KEYTRUDA® (pembrolizumab) In The Adjuvant Treatment Of Patients With Stage IIB And IIC 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-00773 Date of Preparation: May 2024

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KEYTRUDA Indications In Melanoma And Dosing[1]

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 the 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.medicines.org.uk/emc/product/2498/smpc Accessed: April 2024.

Prescribing Information

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 adverse event 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 And IIC Melanoma

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

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**

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1. KKEYTRUDA Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498/smpc Accessed: April 2024

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Click On The Boxes Below To Explore KEYTRUDA In Stage IIB And IIC Melanoma

Do we know the associated risks for patients with resected Stage IIB and IIC melanoma?

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

- KEYNOTE-716

Using KEYTRUDA

GB PI NI PI **Click on these icons to access KEYTRUDA prescribing information**

Click on this icon to return to this page

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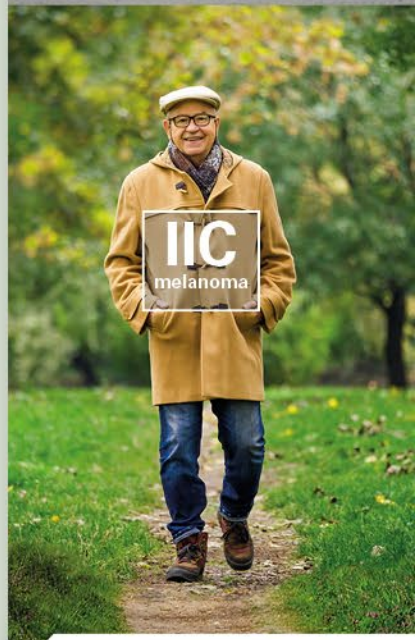
Do We Know The Associated Risks For Patients With Resected Stage IIB And IIC Melanoma?

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

Relapse Rates And Distant Metastasis Rates

Time To Relapse



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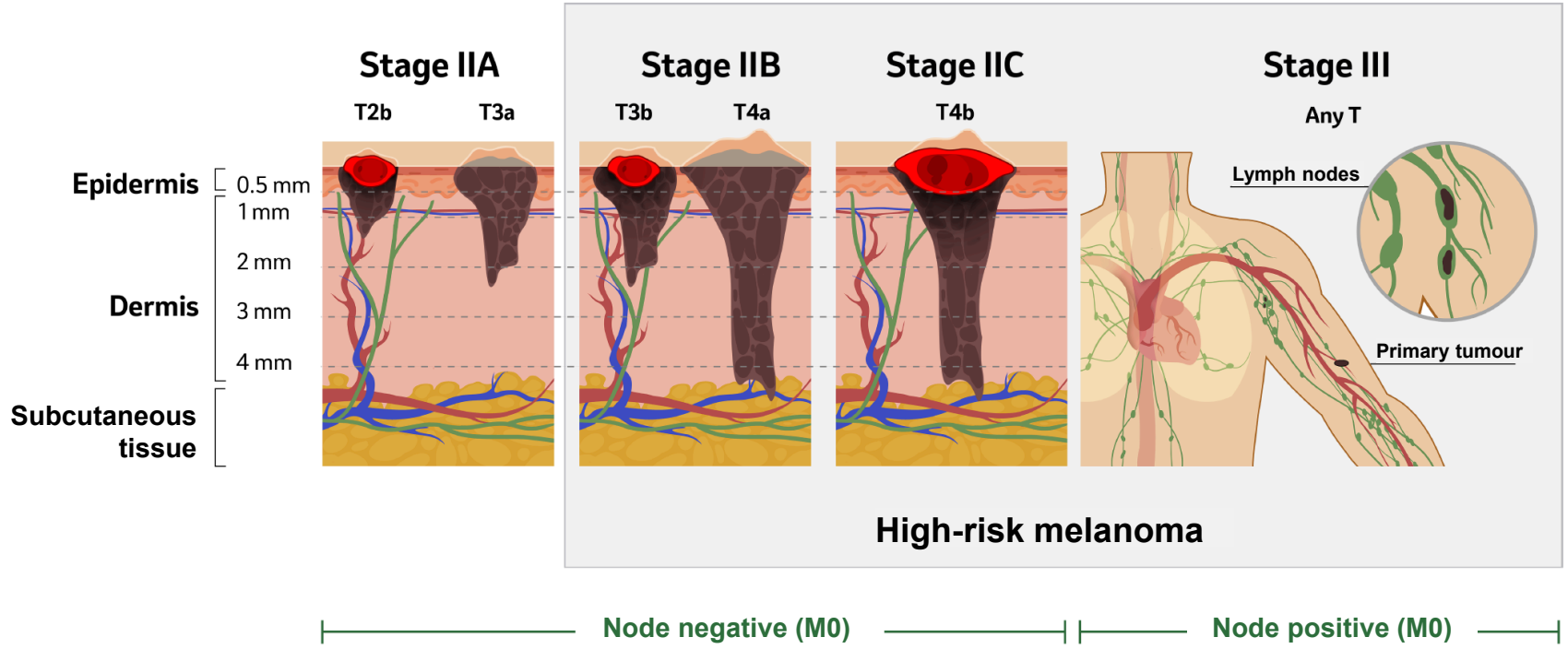
Patients With Melanoma Stage IIB Or Higher Are At Risk Of Recurrence Following Resection*[1–3]

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.

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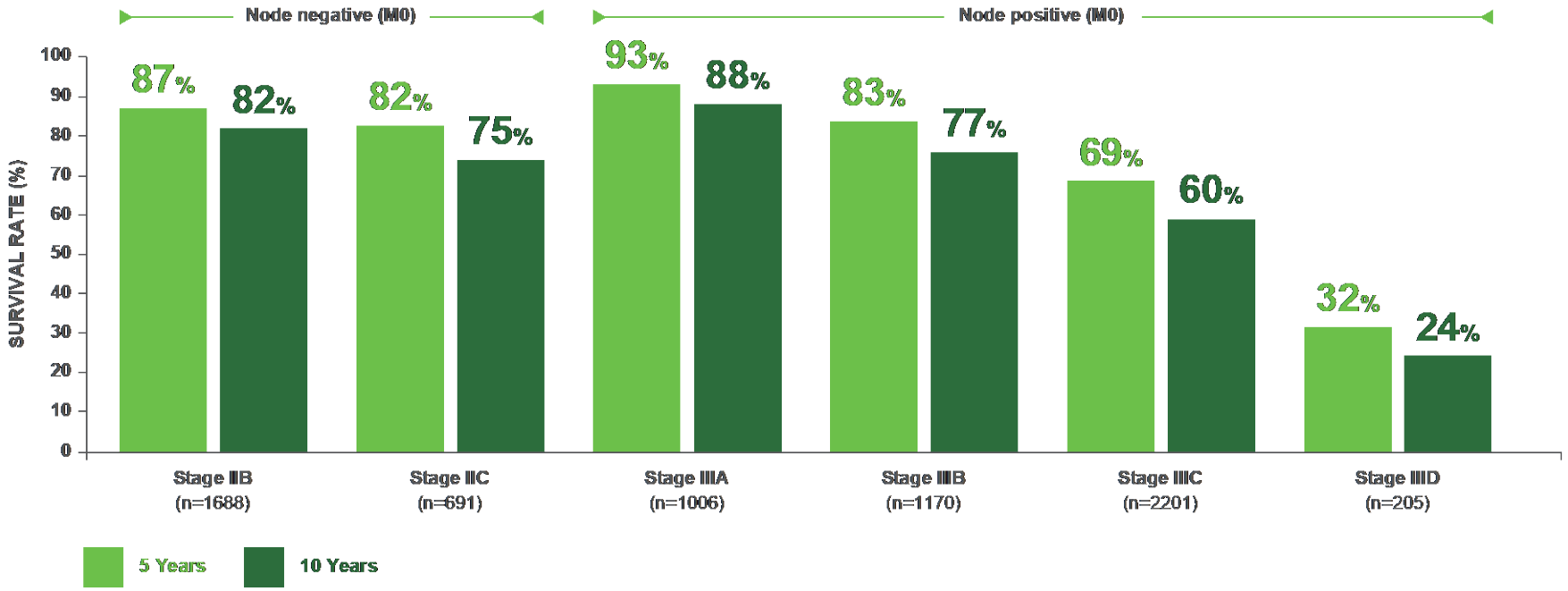
Melanoma-Specific Survival Rates At 5 And 10 Years According To AJCC 8th Edition Pathologic Staging Criteria For Melanoma[1]

- 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]

Based on this survival data, how would your opinion on treating patients with Stage II melanoma change?

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 IIB Melanoma Are 32%, Increasing To 46% In Stage IIC Melanoma[1]

A retrospective review of 738 adult patients from a prospectively maintained, single-institution database, with resected pathologic Stage II primary cutaneous melanoma (AJCC 7th ed.).[1]

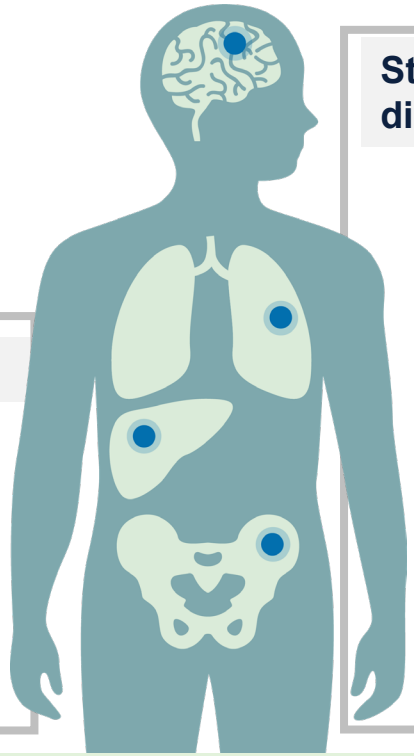
All patients were treated at Memorial Sloan Kettering Cancer Center, USA, between January 1993 and December 2013.

Patients underwent pathological nodal staging by sentinel lymph node biopsy or elective lymph node dissection.

Synchronous initial relapses were scored by the most advanced site. Secondary primary melanomas were not recorded as relapses.

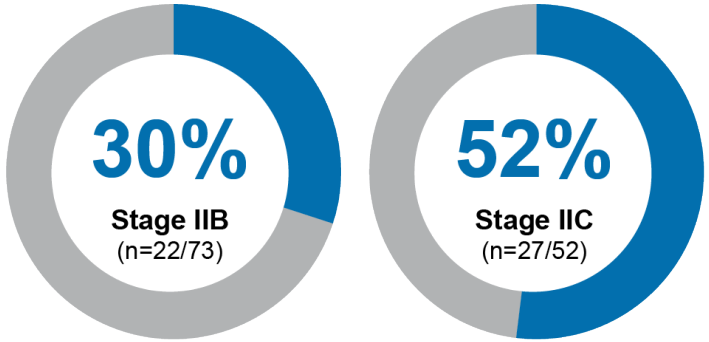
Median follow-up of all patients was 4.3 years (50.2 and 46.2 months for Stage IIB and Stage IIC melanoma, respectively).

Stage IIB and Stage IIC relapse rates[1]



Stage IIB and Stage IIC who relapsed with distant metastasis[1]

Percentage of patients who relapsed with distant metastasis as first relapse



Patients who relapsed with distant metastasis as first relapse

Patients who didn't relapse with distant metastasis as first relapse*

*The remainder of patients experienced a local/in-transit or regional nodal relapse.

Were you aware of the rate of distant relapses across Stages IIB and IIC melanoma?

Relapse Rates & Distant Metastasis Rates in Stage III melanoma ›

AJCC, American Joint Committee on Cancer.

1. Lee AY, *et al. Ann Surg Oncol* 2017;24:939–946.

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The Median Time To Relapse From Resection Is Under 2 Years For Stage IIB And Under 1.5 Years For Stage IIC[1]

A retrospective review of 738 adult patients from a prospectively maintained, single-institution database, with resected pathologic Stage II primary cutaneous melanoma (AJCC 7th ed.).[1]

Median follow-up of all patients was 4.3 years (50.2 and 46.2 months for Stage IIB and Stage IIC melanoma, respectively).

All patients were treated at Memorial Sloan Kettering Cancer Center, USA, between January 1993 and December 2013.

Patients underwent pathological nodal staging by sentinel lymph node biopsy or elective lymph node dissection.

Synchronous initial relapses were scored by the most advanced site. Secondary primary melanomas were not recorded as relapses.

Stage IIB and Stage IIC time to relapse[1]

Median time to relapse among patients who relapsed

Stage IIB
(n=73/226)

Stage IIC
(n=52/112)

Is there more that can be done for patients – beyond observation – to reduce their risk of relapse?

Time to Relapse in Stage III melanoma ›

AJCC, American Joint Committee on Cancer.

1. Lee AY, *et al. Ann Surg Oncol* 2017;24:939–946.

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Summary

- Patients with Stage IIB and IIC melanoma* have 10-year estimated survival rates of 82% and 75%, respectively[1]
- Patients with Stage IIB melanoma† or higher are at risk of relapse following resection[2–4]
  - Relapse rates in patients with Stage IIB and IIC melanoma are 32% and 46%, respectively[2]
  - 30% and 52% of patients with Stage IIB and IIC melanoma relapse with distant metastasis, respectively[2]

- Patients with Stage IIB and IIC melanoma† are still at risk of recurrence, with half of all Stage IIB and IIC relapses occurring within 2 years[2]

Patients with Stage IIB/C melanoma could be considered at risk of disease recurrence

*According to AJCC 8th edition Pathological Staging Criteria for Melanoma.[1]
†According to AJCC 7th edition Pathologic Staging Criteria for Melanoma.[2]
AJCC, American Joint Committee on Cancer.

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

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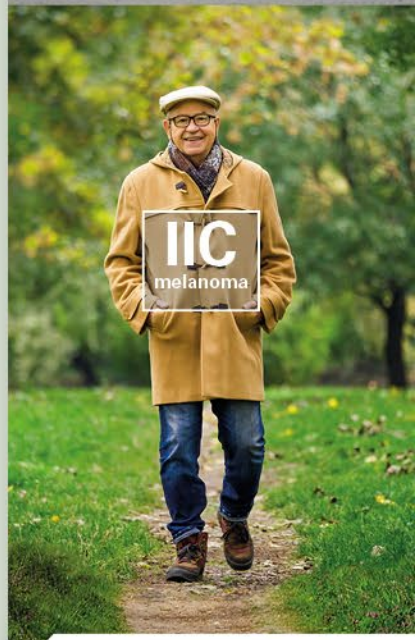
How Can KEYTRUDA Support Patients With Stage II Melanoma In The Adjuvant Setting?



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Meet Mark And Tom*

Name: Mark
Age: 42
Medical history:

- Non-smoker with a fit and active lifestyle
- Saw his doctor after an increase in the size of an existing mole with an irregular border
- A biopsy diagnosed melanoma and the mole was excised
- Review confirmed the diagnosis of Stage IIB melanoma:
  - Ulcerated primary tumour (2–4 mm with ulceration)
  - No nodal involvement

Name: Tom
Age: 68
Medical history:

- Retired chemistry teacher with no history of cancer but has a family history of melanoma
- Saw his doctor about a dark spot on his back which would bleed when rubbed with a towel
- A biopsy diagnosed melanoma and the tumour was excised
- Review confirmed the diagnosis of Stage IIC melanoma:
  - Deep ulcerated primary tumour (>4 mm)
  - No nodal involvement
  - High mitotic rate
  - T4b Breslow tumour thickness

Would you consider Mark and Tom to be at risk of disease relapse?

*Hypothetical patient cases.

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Learn How Patients With Stage IIB/C Melanoma May Benefit From KEYTRUDA Treatment

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- Phase III trial of KEYTRUDA for the adjuvant treatment of patients with completely resected Stage IIB or IIC melanoma

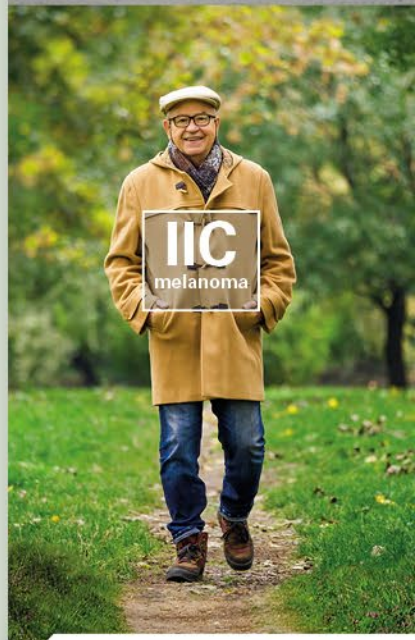
Study Design

Initial Analysis Efficacy And Safety Data

Third Interim Analysis Efficacy And Safety Data

Final Analysis Efficacy And Safety Data

KEYNOTE-716
Study Design



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Study Design[1]

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- KEYNOTE-716 was a multicentre, randomised, double-blind, placebo-controlled Phase III trial in patients with completely resected Stage IIB or IIC melanoma
- In part 1 of KEYNOTE-716, KEYTRUDA and placebo were given up to 1 year, until disease recurrence or unacceptable toxicity
- Randomisation was stratified by AJCC 8th edition T stage

Inclusion criteria:

- Newly diagnosed, completely resected, histologically confirmed Stage IIB or Stage IIC cutaneous melanoma without regional lymph node involvement
- Complete resection was defined as adequate surgical margins per standard of care and identification and removal of at least one sentinel node

Additional eligibility criteria:

- Aged ≥12 years
- No prior systemic therapy for melanoma
- No autoimmune disease or uncontrolled infections
- No use of systemic glucocorticoids
- ECOG PS 0–1

Exclusion criteria:

- Prior therapy for melanoma other than surgery, including adjuvant radiation to the primary resection site

Refer to the Supplementary Appendix for the list of inclusion and exclusion criteria.[2]

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; T, tumour.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729; **2.** Luke JJ, *et al. Lancet* 2022;399:1718–1729. Supplementary appendix.

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Study Design[1,2]

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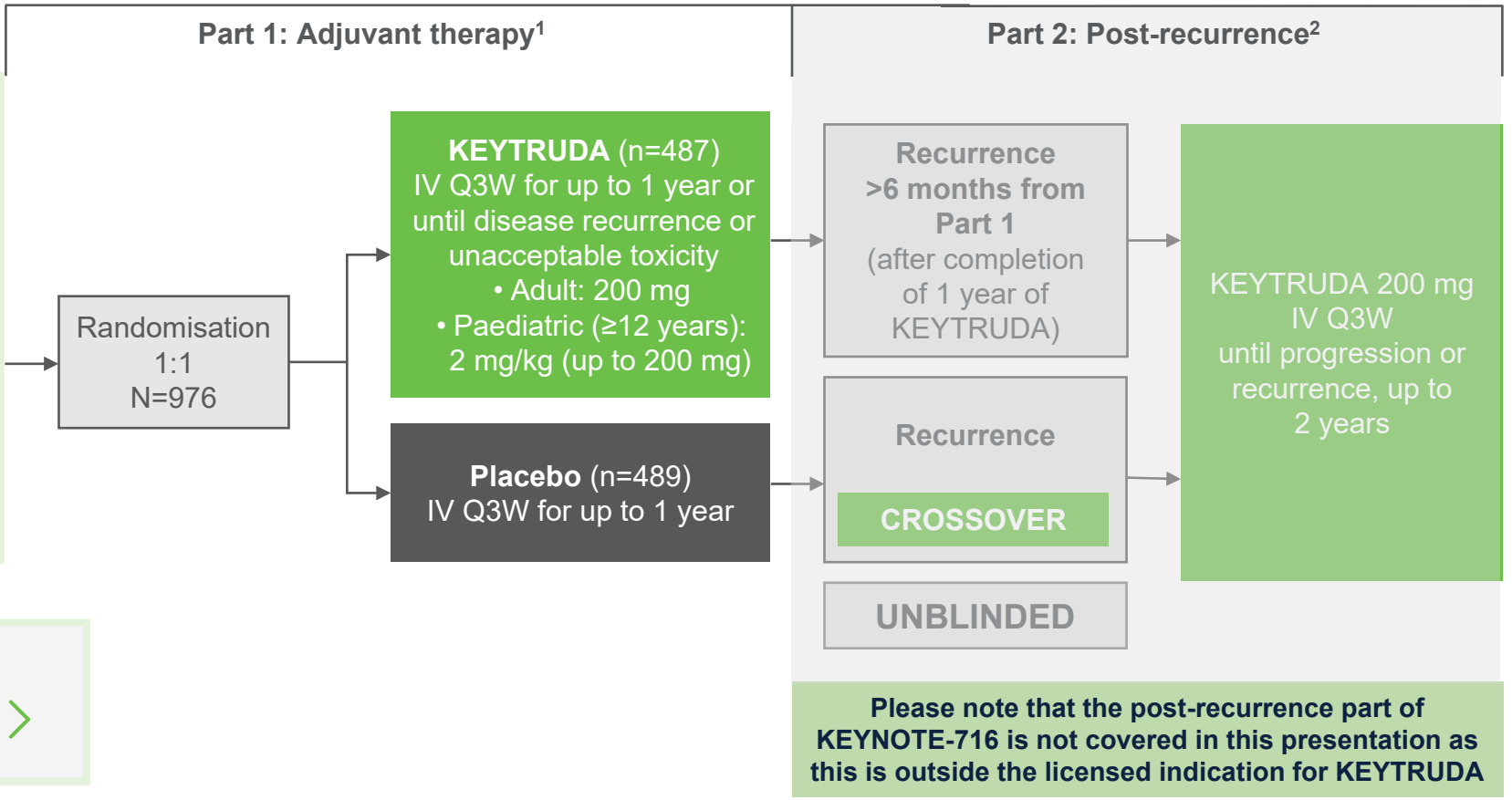
Select eligibility criteria:[1,2]

- Age ≥12 years
- With completely resected Stage IIB or IIC melanoma
- No previous treatment for melanoma beyond complete surgical resection
- ECOG PS 0 or 1



Please note that the post-recurrence part of KEYNOTE-716 is not covered in this presentation as this is outside the licensed indication for KEYTRUDA

Baseline patient characteristics >

Patients underwent imaging at 6 months from the date of randomisation, then every 6 months from Years 2–4 after randomisation and then once in Year 5 from or until recurrence, whichever came first or as clinically indicated.[1]

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; Q3W, every 3 weeks.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729; **2.** Luke JJ, *et al. Future Oncol* 2020;16:4429–4438.

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Key Trial Endpoints[1]

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The efficacy analysis was done in the ITT population, which included all patients randomly assigned to treatment.
Safety was assessed in all patients randomly assigned to treatment who received at least one dose of study treatment.

1

Primary efficacy endpoint:

- Investigator-assessed recurrence-free survival (RFS) (defined as the time between the date of randomisation and the date of first recurrence [local, regional or distant metastases] or death, whichever occurred first) in the ITT population

2

Secondary endpoints:

- Distant metastasis-free survival (DMFS) and overall survival (OS) in the ITT population
- Safety and tolerability of KEYTRUDA*

The primary endpoint was met if RFS was significantly improved for KEYTRUDA versus placebo. The overall type 1 error was controlled at a one-sided alpha of 2.5%. The study met the prespecified RFS endpoint on the basis of results of the first interim analysis with 136 RFS events observed

*Data on adverse events were collected throughout the study through self-report by patient or reported by caregivers and reviewed by investigators during screening and then every 3 weeks from randomisation, and up to 30 days (90 days for serious adverse events) after treatment discontinuation and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[1]
DMFS, distant metastasis-free survival; ITT, intent-to-treat; OS, overall survival; RFS, recurrence-free survival.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

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KEYNOTE-716 Trial And Approval Timeline

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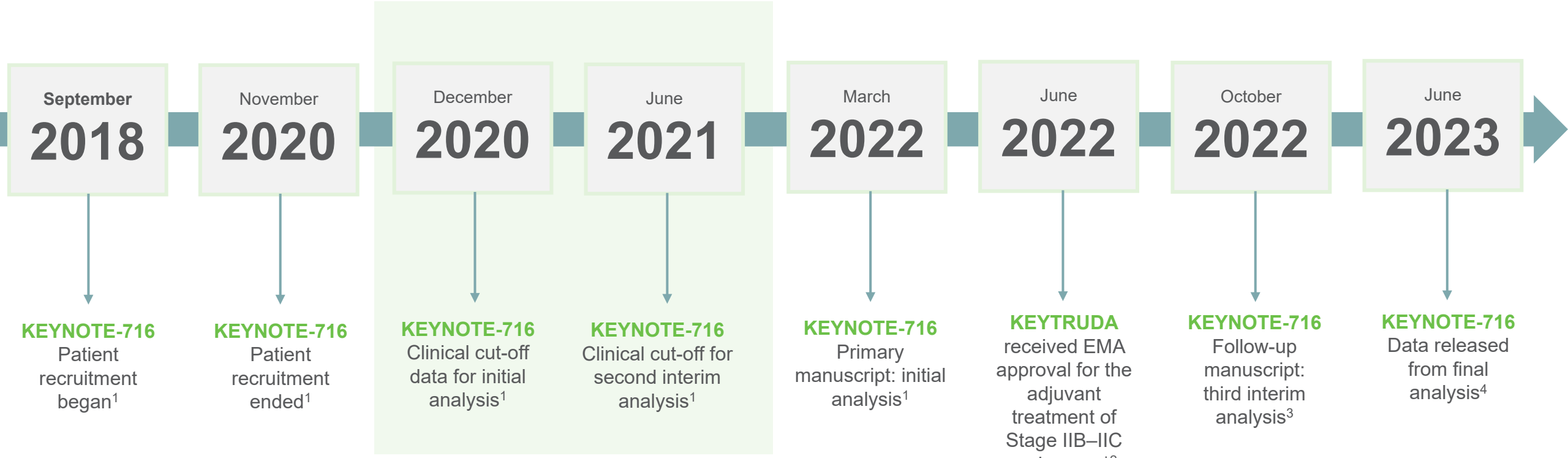

*EMA approval in NI received in June 2022 and MHRA approval received in the rest of the UK in July 2022.[2]
EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; NI, Northern Ireland; UK, United Kingdom.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729; **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.** Long GV, *et al. Lancet Oncol* 2022;.23:1378–1388; **4.** Luke JJ, *et al*. Pembrolizumab versus placebo as adjuvant therapy in Stage IIB or IIC melanoma: Final distant metastasis-free survival analysis in the Phase 3 KEYNOTE-716 study. ASCO. 2–6 June 2023. Chicago, IL, USA. Oral presentation.

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Trial Analyses[1–4]

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1

Initial analysis (IA1)[1]

Primary efficacy endpoint and safety

- Cut-off date (4 December 2020); median time since randomisation: KEYTRUDA monotherapy 14.4 months, placebo 14.3 months; 136 RFS* events
- The RFS comparison was significant – the 2.5% alpha was re-allocated to the DFMS comparison

Click here to view the initial analysis data

3

Third interim analysis (IA3)[2]

Primary efficacy endpoint and safety

- Cut-off date (4 January 2022); median time since randomisation: KEYTRUDA monotherapy 27.4 months, placebo 27.3 months; 234 RFS* events
- Statistical superiority of KEYTRUDA versus placebo for RFS was not tested at IA3
- The DMFS comparison was significant

Click here to view the third interim analysis data

4

Final analysis[3,4]

Primary efficacy endpoint and safety

- Cut-off date (4 January 2023); median time since randomisation: KEYTRUDA monotherapy 39.4 months, placebo 39.4 months; 291 RFS* events and 193 DMFS events
- No formal hypothesis testing was performed as statistical significance of KEYTRUDA versus placebo for RFS and DMFS was met at previous interim analyses

Click here to view the final analysis data

*Recurrence-free survival was defined as the time from randomisation until the date of first recurrence (local, regional or distant metastasis) or death from any cause.[1,2]
DMFS, distant metastasis-free survival; IA, interim analysis; RFS, recurrence-free survival.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729; **2.** Long GV, *et al. Lancet Oncol* 2022;.23:1378–1388; **3.** Luke JJ, *et al.* Pembrolizumab versus placebo as adjuvant therapy in Stage IIB or IIC melanoma: Final distant metastasis-free survival analysis in the Phase 3 KEYNOTE-716 study. ASCO. 2–6 June 2023. Chicago, IL, USA. Oral presentation; **4.** Luke JJ, *et al.* Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the Phase 3 KEYNOTE-716 study. ASCO. 2–6 June 2023. Chicago, IL, USA. Abstract LBA9505.

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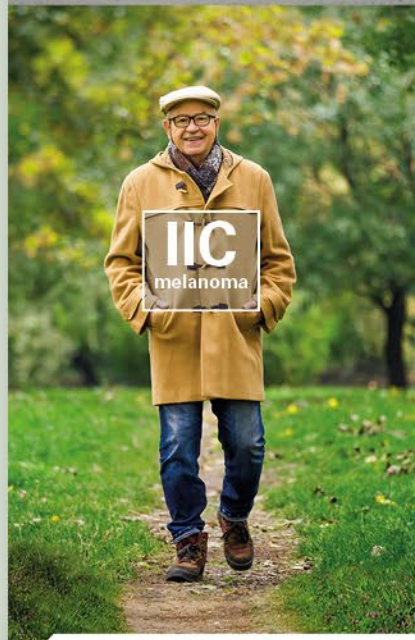
KEYNOTE-716
Efficacy Data From Initial Analysis (14.4-Month Median Follow-Up)



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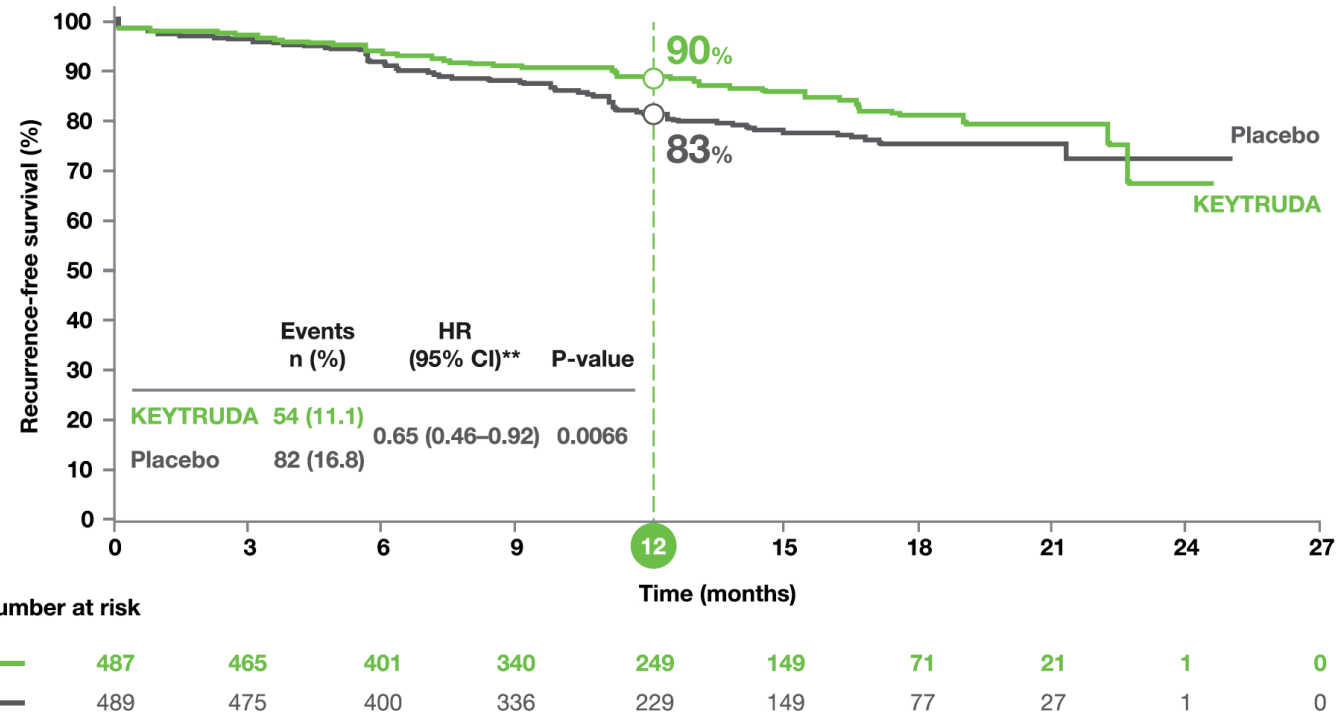
Recurrence-Free Survival Following Treatment With KEYTRUDA Versus Placebo[1]

Kaplan-Meier estimates of RFS* in the ITT population at the first interim analysis†
Median follow-up: 14.4 months



HR: 0.65 demonstrated a 35% risk reduction in disease recurrence with KEYTRUDA versus placebo

Adapted from Luke JJ, *et al.* 2022[1]

IA1 data cut-off: 4 December 2020. The n number displayed represents the number of events in the treatment arm.
*RFS was defined as time from randomisation to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurred first.[1]
†Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T category (T3b versus T4a versus T4b).[1]
CI, confidence interval; HR, hazard ratio; IA, interim analysis; ITT, intent-to-treat; RFS, recurrence-free survival; T, tumour.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

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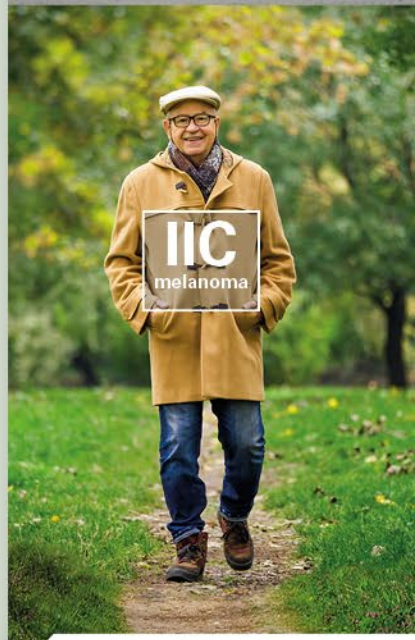
KEYNOTE-716
Safety Data From Initial Analysis (14.4-Month Median Follow-Up)



KEYTRUDA®
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The Safety Profile Of KEYTRUDA Among The Patients With Resected Melanoma Enrolled In KEYNOTE-716 Was Consistent With Previous Studies*[1]

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Treatment-related adverse events at the first interim analysis (1/2)[1]

	KEYTRUDA (n=483)		Placebo (n=486)	
	Any	Grade ≥3	Any	Grade ≥3
Any cause adverse event	449 (93%)	125 (26%)	433 (89%)	83 (17%)†
Any treatment-related adverse event	386 (80%)	78 (16%)	296 (61%)	21 (4%)
Treatment-related events occurring in ≥5% of patients in each group				
Hypothyroidism	70 (14%)	0	12 (2%)	0
Hyperthyroidism	48 (10%)	1 (<1%)	3 (1%)	0
Diarrhoea	85 (18%)	5 (1%)	51 (10%)	1 (<1%)
Nausea	38 (8%)	0	31 (6%)	0
Fatigue	98 (20%)	1 (<1%)	87 (18%)	0
Asthenia	43 (9%)	1 (<1%)	40 (8%)	0
Arthralgia	69 (14%)	1 (<1%)	35 (7%)	0
Myalgia	27 (6%)	2 (<1%)	14 (3%)	0
Increased alanine aminotransferase	34 (7%)	4 (1%)	18 (4%)	1 (<1%)
Increased aspartate aminotransferase	28 (6%)	1 (<1%)	8 (2%)	1 (<1%)
Pruritus	112 (23%)	3 (1%)	48 (10%)	0
Rash	75 (16%)	7 (1%)	29 (6%)	1 (<1%)
Rash maculopapular	34 (7%)	2 (<1%)	8 (2%)	0

Adapted from Luke JJ, *et al.* 2022.[1]

For further details on adverse events and risk management, please refer to the SmPC and Risk Management Materials.

IA1 data cut-off: 4 December 2020.

*The safety population included all patients who were randomly assigned to treatment and received at least one dose of study treatment.[1]

†Four deaths occurred: one due to COVID-19-related pneumonia, one due to pneumonia, one due to recurrent cancer and one due to suicide.[1]

COVID-19, coronavirus disease 2019; IA, interim analysis; SmPC, Summary of Product Characteristics.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

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The Safety Profile Of KEYTRUDA Among The Patients With Resected Melanoma Enrolled In KEYNOTE-716 Was Consistent With Previous Studies*[1]

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Treatment-related adverse events at the first interim analysis (2/2)[1†]

	KEYTRUDA (n=483)		Placebo (n=486)	
	Any	Grade ≥3	Any	Grade ≥3
Hypothyroidism	76 (16%)	0	17 (3%)	0
Hyperthyroidism	50 (10%)	1 (<1%)	3 (1%)	0
Colitis	17 (4%)	8 (2%)	4 (1%)	0
Adrenal insufficiency	11 (2%)	4 (1%)	0	0
Hepatitis	10 (2%)	8 (2%)	3 (1%)	2 (<1%)
Hypophysitis	10 (2%)	3 (1%)	0	0
Infusion reactions	5 (1%)	0	6 (1%)	0
Myasthenic syndrome	2 (<1%)	2 (<1%)	0	0
Myelitis	1 (<1%)	1 (<1%)	0	0
Myocarditis	0	0	1 (<1%)	1 (<1%)
Myositis	6 (1%)	3 (1%)	0	0
Nephritis	7 (1%)	2 (<1%)	0	0
Pancreatitis	2 (<1%)	2 (<1%)	0	0
Pneumonitis	9 (2%)	1 (<1%)	3 (1%)	0
Sarcoidosis	5 (1%)	0	0	0
Severe skin reactions	14 (3%)	13 (3%)	3 (1%)	3 (1%)
Thyroiditis	8 (2%)	0	2 (<1%)	0
Type 1 diabetes	2 (<1%)	2 (<1%)	0	0
Uveitis	1 (<1%)	0	0	0

Adapted from Luke JJ, *et al.* 2022.[1]

For further details on adverse events and risk management, please refer to the SmPC and Risk Management Materials.

IA1 data cut-off: 4 December 2020.

*The safety population included all patients who were randomly assigned to treatment and received at least one dose of study treatment.[1]

†Adverse events of interest (immune-mediated adverse events and infusion reactions) were based on a list of terms specified by the sponsor, regardless of attribution to any study treatment by investigators.[1]

All adverse events of interest are reported. Only the highest reported grade of a given adverse event is counted for an individual patient.[1]

IA, interim analysis; SmPC, Summary of Product Characteristics.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

KEYTRUDA® (pembrolizumab)

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

Summary of adverse events in KEYNOTE-716 at the first interim analysis*

Adverse event, n (%)	KEYTRUDA (n=483)	Placebo (n=486)
Any	449 (93)	433 (89)
Grade 3–5	125 (26)	83 (17)
Led to discontinuation	75 (16)	20 (4)
Led to death	0 (0)	4 (0.8)†
Treatment-related	386 (80)	296 (61)
Grade 3–4	78 (16)	21 (4)
Led to death	0 (0)	0 (0)

Adapted from Luke JJ, *et al.* 2022.[1]

For further details on adverse events and risk management, please refer to the SmPC and Risk Management Materials.

IA1 data cut-off: 4 December 2020.

*The safety population included all patients who were randomly assigned to treatment and received at least one dose of study treatment.[1]

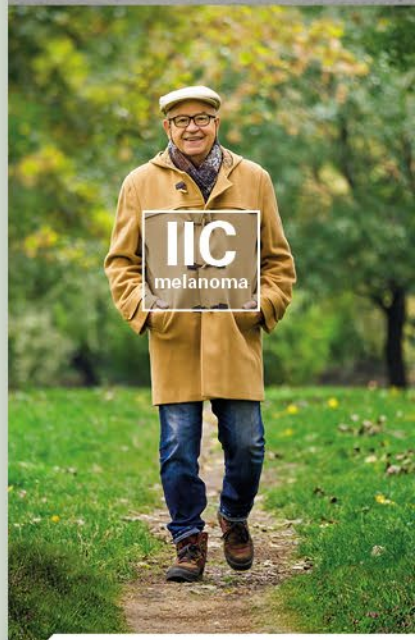
†Four deaths occurred: one due to COVID-19-related pneumonia, one due to pneumonia, one due to recurrent cancer and one due to suicide.[1]

COVID-19, coronavirus disease 2019; IA, interim analysis; SmPC, Summary of Product Characteristics.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

KEYTRUDA® (pembrolizumab)

KEYNOTE-716
Efficacy Data From Third Interim Analysis (27.4-Month Median Follow-Up)



KEYTRUDA®
(pembrolizumab)

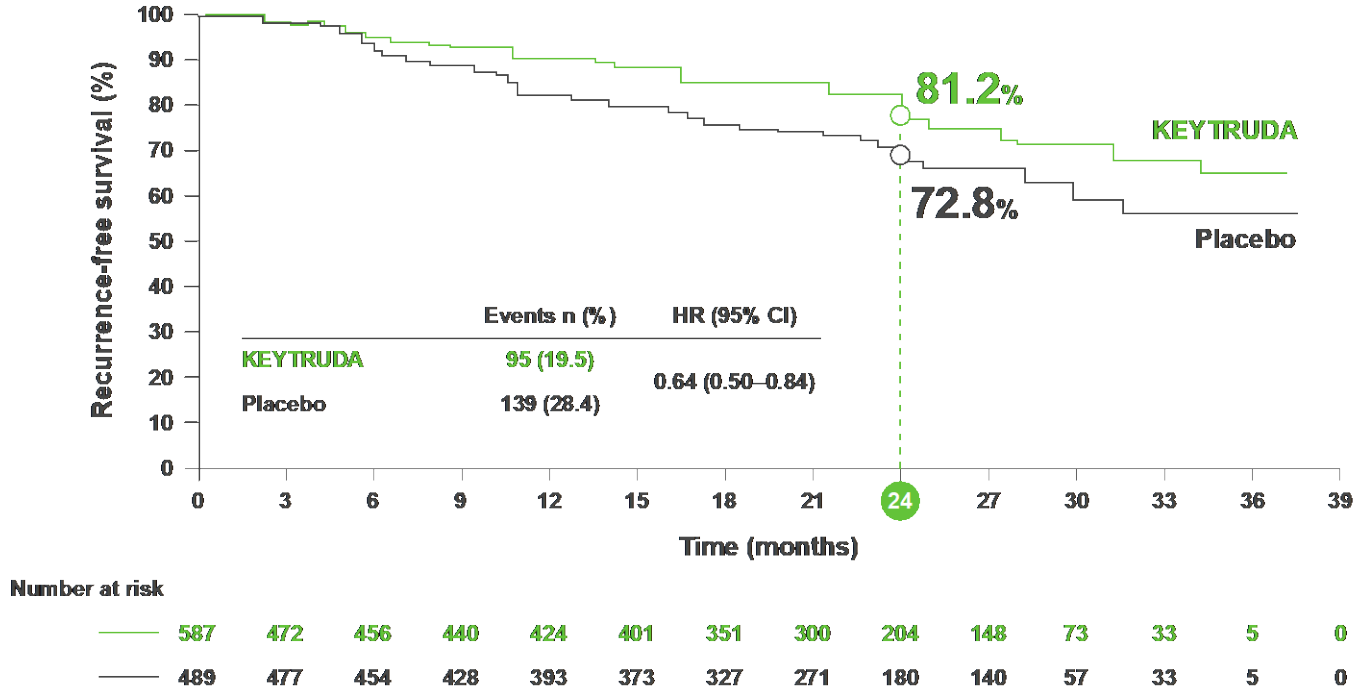
Recurrence-Free Survival* Following Treatment With KEYTRUDA Versus Placebo At The Third Interim Analysis[1]

Kaplan-Meier estimates of RFS in the ITT population at the third interim analysis†[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: 27.4 months



Adapted from Long GV, *et al.* 2022.[2]

The IA3 HR: 0.64, demonstrated a 36% risk reduction in disease recurrence with KEYTRUDA versus placebo[1]

Click here to see the corresponding data from IA1

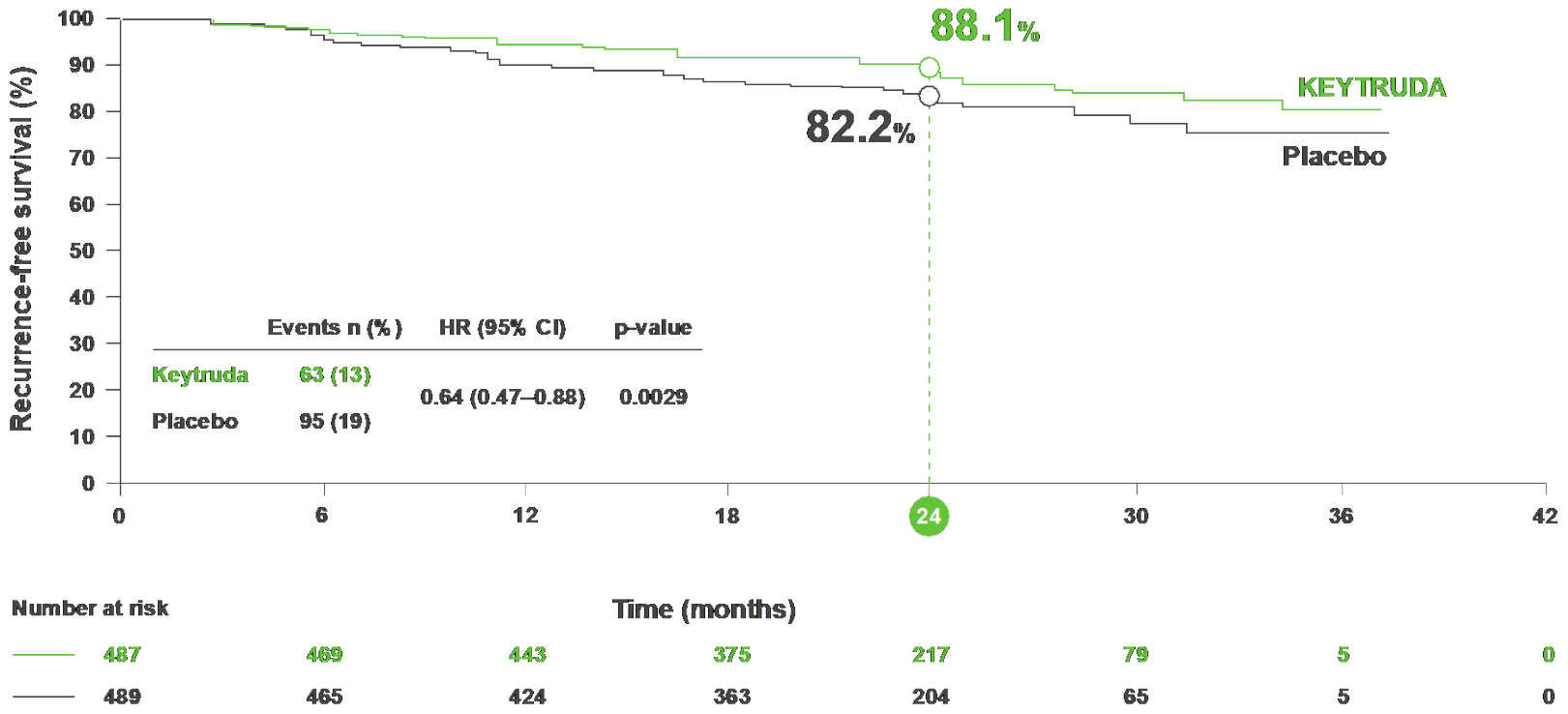
IA3 data cut-off: 4 January 2022.[2] The n number displayed represents the number of events in the treatment arm.
*RFS was defined as time from randomisation to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurred first.[1]
†Statistical significance was met in the initial analysis.[3]
‡Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T category (T3b versus T4a versus T4b).[1]
CI, confidence interval; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; RFS, recurrence-free survival; T, tumour.

1. Long GV, *et al. Lancet Oncol* 2022;23:1378–1388; **2.** Long GV, *et al. Lancet Oncol* 2022;23:1378–1388. Supplementary appendix; **3.** Luke JJ, *et al. Lancet* 2022;399:1718–1729.

KEYTRUDA® (pembrolizumab)

Distant Metastasis-Free Survival* Following Treatment With KEYTRUDA Versus Placebo[1]

Kaplan-Meier estimates of DMFS in the ITT population at the third interim analysis†
Median follow-up: 27.4 months



Adapted from Long GV, *et al.* 2022.[1]

The IA3 HR:0.64, demonstrated a 36% risk reduction in distant metastasis with KEYTRUDA versus placebo[1]

IA3 data cut-off: 4 January 2022.[1] The n number displayed represents the number of events in the treatment arm.
*DMFS was defined as the time from randomisation to the first diagnosis of distant metastasis.[1]
†Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T category (T3b versus T4a versus T4b).[1]
CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; T, tumour.

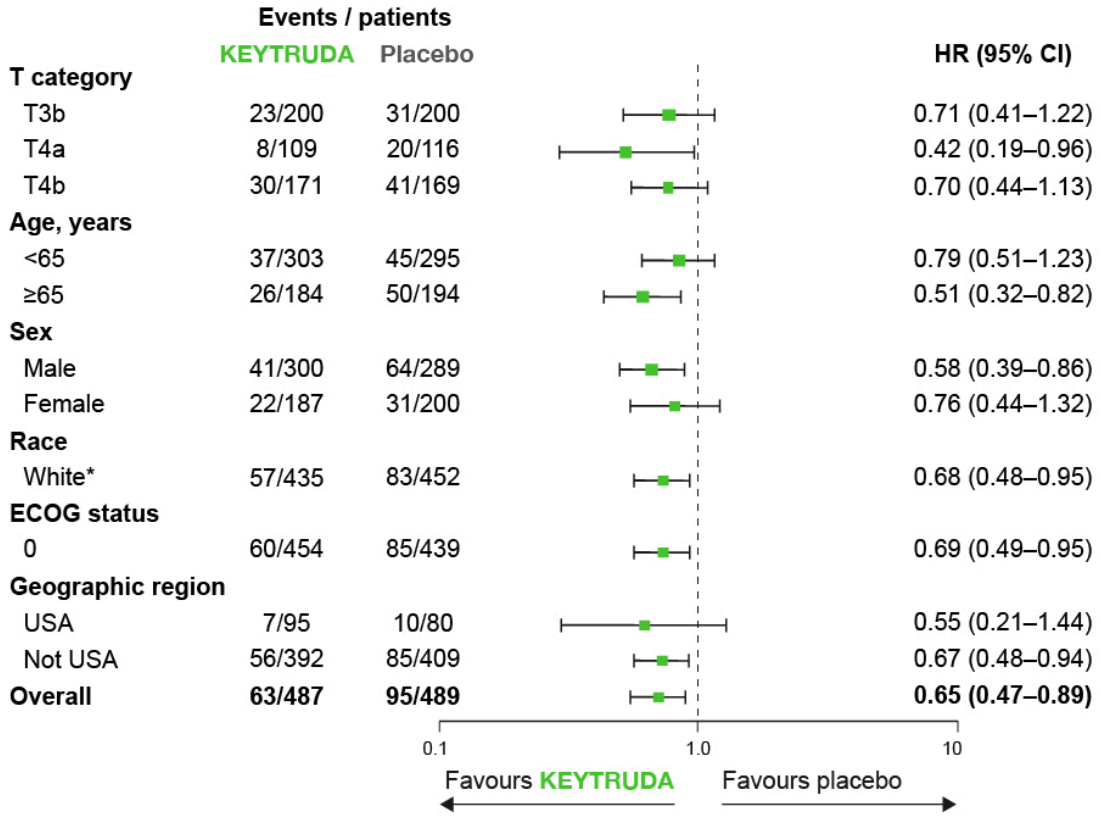
1. Long GV, *et al. Lancet Oncol* 2022;23:1378–1388.

KEYTRUDA® (pembrolizumab)

Analysis Of Distant Metastasis-Free Survival* In Key Patient Subgroups For KEYTRUDA Versus Placebo[1]

KEYNOTE-716 was **not powered** to detect differences in the treatment effect in these subgroups; therefore, results from exploratory analyses should be interpreted with caution because of the modest patient numbers and potential imbalances in baseline characteristics within subgroups

Median follow-up: 27.4 months



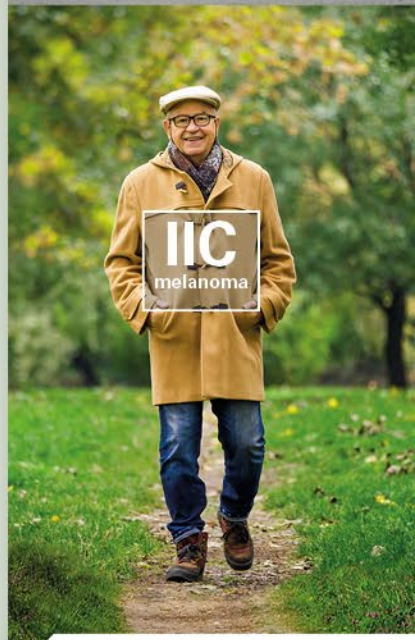
Adapted from Long GV, *et al.* 2022.[1]

IA3 data cut-off: 4 January 2022.[1]
*DMFS was defined as the time from randomisation to the first diagnosis of distant metastasis.[1]
[*]Data from other race subgroups were not estimable due to the small number of patients in these subgroups and hence are not included.[1]
CI, confidence interval; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IA, interim analysis; T, tumour.

1. Long GV, *et al. Lancet Oncol* 2022;23:1378–1388.

KEYTRUDA® (pembrolizumab)

KEYNOTE-716
Safety Data From Third Interim Analysis (27.4-Month Median Follow-Up)



KEYTRUDA®
(pembrolizumab)

The Proportion Of Patients Experiencing Adverse Events At The Third Interim Analysis Was Similar To The Initial Analysis*[1]

Summary of adverse events in KEYNOTE-716 at the third interim analysis*[1]

Adverse event, n (%)	KEYTRUDA (n=483)	Placebo (n=486)
Any	462 (96)	445 (92)
Led to discontinuation	85 (17)	23 (5)
Led to death	1 (<1)†	5 (1)†
Treatment-related	400 (83)	309 (64)
Grade 3–4	83 (17)	24 (5)
Led to discontinuation	77 (16)	12 (3)
Led to death	0 (0)	0 (0)

Adapted from Long GV, *et al.* 2022.[1]

For further details on adverse events and risk management, please refer to the SmPC and Risk Management Materials.

IA3 data cut-off: 4 January 2022.[1]

*The safety population included all patients who were randomly assigned to treatment and received at least one dose of study treatment.[1]

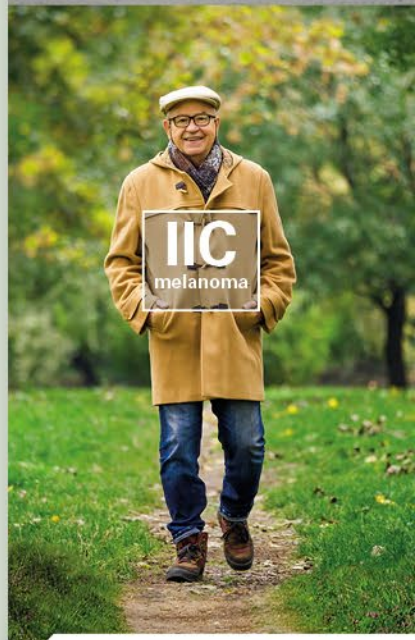
†One death occurred in the KEYTRUDA group due to COVID-19-related pneumonia, five deaths occurred in the placebo group: one due to COVID-19-related pneumonia, one due to pneumonia, one due to malignant neoplasm, one due to recurrent cancer and one due to suicide.[1]

COVID-19, coronavirus disease 2019; IA, interim analysis; SmPC, Summary of Product Characteristics.

1. Long GV, *et al. Lancet Oncol* 2022;23:1378–1388.

KEYTRUDA® (pembrolizumab)

KEYNOTE-716
Efficacy Data From Final Analysis (39.4-Month Median Follow-Up)



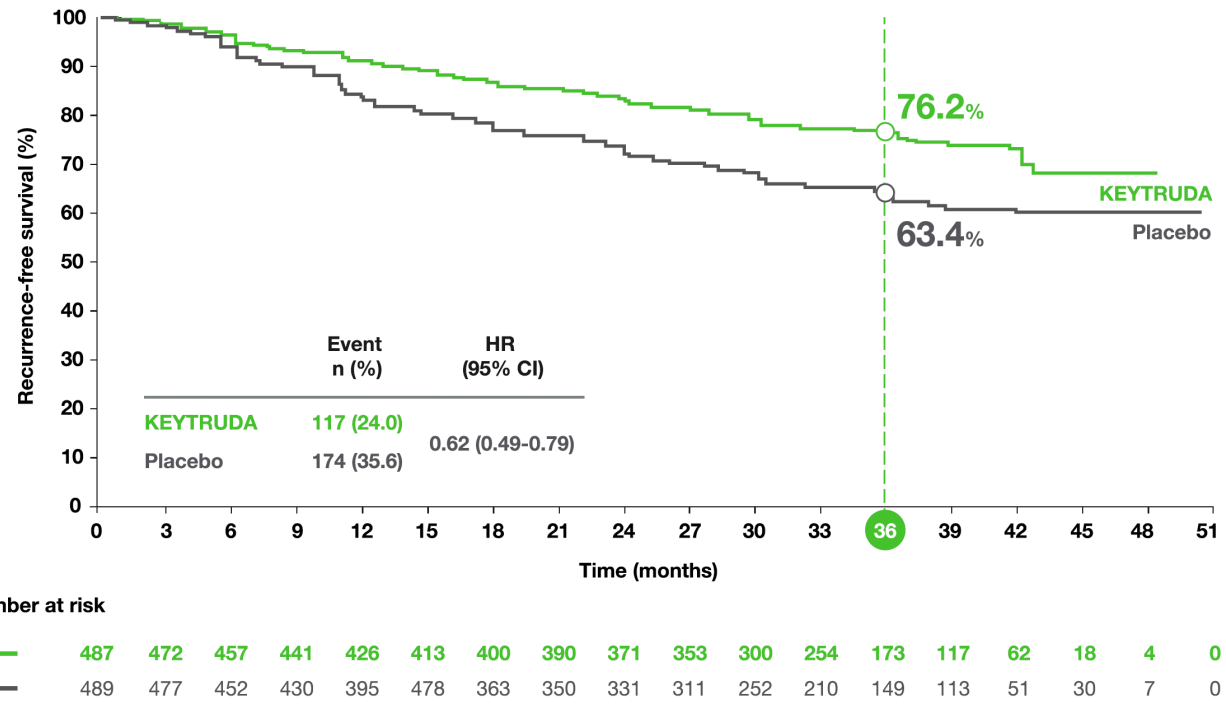
KEYTRUDA®
(pembrolizumab)

Recurrence-Free Survival* Following Treatment With KEYTRUDA Versus Placebo At The Final Analysis[1]

These results are from an exploratory long-term analysis and should be interpreted with caution. Significance was not tested; therefore, no statistical conclusions can be drawn from this analysis.

Kaplan-Meier estimates of RFS in the ITT population at the final analysis†

Median follow-up: 39.4 months



The final analysis HR: 0.62, demonstrated a 38% risk reduction in disease recurrence with KEYTRUDA versus placebo[1]

Click here to view the RFS subgroup analysis

Adapted from: Luke JJ, *et al.* 2023.[1]

Final analysis data cut-off: 4 January 2023.[1] The n number displayed represents the number of events in the treatment arm.

*RFS was defined as time from randomisation to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurred first.[2]

†Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T category (T3b versus T4a versus T4b).[2]

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; RFS, recurrence-free survival, T, tumour.

1. Luke JJ, *et al.* Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the Phase 3 KEYNOTE-716 study. ASCO. 2–6 June 2023. Chicago, IL, USA. Oral presentation; **2**. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

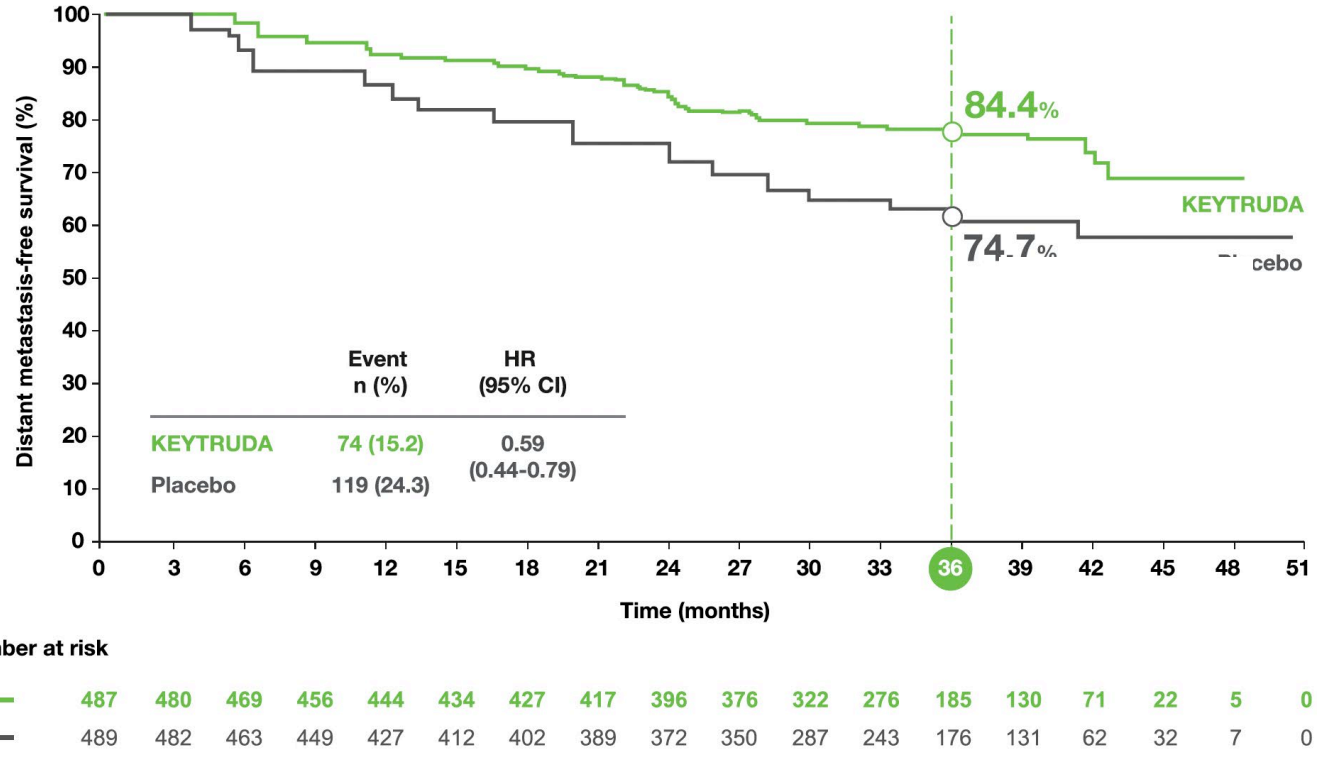
KEYTRUDA® (pembrolizumab)

Distant Metastasis-Free Survival* Following Treatment With KEYTRUDA Versus Placebo At The Final Analysis[1]

These results are from an exploratory long-term analysis and should be interpreted with caution. Significance was not tested; therefore, no statistical conclusions can be drawn from this analysis.

Kaplan-Meier estimates of DMFS in the ITT population at the final analysis†

Median follow-up: 39.4 months



Adapted from: Luke JJ, *et al.* 2023.[1]

The final analysis HR: 0.59, demonstrated a 41% risk reduction in distant metastasis with KEYTRUDA versus placebo[1]

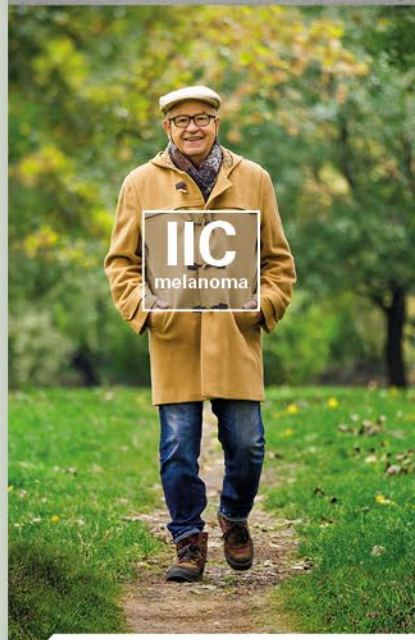
Click here to view the DMFS subgroup analysis ›

Final analysis data cut-off: 4 January 2023.[1] The n number displayed represents the number of events in the treatment arm.
*DMFS was defined as the time from randomisation to the first diagnosis of distant metastasis.[2]
† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by melanoma T category (T3b versus T4a versus T4b).[2]
CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITT, intention-to-treat; T, tumour.

1. Luke JJ, *et al.* Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the Phase 3 KEYNOTE-716 study. ASCO. 2–6 June 2023. Chicago, IL, USA. Oral presentation; **2**. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

KEYTRUDA® (pembrolizumab)

KEYNOTE-716
Safety Data From Final Analysis (39.4-Month Median Follow-Up)



KEYTRUDA®
(pembrolizumab)

The Safety Profile Of KEYTRUDA Among The Patients With Resected Melanoma Enrolled In KEYNOTE-716 Was Consistent With Previous Analyses[1]

Summary of adverse events in KEYNOTE-716 at the final analysis[2]

Adverse event, n (%)	KEYTRUDA (n=483)	Placebo (n=486)
Any	461 (96)	446 (92)
Treatment-related	399 (83)	309 (64)
Grade 3–4	83 (17)	25 (5)
Led to discontinuation	77 (16)	12 (3)
Led to death	0 (0)	0 (0)
Immune-mediated and infusion reactions	183 (38)	46 (10)
Grade 3–4	53 (11)	6 (1)

Adapted from: Luke JJ, *et al.* 2023.[2]

For further details on adverse events and risk management, please refer to the SmPC and Risk Management Materials.

Final analysis data cut-off: 4 January 2023.[2]

SmPC, Summary of Product Characteristics.

1. Long GV, *et al. Lancet Oncol* 2022;23:1378–1388; **2.** Luke JJ, *et al.* Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the Phase 3 KEYNOTE-716 study. ASCO. 2–6 June 2023. Chicago, IL, USA. Oral presentation.

KEYTRUDA® (pembrolizumab)

Patients With Stage IIB/C Could Benefit From KEYTRUDA Treatment Similar To Patients In The KEYNOTE-716 Trial

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Treatment with KEYTRUDA (n=487) in patients with Stage IIB and Stage IIC melanoma in the KEYNOTE-716 trial (N=976):[1]

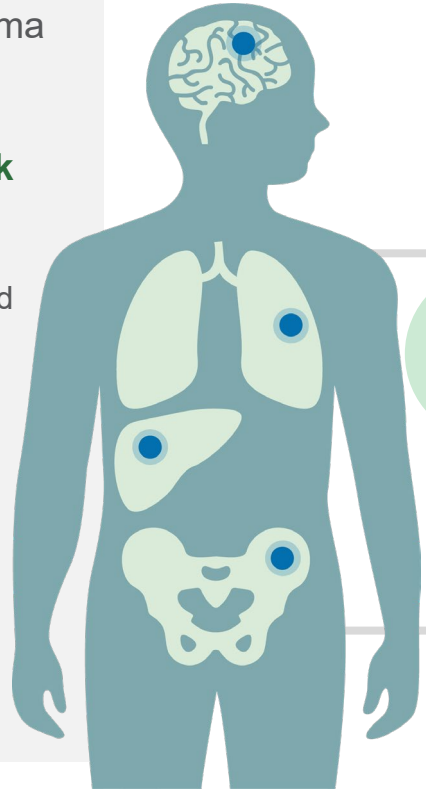
KEYTRUDA significantly **reduced the risk of disease recurrence or death versus placebo** in patients with Stage IIB and IIC melanoma

35% (IA1)

KEYTRUDA demonstrated a 35% reduction in risk of recurrence versus placebo
at a median follow-up of 14.4 months*[1]
- Incidence of recurrence or death was 11% in patients treated with KEYTRUDA versus 17% in those receiving placebo[1]

Final analysis

Adjuvant KEYTRUDA demonstrated a **sustained improvement in DMFS and RFS** at a median follow-up of 39.4 months (final analysis)[2]



At a median follow-up of 39.4 months, KEYTRUDA was associated with **a safety profile consistent with earlier interim analyses of this study[1–3]**

For further details on adverse events and risk management, please refer to the SmPC and Risk Management Materials

*Results in the IA3 analysis were consistent with results in the IA1 analysis.[2]
DMFS, distant metastasis-free survival; IA, interim analysis; RFS, recurrence-free survival; SmPC, Summary of Product Characteristics.
1. Luke JJ, *et al. Lancet* 2022;399:1718–1729; **2.** Luke JJ, *et al.* Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the Phase 3 KEYNOTE-716 study. ASCO. 2–6 June 2023. Chicago, IL, USA. Oral presentation; **3.** Long GV, *et al. Lancet Oncol* 2022;23:1378–1388.

KEYTRUDA® (pembrolizumab)

DOSING AND ADMINISTRATION

KEYTRUDA Offers Flexibility Of Dosing[1]

GB PI | NI PI

Administered as an IV infusion

Over 30 minutes

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.[1]

bw, bodyweight; IV, intravenous.

1. KEYTRUDA Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/product/2498/smpc Accessed: April 2024

KEYTRUDA® (pembrolizumab)

Find Out More About Stage II Melanoma

GB PI | NI PI

Click here or scan the QR code to sign up for MSD emails and be the first to hear about Stage II melanoma news and content

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)

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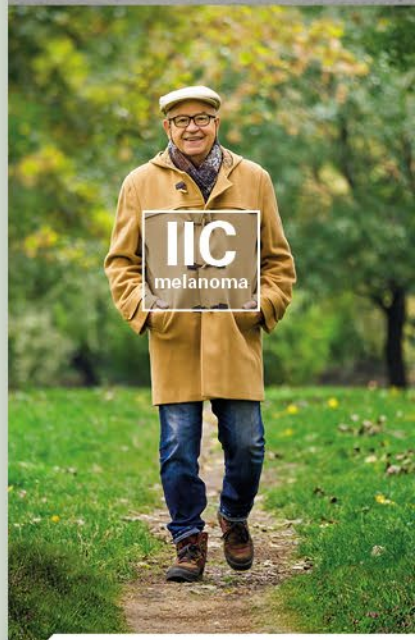
KEYNOTE-716
Appendix

- Baseline Patient Characteristics Appendix
- RFS Subgroup Final Analysis Appendix
- DMFS Subgroup Final Analysis Appendix
- Relapse Rates, Distant Metastasis Rates & Time to Relapse in Stage III melanoma



KEYTRUDA®
(pembrolizumab)

Baseline Patient Characteristics Were Similar Between The KEYTRUDA And Placebo Arms[1]

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T-category is based on TNM staging.[1]
Disease stage is defined by the 8th AJCC 2017 classification.[1]

Click here to view study design

	Pembrolizumab (n=487)	Placebo (n=489)
Age, years (IQR)	60 (51–68)	61 (53–69)
<65 years, n (%)	303 (62)	295 (60)
≥65 years, n (%)	184 (38)	194 (40)
Sex, n (%)		
Female	187 (38)	200 (41)
Male	300 (62)	289 (59)
White, n (%)	435 (89)	439 (90)
Geographic region, n (%)		
Not USA	392 (80)	409 (84)
USA	95 (20)	80 (16)

	Pembrolizumab (n=487)	Placebo (n=489)
ECOG PS, n (%)		
0	454 (93)	452 (92)
1	32 (7)	35 (7)
2	0	1 (<1)
Missing	1 (<1)	1 (<1)
T category, n (%)		
T3a	2 (<1)	0
T3b	200 (41)	201 (41)
T4a	113 (23)	116 (24)
T4b	172 (35)	172 (35)
Disease Stage, n (%)		
IIB	309 (63)	316 (65)
IIC	171 (35)	169 (35)

Adapted from Luke JJ, *et al.* 2022.[1]

AJCC, American Joint Committee on Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; T, tumour.

1. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

KEYTRUDA® (pembrolizumab)

Recurrence-Free Survival* In Key Patient Subgroups In KEYTRUDA Versus Placebo[1]

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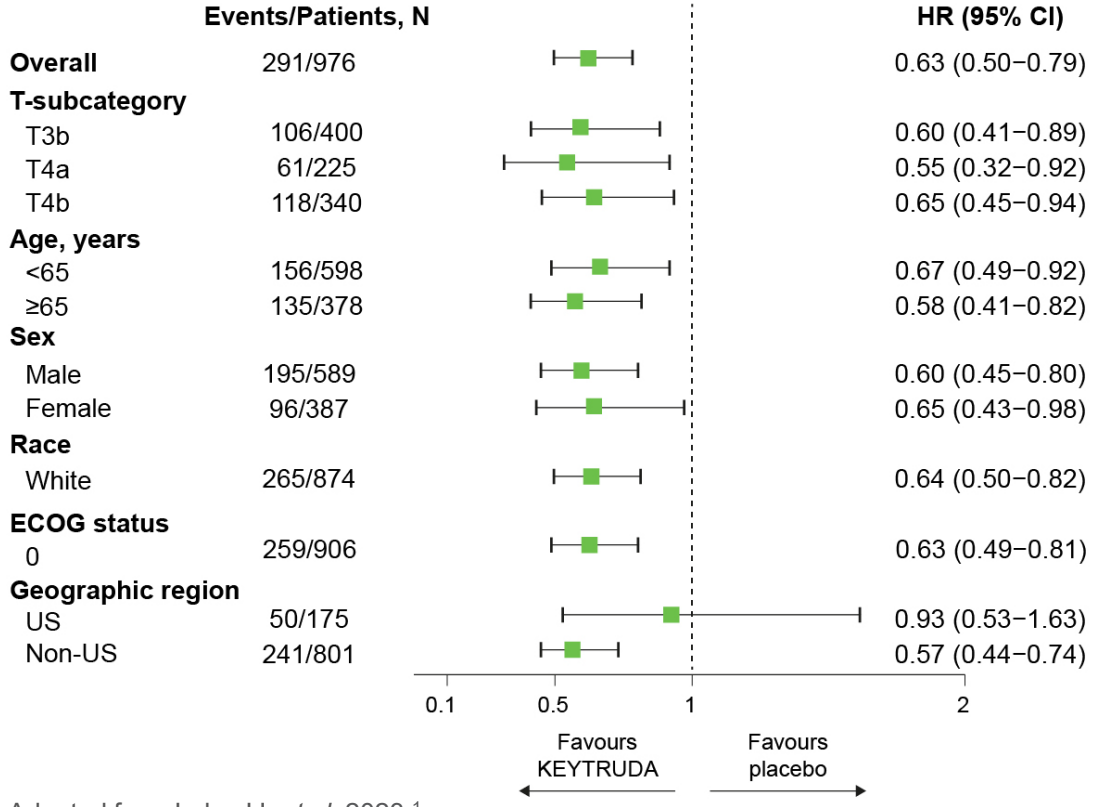
KEYNOTE-716 was **not powered** to detect differences in the treatment effect in these subgroups; therefore, results from exploratory analyses should be interpreted with caution because of the modest patient numbers and potential imbalances in baseline characteristics within subgroups.

Median follow-up: 39.4 months



Adapted from Luke JJ, *et al.* 2023.[1]

Click here to view the RFS final analysis data

Final analysis data cut-off: 4 January 2023.[1]

*RFS was defined as time from randomisation to the date of first recurrence of melanoma at any site (local, in-transit or regional lymph nodes or distant recurrence) or death due to any cause, whichever occurred first.[2]

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; RFS, recurrence-free survival; T, tumour.

1. Luke JJ, *et al.* Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the Phase 3 KEYNOTE-716 study. ASCO. 2–6 June 2023. Chicago, IL, USA. Oral presentation; **2**. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

KEYTRUDA® (pembrolizumab)

Analysis Of Distant-Metastasis-Free Survival* In Key Patient Subgroups In KEYTRUDA Versus Placebo[1]

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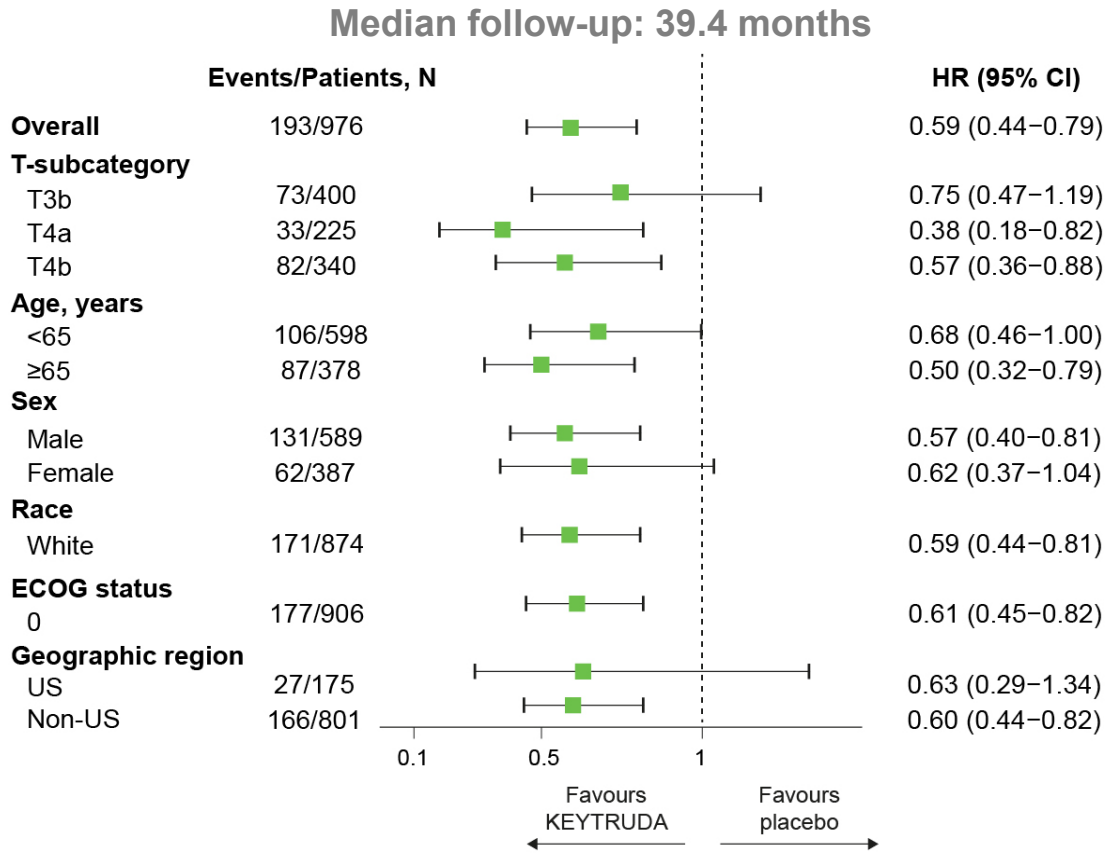
KEYNOTE-716 was **not powered** to detect differences in the treatment effect in these subgroups; therefore, results from exploratory analyses should be interpreted with caution because of the modest patient numbers and potential imbalances in baseline characteristics within subgroups.



Adapted from Luke JJ, *et al.* 2023.[1]

Click here to view the DMFS final analysis data

Final analysis data cut-off: 4 January 2023.[1]
*DMFS was defined as the time from randomisation to the first diagnosis of distant metastasis.[2]
CI, confidence interval; DMFS, distant metastasis-free survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; T, tumour.

1. Luke JJ, *et al.* Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: Final analysis of distant metastasis-free survival in the Phase 3 KEYNOTE-716 study. ASCO. 2–6 June 2023. Chicago, IL, USA. Oral presentation; **2**. Luke JJ, *et al. Lancet* 2022;399:1718–1729.

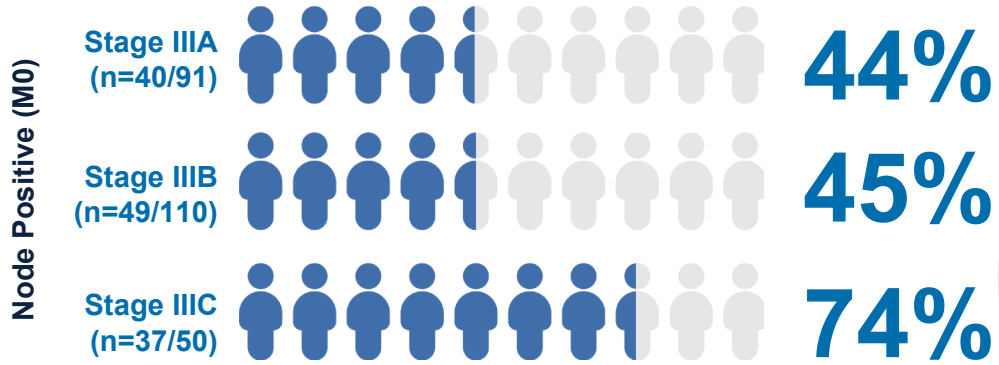
KEYTRUDA® (pembrolizumab)

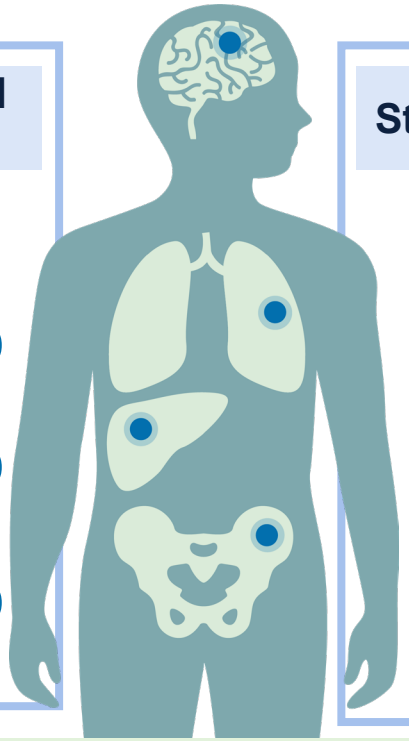
Relapse Rates In Patients With Stage III Melanoma Are 44%, 45% And 74% For Stages IIIA, IIIB And IIIC, Respectively[1]

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] 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.

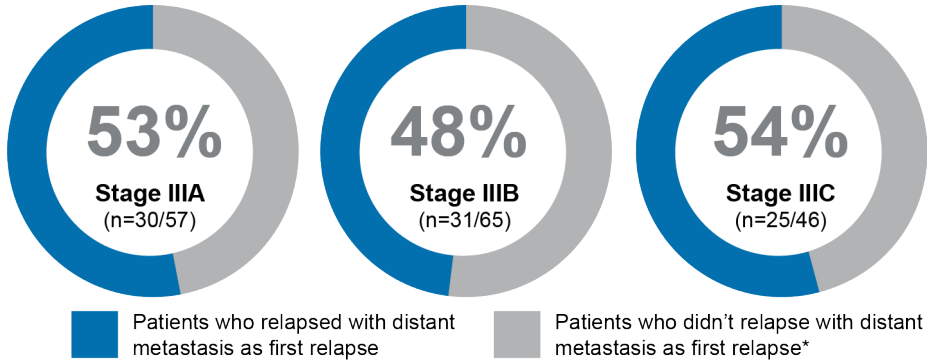
Stage III Relapse Rates In Patients Who Received Watch-and-wait Post-surgery[1]





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 loco-regional 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; RFS, relapse-free survival.

1. Supplementary Appendix to: Mohr P et al. *Melanoma Manag* 2019;6(4):MMT33;
2. Mohr P et al. *Melanoma Manag* 2019;6(4):MMT33.

KEYTRUDA® (pembrolizumab)

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

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[1]

Median Time to Relapse Among Patients Who Relapsed

Stage IIIA	Stage IIIB	Stage IIIC
15.5 MONTHS	12.8 MONTHS	5.2 MONTHS
(n=40/91)	(n=49/110)	(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(4):MMT33.

KEYTRUDA® (pembrolizumab)