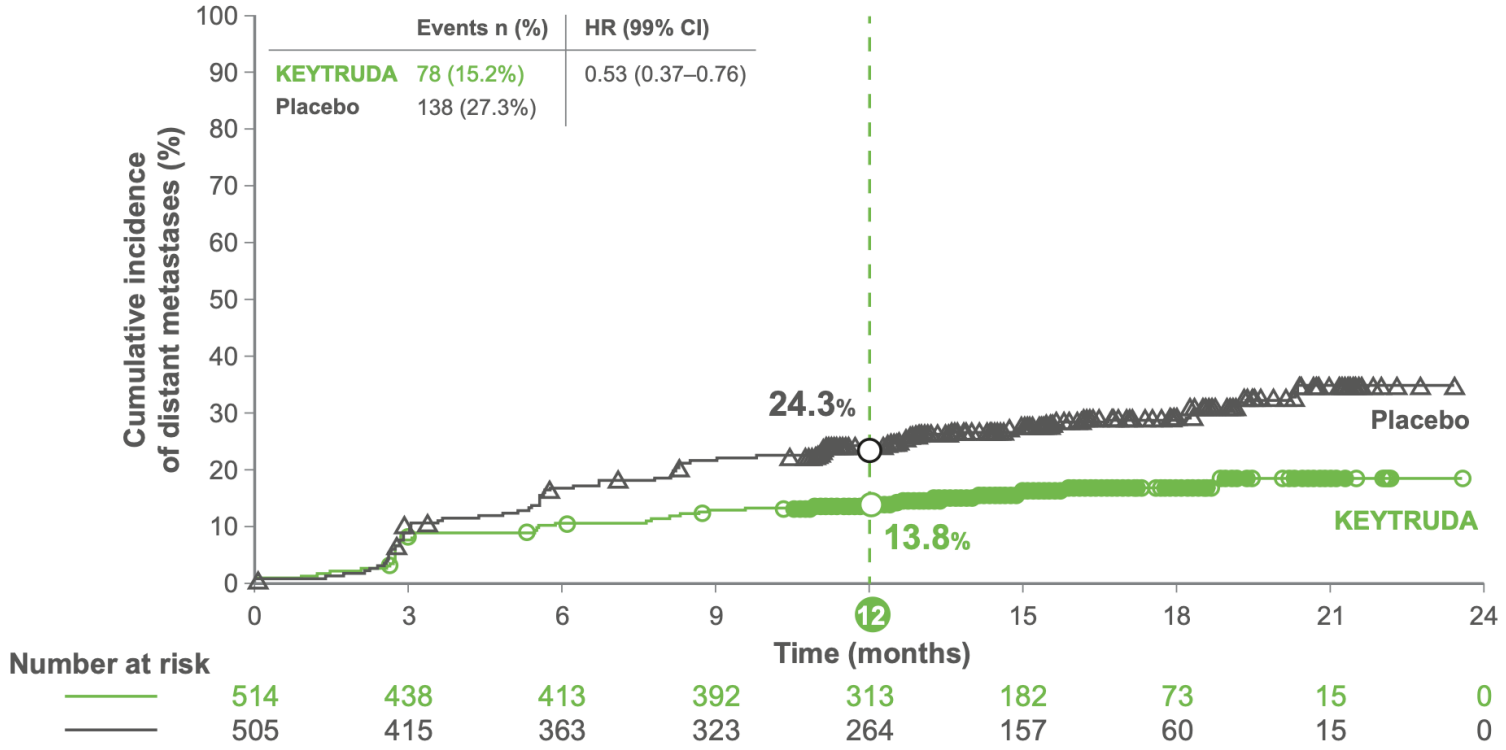
Cumulative incidence of distant metastases as first type of recurrence[1]



Adapted from Eggermont AMM, *et al.* 2018.[1]

Duration of treatment: Q3W for 18 doses (~1 year). Stratified by Stage given at randomisation.
CI, confidence interval; HR, hazard ratio; Q3W, every 3 weeks.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801. Supplementary appendix.

KEYTRUDA® (pembrolizumab)

Patients Receiving KEYTRUDA Adjuvant Therapy Had A Lower Relapse Rate Vs Placebo[1]

	KEYTRUDA (n=514)	Placebo (n=505)	
No RFS event, n (%)	379 (73.7)	289 (57.2)	
Locoregional recurrence only, n (%)	55 (10.7)	77 (15.2)	Relapse rate
Distant metastasis only, n (%)	**69 (13.4)**	**114 (22.6)**	**15.2 vs 27.4%**
Both, diagnosed within 30 days of each other, n (%)	**9 (1.8)**	**24 (4.8)**	
Death without an RFS event, n (%)	2 (0.4)	1 (0.2)	

Adapted from Eggermont AMM, *et al.* 2018.[1]

Duration of treatment: Q3W for 18 doses (~1 year). Stratified by Stage given at randomisation.[1]
Q3W, every 3 weeks; RFS, recurrence-free survival.

1. Eggermont A, *et al.* Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325-MG/Keynote-054 double-blinded Phase III trial. AACR Annual Meeting. 14–18 April 2018, Chicago, IL, USA. Abstract: LBA-10526.

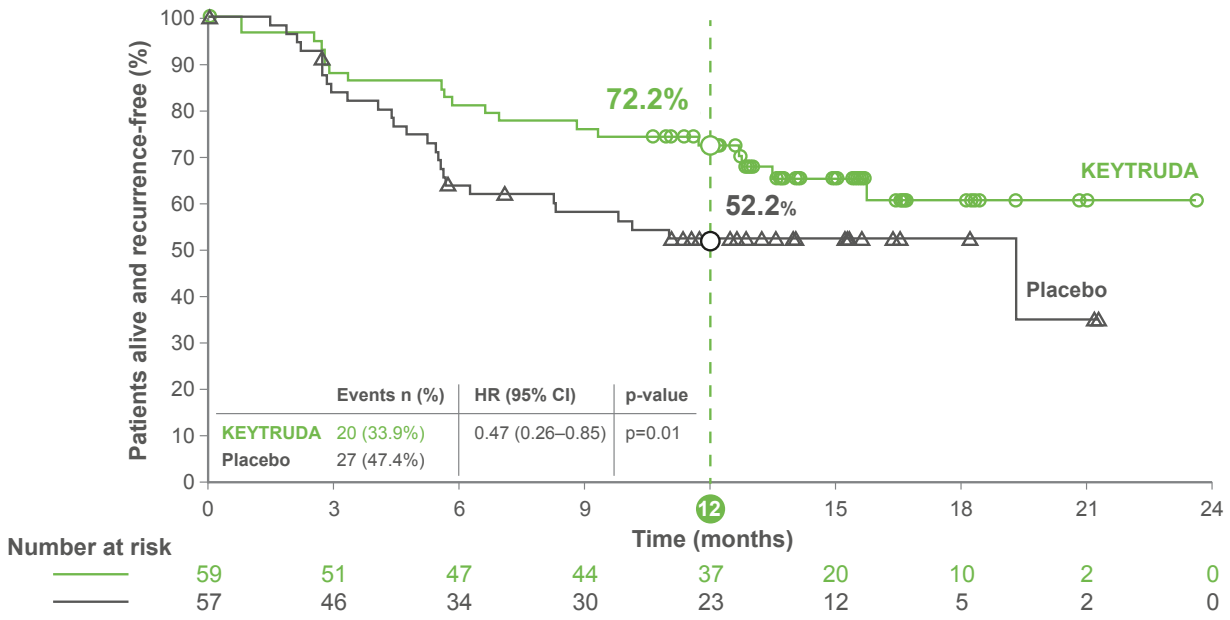
KEYTRUDA® (pembrolizumab)

PD-L1-Negative Patients Showed A Numerically Higher RFS With KEYTRUDA Treatment Vs Placebo[1]

Subgroup analysis was pre-specified but not statistically powered for comparison.

RFS in PD-L1-negative population[1] (pre-specified subgroup)

Median follow-up: 15.1 months



HR: 0.47 demonstrated a 53% reduction in disease recurrence with KEYTRUDA vs placebo

Both the PD-L1-positive and PD-L1-negative subgroups showed a numerically higher RFS with KEYTRUDA adjuvant therapy vs placebo[1]

Adapted from Eggermont AMM, *et al.* 2018.[1]

Duration of treatment: Q3W for 18 doses (~1 year). Stratified by Stage given at randomisation.[1]
CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

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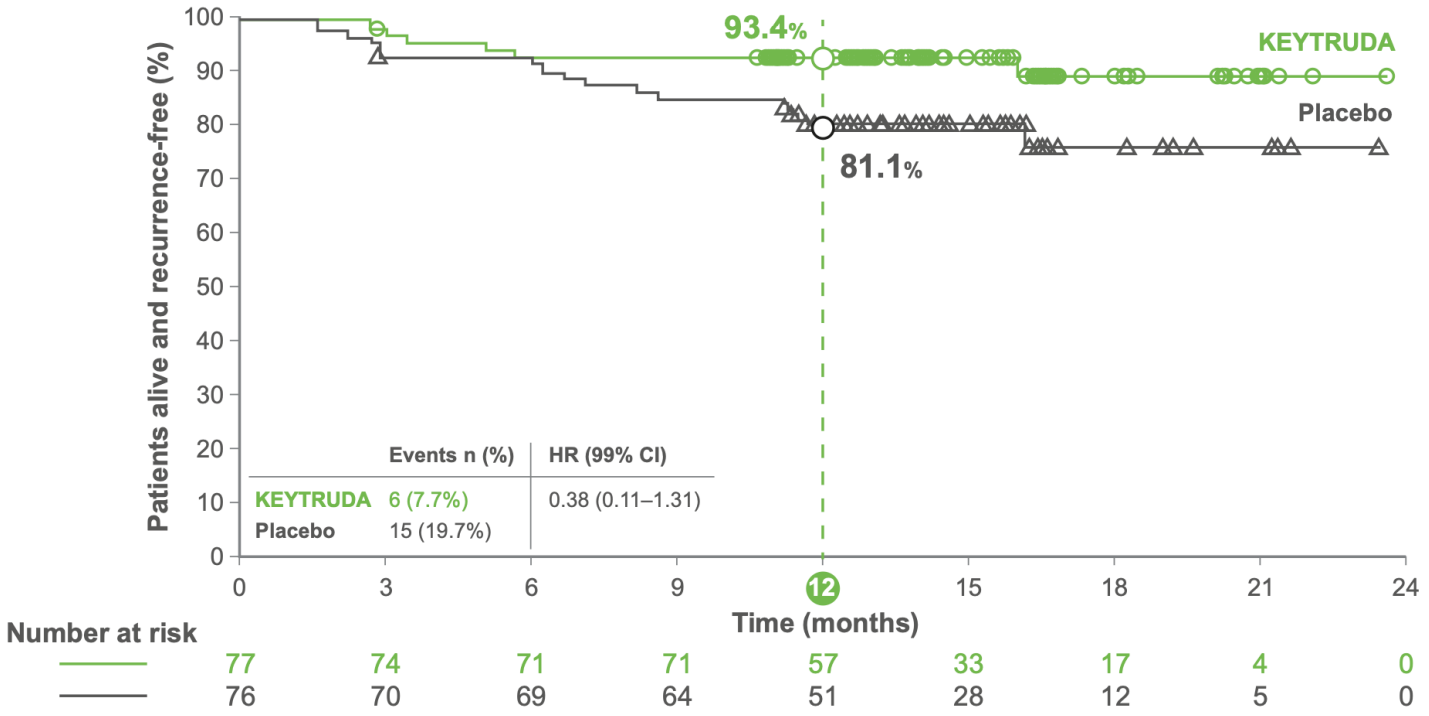
Patients With Stage IIIA Melanoma Showed A Numerically Higher RFS With KEYTRUDA Adjuvant Therapy Vs Placebo[1]

Subgroup analysis was pre-specified but not statistically powered for comparison.

RFS in Stage IIIA patients

Median follow-up: 15.1 months[2]



HR: 0.38 demonstrated a 62% reduction in disease recurrence with KEYTRUDA vs placebo[2]

Adapted from Eggermont AMM, *et al.* 2018.[1,2]

Data cut-off: 2 October 2017.[2] Stratified by stage given at randomisation. Staging per AJCC 7th edition. Stage IIIA melanoma according to the AJCC 8th edition identifies a patient population with a better prognosis compared to stage IIIA according to AJCC 7th edition.[3]
AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; RFS, recurrence-free survival.

1. Eggermont A, *et al.* Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325-MG/Keynote-054 double-blinded Phase III trial. AACR Annual Meeting. 14–18 April 2018, Chicago, IL, USA. Abstract: LBA-10526; **2.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801. **3.** Keung EZ & Gershenwald JE. *Expert Rev Anticancer Ther* 2018;18:775–784.

KEYTRUDA® (pembrolizumab)

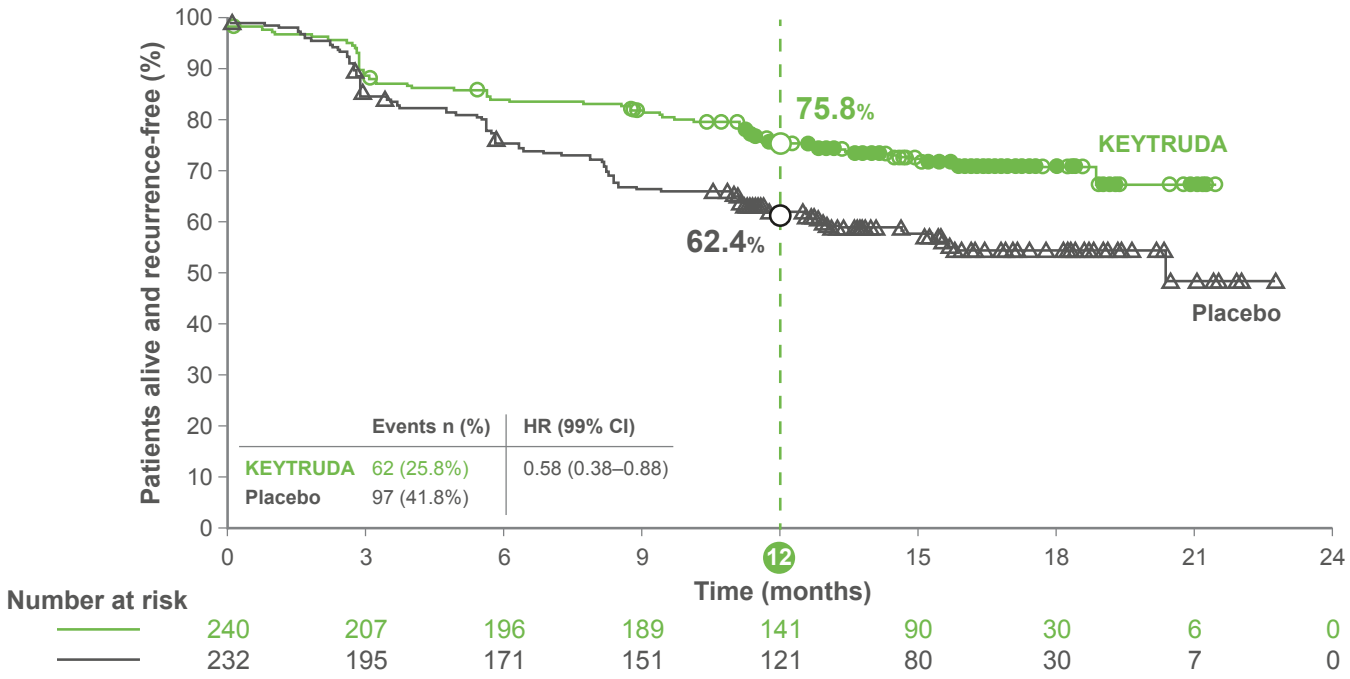
Patients With Stage IIIB Melanoma Also Showed A Numerically Higher RFS With KEYTRUDA Adjuvant Therapy Vs Placebo[1]

Back to RFS data selection page
GB PI
NI PI

Subgroup analysis was pre-specified but not statistically powered for comparison.

RFS in Stage IIIB patients

Median follow-up: 15.1 months[2]



HR: 0.58 demonstrated a 42% reduction in disease recurrence with KEYTRUDA vs placebo[2]

Adapted from Eggermont AMM, *et al.* 2018.[1,2]

Data cut-off: 2 October 2017.[2] Stratified by stage given at randomisation. Staging per AJCC 7th edition. Stage IIIA melanoma according to the AJCC 8th edition identifies a patient population with a better prognosis compared to stage IIIA according to AJCC 7th edition.[3]

AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; RFS, recurrence-free survival.

1. Eggermont A, *et al.* Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325-MG/Keynote-054 double-blinded Phase III trial. AACR Annual Meeting. 14–18 April 2018, Chicago, IL, USA. Abstract: LBA-10526; **2.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801. **3.** Keung EZ & Gershenwald JE. *Expert Rev Anticancer Ther* 2018;18:775–784.

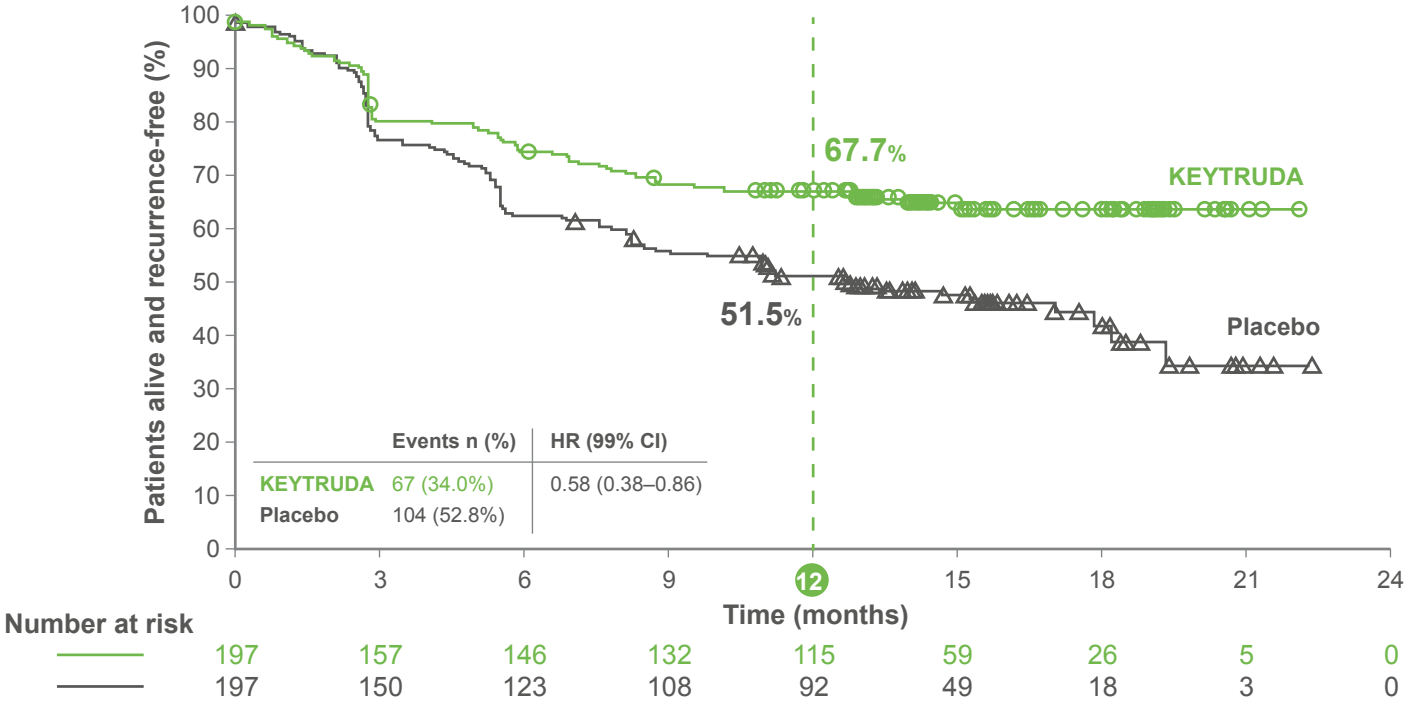
KEYTRUDA® (pembrolizumab)

Patients With Stage IIIC Melanoma Also Showed A Numerically Higher RFS With KEYTRUDA Adjuvant Therapy Vs Placebo[1]

Subgroup analysis was pre-specified but not statistically powered for comparison.

RFS in Stage IIIC patients

Median follow-up: 15.1 months[2]



HR: 0.58 demonstrated a 42% reduction in disease recurrence with KEYTRUDA vs placebo[2]

Adapted from Eggermont AMM, *et al.* 2018.[1,2]

Data cut-off: 2 October 2017.[2]Stratified by stage given at randomisation. Staging per AJCC 7th edition. Stage IIIA melanoma according to the AJCC 8th edition identifies a patient population with a better prognosis compared to stage IIIA according to AJCC 7th edition.[3]

AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; RFS, recurrence-free survival.

1. Eggermont A, *et al.* Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325-MG/Keynote-054 double-blinded Phase III trial. AACR Annual Meeting. 14–18 April 2018, Chicago, IL, USA. Abstract: LBA-10526; **2.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801. **3.** Keung EZ & Gershenwald JE. *Expert Rev Anticancer Ther* 2018;18:775–784.

KEYTRUDA® (pembrolizumab)

Patients In The *BRAF-V600E/K* Subgroup Showed Consistent RFS With KEYTRUDA Adjuvant Therapy Vs Placebo[1]

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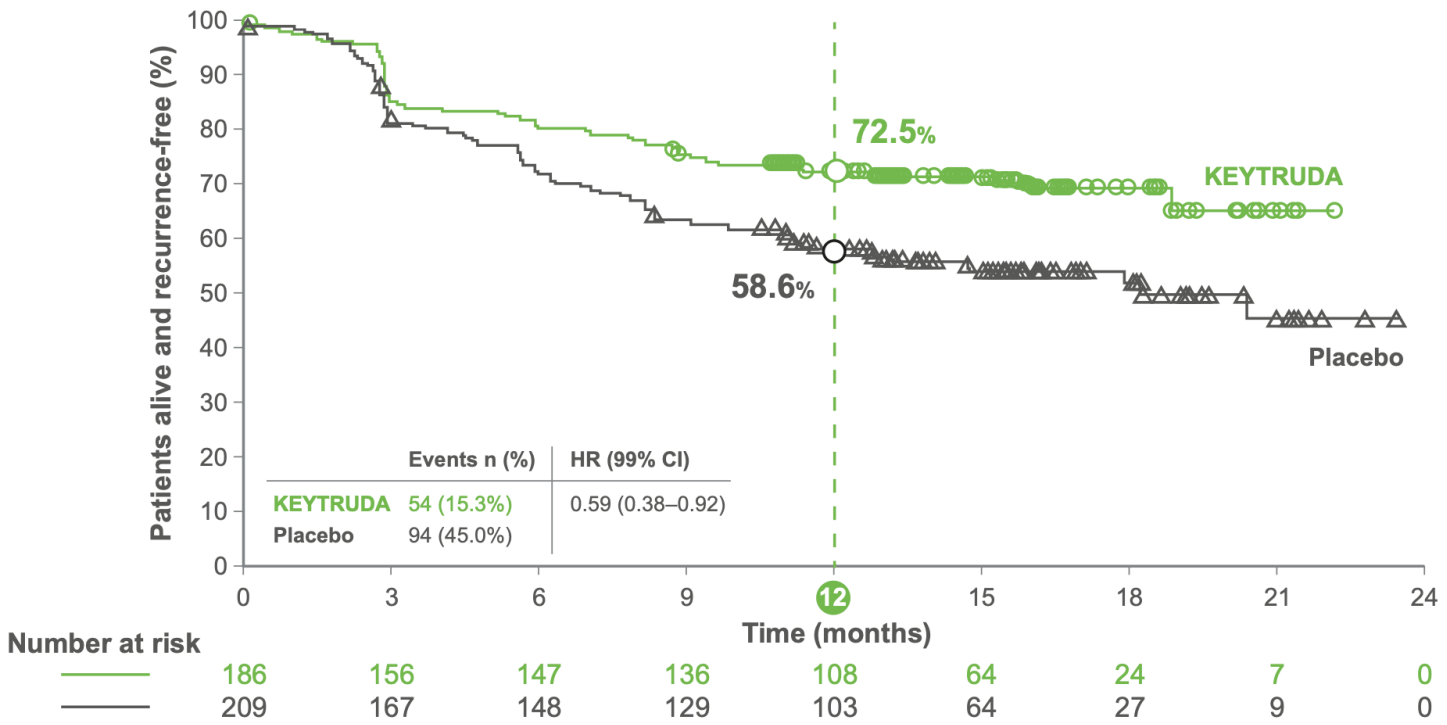
Subgroup analysis was pre-specified but not statistically powered for comparison.

RFS in the ITT population with a *BRAF*-V600E/K mutation

Median follow-up: 15.1 months[2]



HR: 0.59 demonstrated a 41% reduction in disease recurrence with KEYTRUDA vs placebo[2]

RFS results with KEYTRUDA in the *BRAF* subgroups were consistent with the ITT population[1]

Adapted from Eggermont AMM, *et al.* 2018.[1,2]

Data cut-off: 2 October 2017.[2]
NB: Stratified by stage given at randomisation.[2]
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival.

1. Eggermont A, *et al.* Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325-MG/Keynote-054 double-blinded Phase III trial. AACR Annual Meeting. 14–18 April 2018, Chicago, IL, USA. Abstract: LBA-10526; **2.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

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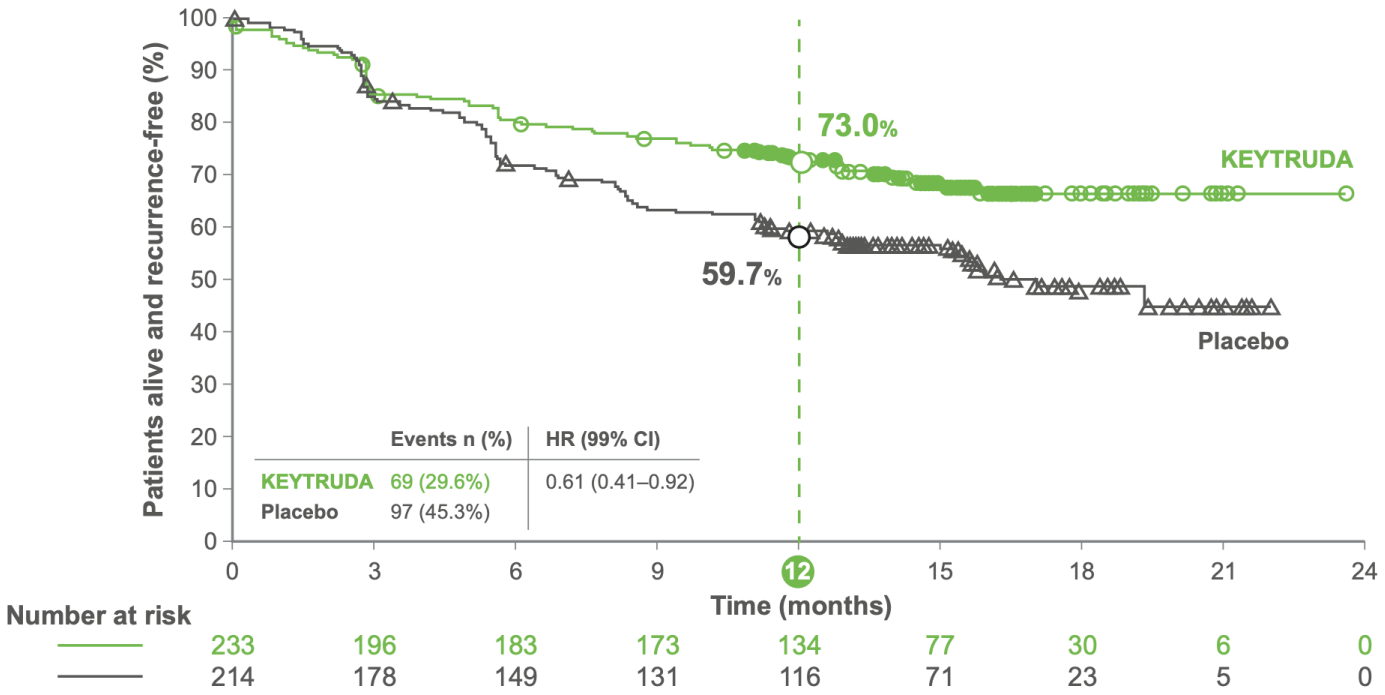
Patients In The *BRAF*-WT Subgroup Showed A Numerically Higher RFS With KEYTRUDA Adjuvant Therapy Vs Placebo[1]

Subgroup analysis was pre-specified but not statistically powered for comparison.

RFS in the ITT population who were *BRAF*-wild type

Median follow-up: 15.1 months[2]



HR: 0.61 demonstrated a 39% reduction in disease recurrence with KEYTRUDA vs placebo[2]

RFS results with KEYTRUDA in the *BRAF* subgroups were consistent with the ITT population[1]

Adapted from Eggermont AMM, *et al.* 2018.[1,2]

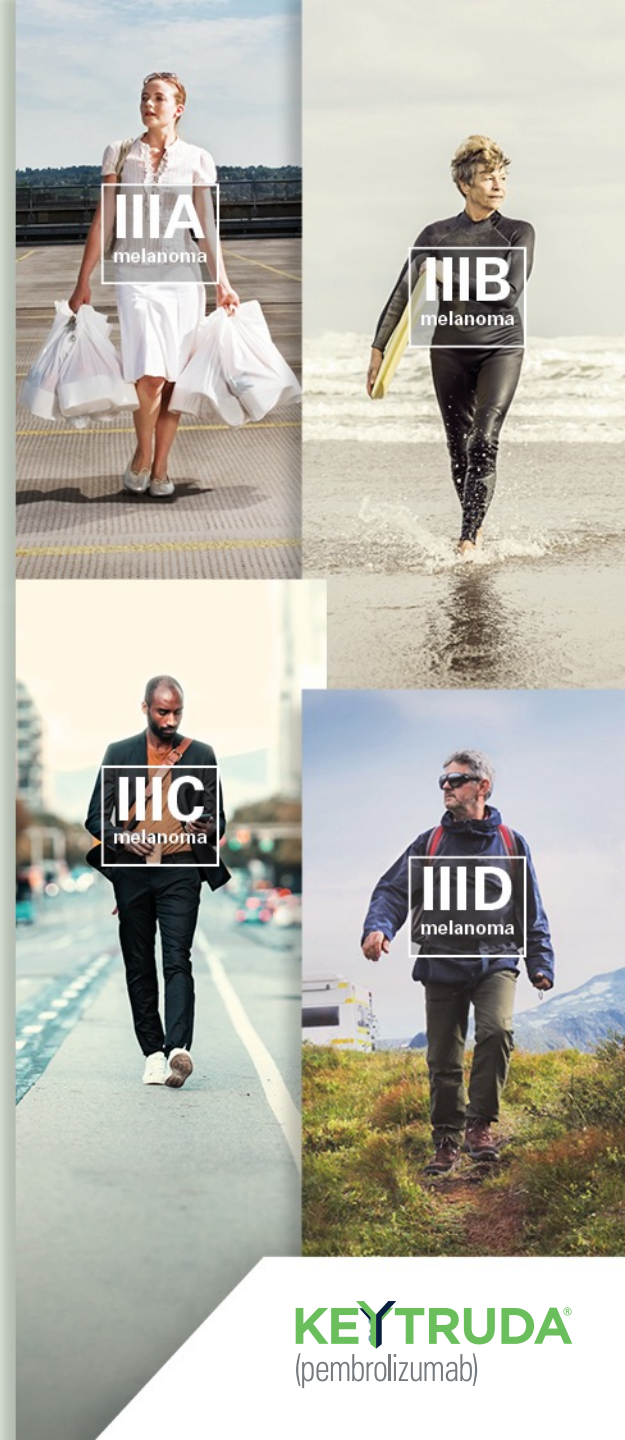
Data cut-off: 2 October 2017.[1]
NB: Stratified by stage given at randomisation.[1]
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival; WT, wild-type.

1. Eggermont A, *et al.* Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma: efficacy and safety results from the EORTC 1325-MG/Keynote-054 double-blinded Phase III trial. AACR Annual Meeting. 14–18 April 2018, Chicago, IL, USA. Abstract: LBA-10526; **2.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

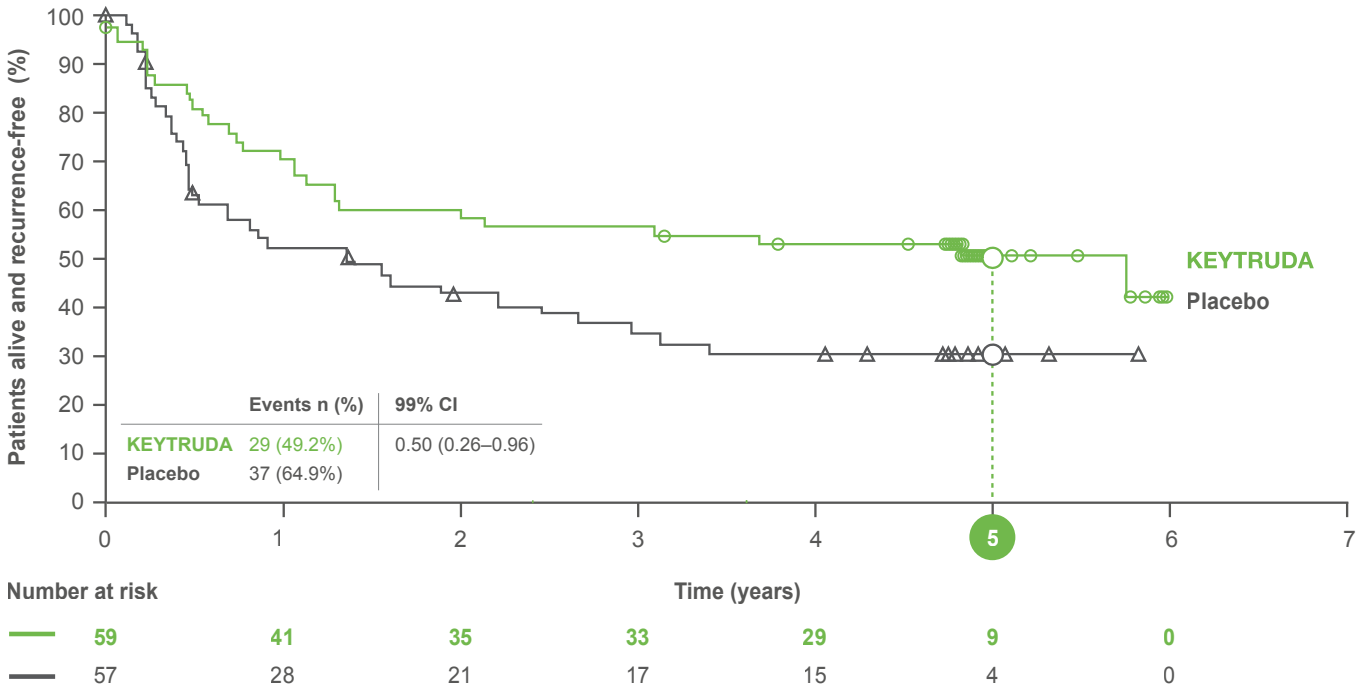
KEYNOTE-054

5-Year Follow-Up Appendix (4.9-Year Median Follow-Up)



The PD-L1-Negative Patient Subgroup Showed Higher RFS with KEYTRUDA Vs Placebo[1,2]

Subgroup analysis was pre-specified but not statistically powered for comparison.*[1]
Exploratory subgroup analysis; RFS in PD-L1-negative population[1,2]
Median follow-up: 4.9 years[1]



HR: 0.50 demonstrated a 50% reduction in disease recurrence with KEYTRUDA vs placebo[2]

KEYTRUDA resulted in higher RFS in patients with PD-L1-positive and PD-L1-negative tumours vs placebo[1,2]

Adapted from Eggermont AMM, *et al.* 2022 & Eggermont AMM, *et al.* 2018.[2,3]

Data cut-off: 17 January 2022.[1]
The HR and its CI were estimated using the Cox proportional hazards model stratified by Stage provided at randomisation.[1]
*Statistical significance was met in the initial analysis.[2]
CI, confidence interval; HR, hazard ratio; IA, interim analysis; PD-L1, programmed death-ligand 1; RFS, recurrence-free survival.
1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **3.** Eggermont AMM, *et al. N Engl J Med* 2018;378:1789–1801.

KEYTRUDA® (pembrolizumab)

In Stage IIIA Patients KEYTRUDA Showed Higher DMFS At A Median Follow-up Of 4.9 Years Vs Placebo[1]

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GB PI
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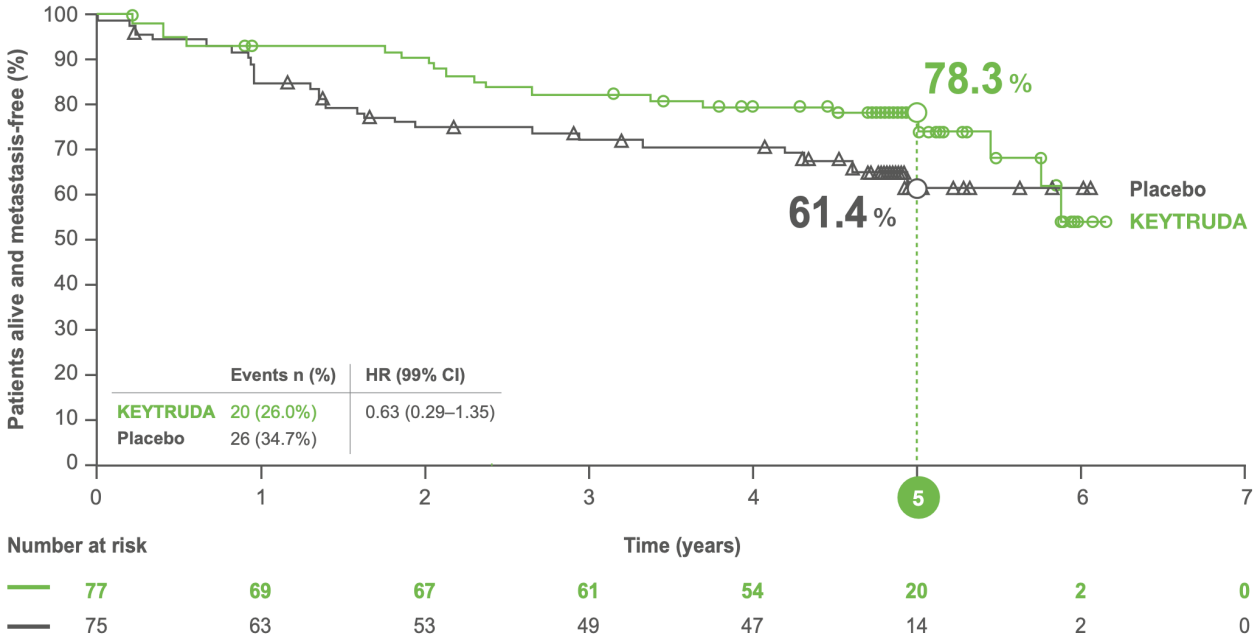
Subgroup analysis was pre-specified but not statistically powered for comparison.*[1]

Exploratory subgroup analysis: DMFS in Stage IIIA patients[1]

Median follow-up: 4.9 years[2]



Adapted from Eggermont AMM, *et al.* 2022.[1]

HR: 0.63 demonstrated a 37% risk reduction in distant metastasis with KEYTRUDA vs placebo[1]

The DMFS in patients with AJCC 7th Stage IIIA, IIIB and IIIC melanoma at a median follow-up of 4.9 years was higher for KEYTRUDA adjuvant therapy vs placebo, consistent with the ITT population[1]

Data cut-off: 17 January 2022.[2]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses.[2,3]
Staging was performed according to AJCC 7th edition pathologic staging criteria for melanoma.[2]
*The overall HR is given with 95% CI.
AJCC, American Joint Committee on Cancer; CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival.
1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **3.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

KEYTRUDA® (pembrolizumab)

In Stage IIIB Patients KEYTRUDA Showed Higher DMFS At A Median Follow-up Of 4.9 Years Vs Placebo[1]

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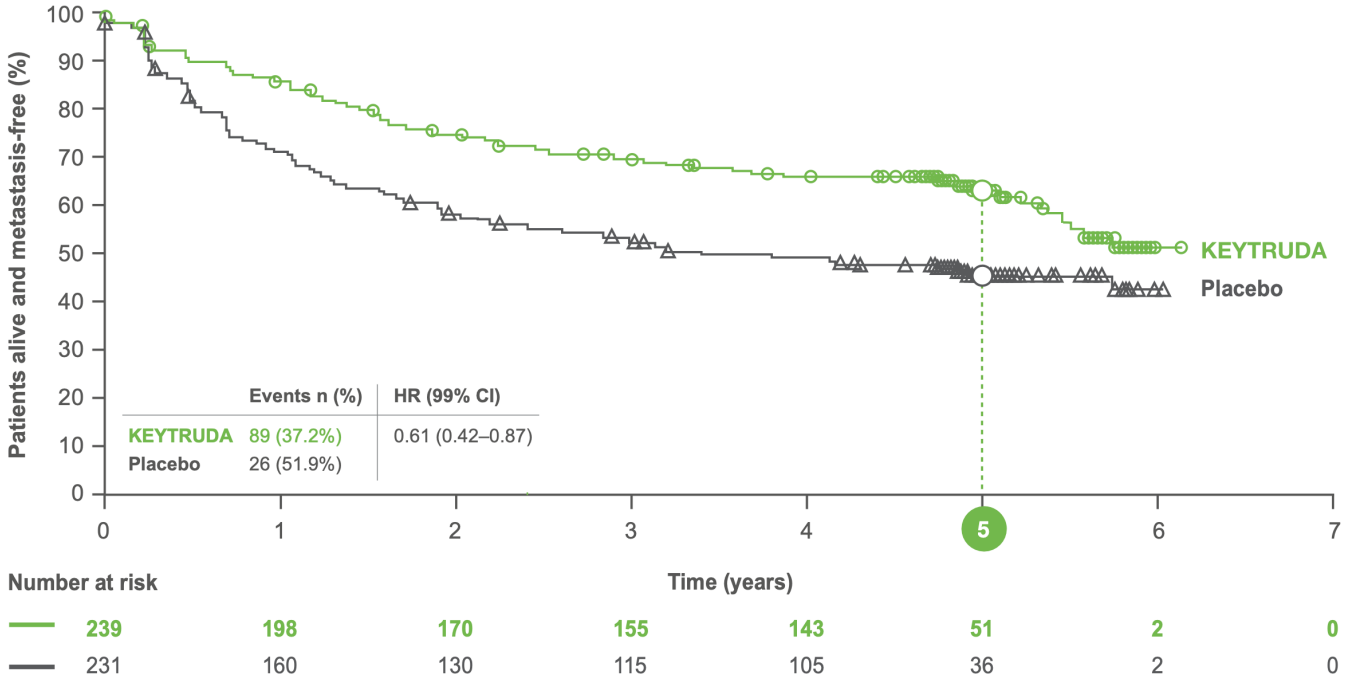
Subgroup analysis was pre-specified but not statistically powered for comparison.*[1]

Exploratory subgroup analysis: DMFS in Stage IIIB patients[1]

Median follow-up: 4.9 years[2]



Adapted from Eggermont AMM, *et al.* 2022.[1]

HR: 0.61 demonstrated a 39% risk reduction in distant metastasis with KEYTRUDA vs placebo[1]

The DMFS in patients with AJCC 7th Stage IIIA, IIIB and IIIC melanoma at a median follow-up of 4.9 years was higher for KEYTRUDA adjuvant therapy vs placebo, consistent with the ITT population[1]

Data cut-off: 17 January 2022.[2]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses.[2,3]
Staging was performed according to AJCC 7th edition pathologic staging criteria for melanoma.[2]
*The overall HR is given with 95% CI.
AJCC, American Joint Committee on Cancer; CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **3.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

KEYTRUDA® (pembrolizumab)

In Stage IIIC Patients KEYTRUDA Showed Higher DMFS At A Median Follow-up Of 4.9 Years Vs Placebo[1]

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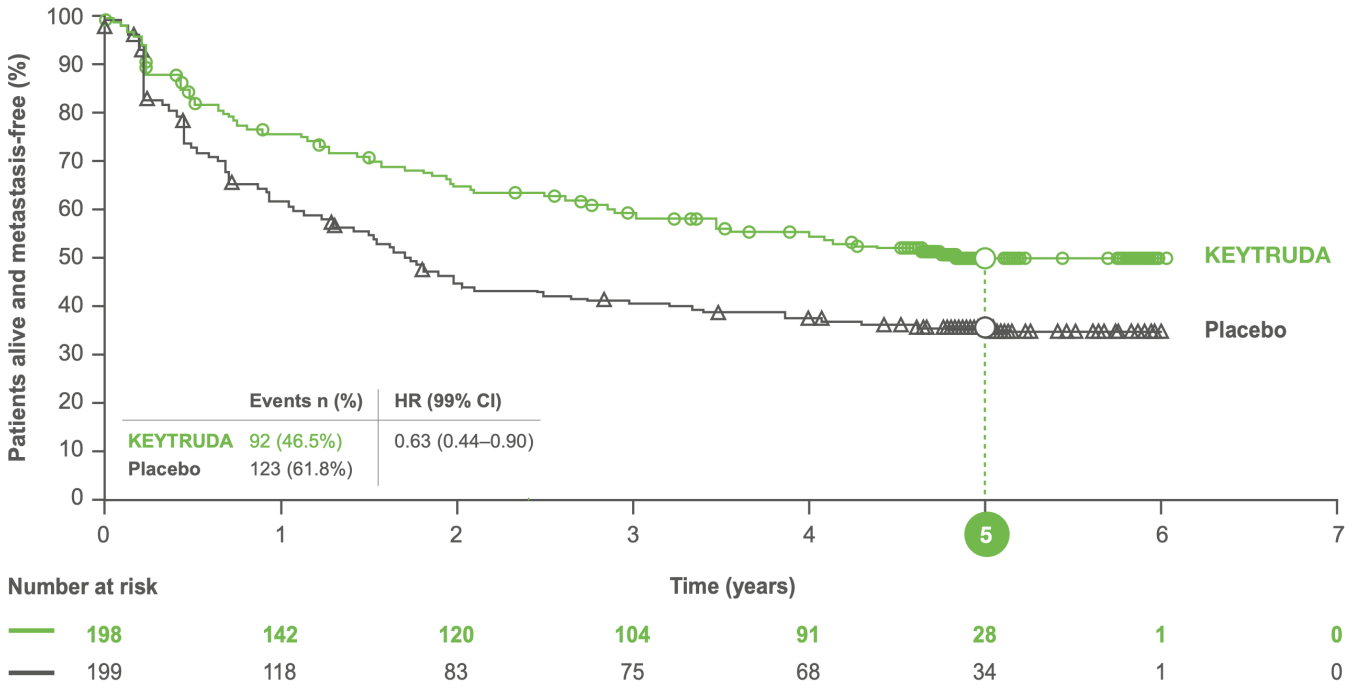
GB PI
NI PI

Subgroup analysis was pre-specified but not statistically powered for comparison.*[1]

Exploratory subgroup analysis: DMFS in Stage IIIC patients[1]

Median follow-up: 4.9 years[2]



Adapted from Eggermont AMM, *et al.* 2022.[1]

HR: 0.63 demonstrated a 37% reduction in distant metastasis with KEYTRUDA vs placebo[1]

The DMFS in patients with AJCC 7th Stage IIIA, IIIB and IIIC melanoma at a median follow-up of 4.9 years was higher for KEYTRUDA adjuvant therapy vs placebo, consistent with the ITT population[1]

Data cut-off: 17 January 2022.[2]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses.[2,3]
Staging was performed according to AJCC 7th edition pathologic staging criteria for melanoma.[2]
*The overall HR is given with 95% CI.
AJCC, American Joint Committee on Cancer; CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **3.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

KEYTRUDA® (pembrolizumab)

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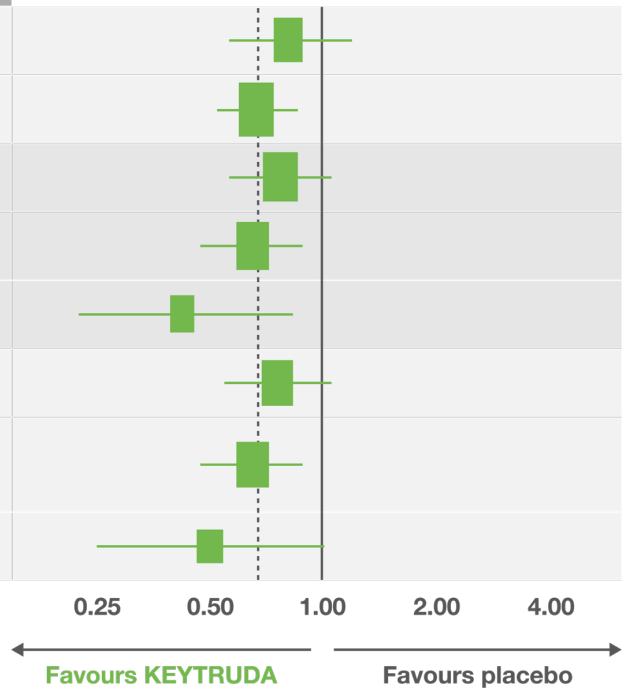
KEYTRUDA Showed Consistent DMFS Across *BRAF* Mutation Status At A Median Follow-up Of 4.9 Years[1]

Subgroup analysis was pre-specified but not statistically powered for comparison.*[1]

Exploratory subgroup analysis: DMFS according to *BRAF* mutation status[1]

Median follow-up: 4.9 years[2]

		KEYTRUDA (n/N)	Placebo (n/N)	HR (99% CI)*
Lymph node involvement	Microscopic	68/185	70/160	0.74 (0.48–1.14)
	Macroscopic	133/329	199/345	0.59 (0.44–0.79)
Ulceration	No	91/230	123/251	0.73 (0.51–1.04)
	Yes	92/208	116/197	0.60 (0.42–0.86)
	Not reported	18/76	30/57	0.37 (0.17–0.79)
***BRAF* mutation status**	Wild type	98/234	111/215	0.72 (0.50–1.02)
	BRAF-V600E or *BRAF*-V600K mutation	86/209	130/231	0.60 (0.42–0.85)
	Other or not reported	17/71	28/59	0.45 (0.20–0.99)
		201/514	**269/505**	**0.62 (0.52–0.75)**



Adapted from Eggermont AMM, *et al.* 2022.[1]

Data cut-off: 17 January 2022.[2]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses.[2,3]
*The overall HR is given with 95% CI.
CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **3.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

KEYTRUDA® (pembrolizumab)

In Patients With *BRAF*-V600E/K Mutation Status KEYTRUDA Showed Improved DMFS At A Median Follow-up Of 4.9 Years Vs Placebo[1]

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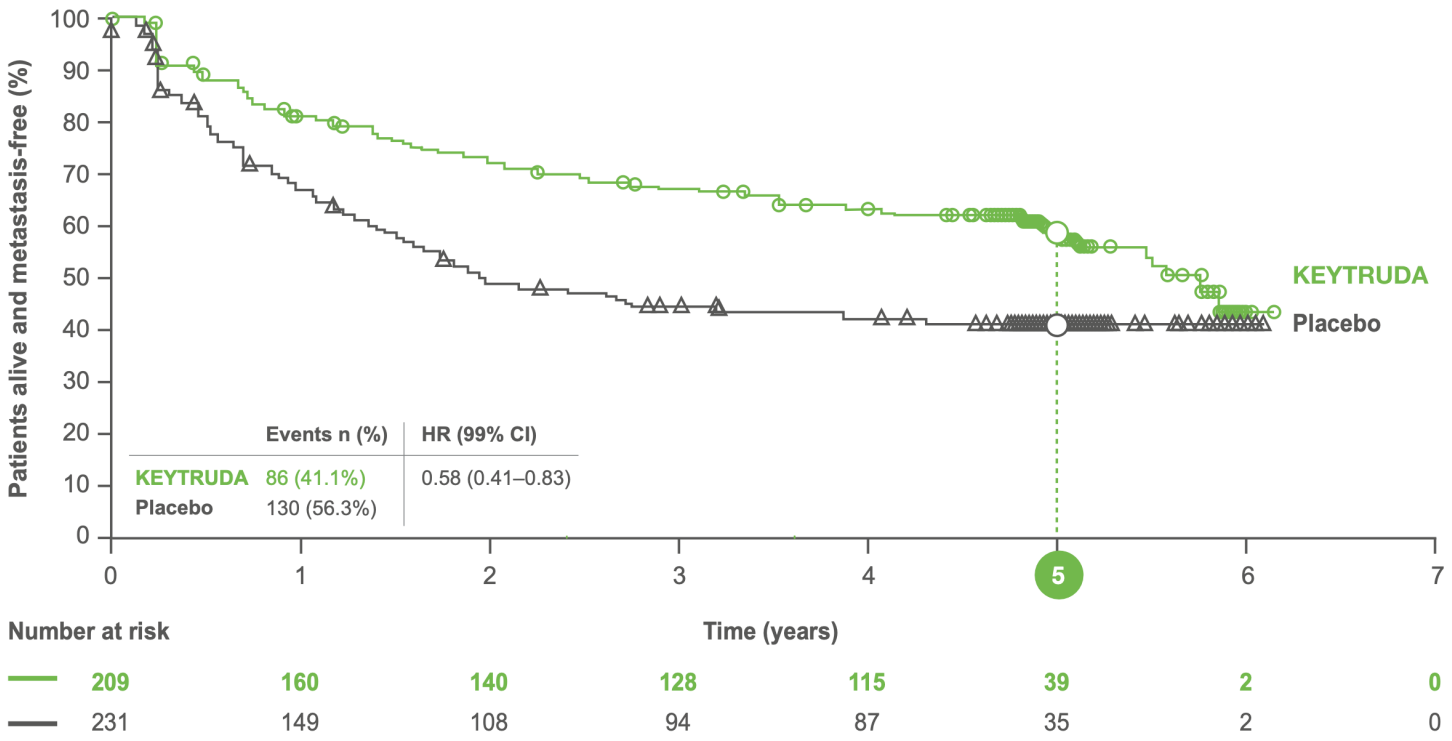
NI PI

Subgroup analysis was pre-specified but not statistically powered for comparison.*[1]
Exploratory subgroup analysis: DMFS in patients with *BRAF*-V600E/K mutation status[1]

Median follow-up: 4.9 years[2]



Adapted from Eggermont AMM, *et al.* 2022.[1]

HR: 0.58 demonstrated a 42% risk reduction in distant metastasis with KEYTRUDA vs placebo[1]

The *BRAF*-V600E/K mutation and *BRAF*-WT subgroups showed higher DMFS with KEYTRUDA adjuvant therapy vs placebo at a median follow-up of 4.9 years, consistent with the ITT population[1,2]

Data cut-off: 17 January 2022.[2]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses.[2,3]
*The overall HR is given with 95% CI.
CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival.
1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **3.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

KEYTRUDA® (pembrolizumab)

In Patients With *BRAF*-WT KEYTRUDA Showed Improved DMFS At A Median Follow-up Of 4.9 Years Vs Placebo[1]

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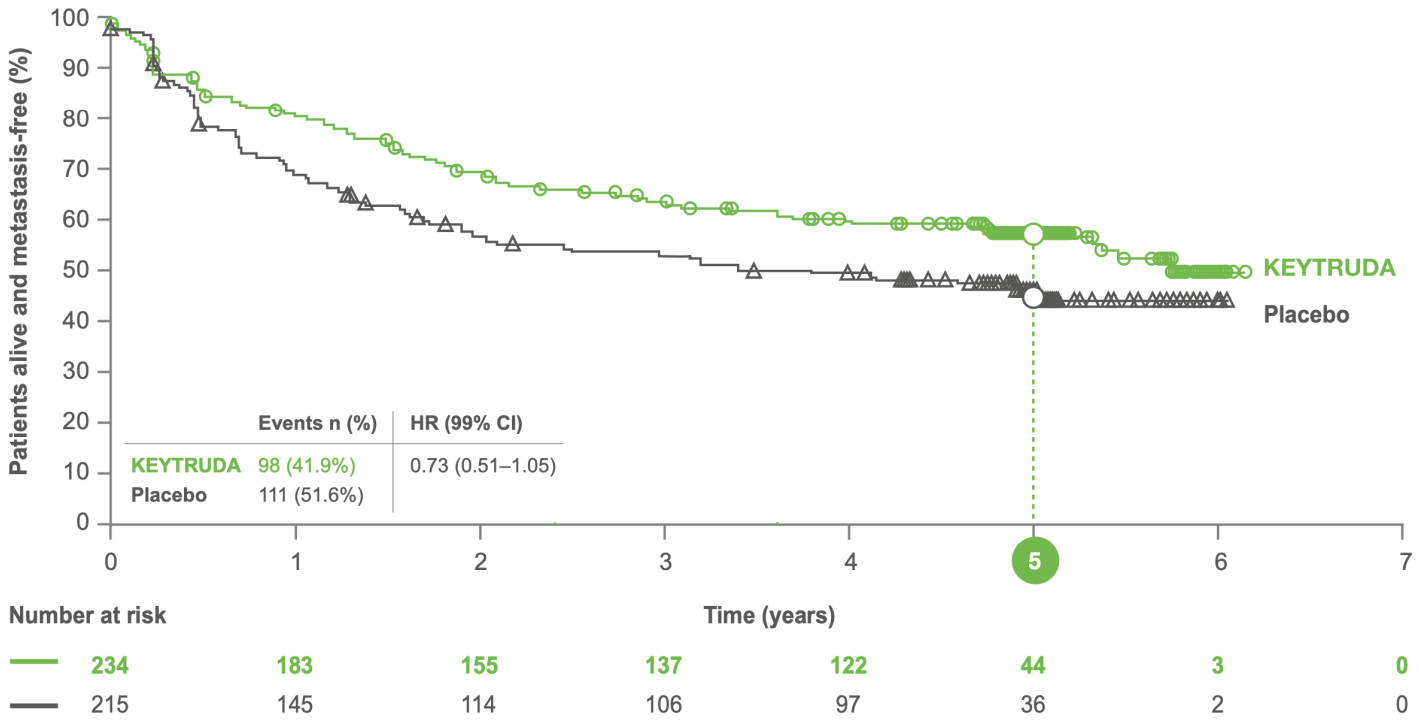
GB PI
NI PI

Subgroup analysis was pre-specified but not statistically powered for comparison.*[1]
Exploratory subgroup analysis: DMFS in patients with *BRAF*-WT[1]

Median follow-up: 4.9 years[2]



Adapted from Eggermont AMM, *et al.* 2022.[1]

HR: 0.73 demonstrated a 27% reduction in distant metastasis with KEYTRUDA vs placebo[1]

The *BRAF*-V600E/K mutation and *BRAF*-WT subgroups showed higher DMFS with KEYTRUDA adjuvant therapy vs placebo at a median follow-up of 4.9 years, consistent with the ITT population[1,2]

Data cut-off: 17 January 2022.[2]
RFS was the primary endpoint. DMFS was a secondary endpoint and data were only available at the 42.3-month and 4.9-year analyses.[2,3]
*The overall HR is given with 95% CI.
CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival; WT, wild-type.

1. Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214. Supplementary appendix; **2.** Eggermont AMM, *et al. N Engl J Med Evid* 2022;22:1:EVIDoa2200214; **3.** Eggermont AMM, *et al. Lancet Oncol* 2021;22:643–654.

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