Cancer Trials Ireland CLG
RCSI House
121 St Stephen's Green
Dublin 2
D02 H903
Ireland
e: info@cancertrials.ie
t: +353 (0)1 6677211
f: +353 (0)1 6697869

24-Feb-2025

Trial **2011-004257-29**, ECOG 1609

A Phase III Randomized Study of Adjuvant Ipilimumab Anti-CTLA4 Therapy Versus High-Dose Interferon α-2b for Resected High-Risk Melanoma

Clinical Trial Results:

This trial was sponsored by Cancer Trials Ireland in Europe however was led and sponsored by NCI in the US. The trial never opened in the EU. Due to differences in the reporting of specific data fields in the US and EU, certain details required for validation of trial results in EudraCT are not available to us.

The attached download from ClinicalTrials.gov and articles by McLouth et al and Saad et al are the full extent of results available to us for the trial.

Results can be accessed at this link: Results Posted | Ipilimumab or High-Dose Interferon Alfa-2b in Treating Patients With High-Risk Stage III-IV Melanoma That Has Been Removed by Surgery | ClinicalTrials.gov

We as sponsor are therefore posting a PDF file of results incl. a justification.

Cancer Trials Ireland Quality & Training Manager
Charity Regulatory Authority No. 20036676 | Revenue Number CHY12492 | Company Number 268044 a: Cancer Trials Ireland , RCSI House, 121 St. Stephen's Green , Dublin 2 , D02 H903
t: +353 1 667 7211 | f: +353 1 669 7869 |

Active, not recruiting

Ipilimumab or High-Dose Interferon Alfa-2b in Treating Patients With High-Risk Stage III-IV Melanoma That Has Been Removed by Surgery

ClinicalTrials.gov ID NCT01274338

Sponsor National Cancer Institute (NCI)

Information provided by National Cancer Institute (NCI) (Responsible Party)

Last Update Posted 2025-02-06

Results Posted Tab

Results Overview

Conditions

Melanoma of Unknown Primary
Recurrent Melanoma
Stage IIIB Cutaneous Melanoma AJCC v7
Stage IIIC Cutaneous Melanoma AJCC v7
Stage IV Cutaneous Melanoma AJCC v6 and v7

Intervention/Treatment

- Biological: Ipilimumab
- Other: Quality-of-Life Assessment
- Biological: Recombinant Interferon Alfa-2b

Other Study ID Numbers

- NCI-2011-02649
- NCI-2011-02649 (Registry Identifier) (REGISTRY: CTRP (Clinical Trial Reporting Program))

Study Design

Allocation: Randomized
Interventional Model: Parallel Assignment
Masking: None (Open Label)
Primary Purpose: Treatment

Results Point of Contact

Name/Title: Study Statistician
Organization: ECOG-ACRIN Biostatistics Center
Phone: 617-632-3012
Email: eatrials@jimmy.harvard.edu

Enrollment (Actual)

1673

Study Type

Interventional

Study Record Dates

These dates track the progress of study record and summary results submissions to ClinicalTrials.gov. Study records and reported results are reviewed by the National Library of Medicine (NLM) to make sure they meet specific quality control standards before being posted on the public website.

Study Registration Dates

First Submitted
2011-01-08

First Posted (Estimated)
2011-01-11

Results Reporting Dates

Results First Submitted
2021-03-22

Results First Posted

2021-05-27

Study Record Updates

Last Update Posted (Estimated)

2025-02-06

Last Verified

2025-01

Participant Flow

Recruitment Details

A total of 1673 patients, including 1670 adult patients and 3 pediatric patients, were accrued between May 25, 2011 and July 26, 2016. Accrual of adult patients were completed on August 15, 2014. The study was reactivated to accrue pediatric patients on September 23, 2014.

Pre-assignment Details

[Not Specified]

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
Arm/Group Description	Patients receive induction high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 21 days for a total of 4 courses in the absence of disease progression or unacceptable toxicity. Beginning on week 24, patients receive maintenance high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 12 weeks for a maximum of 4 courses in the absence of disease progression or unacceptable toxicity.	Patients receive high-dose recombinant interferon alpha-2b days 1-5, 8-12, 15-19, and 22-26 absence of disease progression unacceptable toxicity. Patients t receive maintenance high-dose recombinant interferon alpha-2b on days 1, 3, and 5. Treatment re every week for 48 weeks in the absence of disease progression unacceptable toxicity.

Period Title: **Overall Study**

Started	511	636
Received Treatment	503	520

Data Available for the FACT-G and FACT-BRM Analyses	110	114
Data Available for FACIT-D Analysis	109	114
Completed	108	182
Not Completed	403	454

Reason Not Completed

Lack of Efficacy	72	108
Adverse Event	272	105
Death	8	1
Withdrawal by Subject	27	99
Did not start treatment	8	116
Alternative therapy	0	1
Other complicating diseases	0	3
Treatment arm was suspended due to toxicity	4	0
Pregnancy	0	0
Reason not reported	12	21

Baseline Characteristics

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
Arm/Group Description	Patients receive induction high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 21 days for a total of 4 courses in the absence of disease progression or unacceptable toxicity. Beginning on week 24, patients receive maintenance high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 12 weeks for a maximum of 4 courses in the absence of disease progression or unacceptable toxicity.	Patients receive high-dose recombinant interferon alpha-2b days 1-5, 8-12, 15-19, and 22-26 absence of disease progression unacceptable toxicity. Patients t receive maintenance high-dose recombinant interferon alpha-2b on days 1, 3, and 5. Treatment re every week for 48 weeks in the absence of disease progression unacceptable toxicity.
Overall Number of Baseline Participants	511	636
Baseline Analysis Population Description	All randomized patients	

Expand all / Collapse all

Age, Continuous

Median (Full Range) | Unit of measure: years

Number Analyzed	511 participants	636 participants
	54 (18 to 60)	54 (18 to 83)

Sex: Female, Male

Measure Type: Count of Participants | Unit of measure: Participants

Number Analyzed	511 participants	636 participants
Female	169 33.1%	241 37.9%
Male	342 66.9%	395 62.1%

Ethnicity (NIH/OMB)

Measure Type: Count of Participants | Unit of measure: Participants

Number Analyzed	511 participants	636 participants
Hispanic or Latino	8 1.6%	20 3.1%
Not Hispanic or Latino	484 94.7%	591 92.9%
Unknown or Not Reported	19 3.7%	25 3.9%

Race (NIH/OMB)

Measure Type: Count of Participants | Unit of measure: Participants

Number Analyzed	511 participants	636 participants
American Indian or Alaska Native	0 0.0%	0 0.0%
Asian	6 1.2%	2 0.3%
Native Hawaiian or Other Pacific Islander	0 0.0%	0 0.0%
Black or African American	1 0.2%	4 0.6%
White	497 97.3%	620 97.5%
More than one race	0 0.0%	1 0.2%
Unknown or Not Reported	7 1.4%	9 1.4%

Outcome Measures

Expand all / Collapse all

1. Recurrence-free Survival (RFS; Arm B [HDI] vs. Arm C [LIP])

Type: Primary | Time Frame: Assessed every 3 months for 2 years, then every 6 months for years 3-5 and then annually up to 8 years

Description	Recurrence-free survival is defined as the time from randomization to recurrence or death, whichever occurs first. The following criteria constitute the only acceptable evidence of disease recurrence.

	Lung and liver: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease. Central Nervous System: A positive brain CT or MRI scan or CSF cytology. Cutaneous, Subcutaneous and Lymph Node Recurrence: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease. Bone and Other Organs: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease identified on two different radiologic studies: i.e., positive nuclear bone scan or PET scan and contrast GI series or ultrasound, X-ray or CT of abdomen for abdominal disease.
Time Frame	Assessed every 3 months for 2 years, then every 6 months for years 3-5 and then annually up to 8 years
Analysis Population Description	Concurrently randomized patients on Arms B and C

Arm/Group Title	Arm B (HDI)	Arm C (LIP)
Arm/Group Description	Patients receive high-dose recombinant interferon alpha-2b IV on days 1-5, 8-12, 15-19, and 22-26 in the absence of disease progression or unacceptable toxicity. Patients then receive maintenance high-dose recombinant interferon alpha-2b SC on days 1, 3, and 5. Treatment repeats every week for 48 weeks in the absence of disease progression or unacceptable toxicity.	Patients receive induction low-d ipilimumab IV over 90 minutes c 1. Treatment repeats every 21 d for a total of 4 courses in the ab of disease progression or unacceptable toxicity. Beginnin week 24, patients receive maintenance low-dose ipilimum over 90 minutes on day 1. Treat repeats every 12 weeks for a maximum of 4 courses in the ab of disease progression or unacceptable toxicity.
Overall Number of Participants Analyzed	528	523
Median (95% Confidence Interval) | Unit of Measure: years	2.5 (1.7 to 3.3)	4.5[1] (2.6 to NA)

[1] The upper limit of the 95% confidence interval was not calculable because an insufficient number of participants reached the event at the final time point for assessment.

Statistical Analysis 1

Statistical Analysis Overview

Comparison Group Selection	Arm B (HDI), Arm C (LIP)
Comments	This study has a two-step hierarchical approach. In the first step, the low-dose Ipi (LIP) will be compared with HDI. If the low-dose Ipi is significantly better than HDI, then the high-dose Ipi will be compared with HDI as a second step. When comparing the two investigational treatment groups, the primary comparison will be an intent to treat analysis of recurrence free survival (RFS; First Co-primary Endpoint) and overall survival (OS; Second Co-primary Endpoint).

Type of Statistical Test	Superiority
Comments	[Not Specified]

Statistical Test of Hypothesis

P-Value	0.065
Comments	This design provides at least 80% power at a one sided type I error rate of 0.003.
Method	Log Rank
Comments	Stratified logrank test

2. 5-year Overall Survival (OS) Rate (Arm B [HDI] vs. Arm C [LIP])

Type: Primary | Time Frame: Assessed every 3 months for 2 years, then every 6 months for years 3-5

Description	Overall survival is defined as the time from randomization to death or date last known alive.
Time Frame	Assessed every 3 months for 2 years, then every 6 months for years 3-5
Analysis Population Description	Concurrently randomized patients on Arms B and C

Arm/Group Title	Arm B (HDI)	Arm C (LIP)
Arm/Group Description	Patients receive high-dose recombinant interferon alpha-2b IV on days 1-5, 8-12, 15-19, and 22-26 in the absence of disease progression or unacceptable toxicity. Patients then receive maintenance high-dose recombinant interferon alpha-2b SC on days 1, 3, and 5. Treatment repeats every week for 48 weeks in the absence of disease progression or unacceptable toxicity.	Patients receive induction low-d ipilimumab IV over 90 minutes c 1. Treatment repeats every 21 d for a total of 4 courses in the ab of disease progression or unacceptable toxicity. Beginnin week 24, patients receive maintenance low-dose ipilimum over 90 minutes on day 1. Treat repeats every 12 weeks for a maximum of 4 courses in the ab of disease progression or unacceptable toxicity.
Overall Number of Participants Analyzed	528	523
Measure Type: Number (95% Confidence Interval) | Unit of Measure: proportion of participants	0.67 (0.62 to 0.72)	0.72 (0.68 to 0.76)

Statistical Analysis 1

Statistical Analysis Overview

Comparison Group Selection	Arm B (HDI), Arm C (LIP)
Comments	This study has a two-step hierarchical approach. In the first step, the low-dose Ipi (LIP) will be compared with HDI. If the low-dose Ipi is significantly better than HDI, then the high-dose Ipi will be compared with HDI as a second step. When comparing the two investigational treatment groups, the primary comparison will be an intent to treat analysis of recurrence free survival (RFS; First Co-primary Endpoint) and overall survival (OS; Second Co-primary Endpoint).
Type of Statistical Test	Superiority

Comments	This design will provide 80% power to detect the difference between the two arms at a one-sided type I error rate of 0.022.

Statistical Test of Hypothesis

P-Value	0.044
Comments	[Not Specified]
Method	Log Rank
Comments	Stratified logrank test

3. Recurrence-free Survival (RFS; Arm A [HIP] vs. Arm B [HDI])

Type: Primary | Time Frame: Assessed every 3 months for 2 years, then every 6 months for years 3-5 and then annually up to 8 years

Description	Recurrence-free survival is defined as the time from randomization to recurrence or death, whichever occurs first. The following criteria constitute the only acceptable evidence of disease recurrence. Lung and liver: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease. Central Nervous System: A positive brain CT or MRI scan or CSF cytology. Cutaneous, Subcutaneous and Lymph Node Recurrence: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease. Bone and Other Organs: Positive cytology or biopsy in the presence of a single new lesion or the appearance of multiple lesions consistent with metastatic disease identified on two different radiologic studies: i.e., positive nuclear bone scan or PET scan and contrast GI series or ultrasound, X-ray or CT of abdomen for abdominal disease.
Time Frame	Assessed every 3 months for 2 years, then every 6 months for years 3-5 and then annually up to 8 years
Analysis Population Description	Concurrently randomized patients on Arms A and B

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
Arm/Group Description	Patients receive induction high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 21 days for a total of 4 courses in the absence of disease progression or unacceptable toxicity. Beginning on week 24, patients receive maintenance high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 12 weeks for a maximum of 4 courses in the absence of disease progression or unacceptable toxicity.	Patients receive high-dose recombinant interferon alpha-2b days 1-5, 8-12, 15-19, and 22-26 absence of disease progression unacceptable toxicity. Patients t receive maintenance high-dose recombinant interferon alpha-2b on days 1, 3, and 5. Treatment re every week for 48 weeks in the absence of disease progression unacceptable toxicity.
Overall Number of Participants Analyzed	511	478
Median (95% Confidence Interval) | Unit of Measure: years	3.9 [1] (2.9 to NA)	2.4 (1.6 to 3.0)

[1] The upper limit of the 95% confidence interval was not calculable because an insufficient number of participants reached the event at the final time point for assessment.

4. 5-year Overall Survival (OS) Rate (Arm A [HIP] vs. Arm B [HDI])

Type: Primary | Time Frame: Assessed every 3 months for 2 years, then every 6 months for years 3-5

Description	Overall survival is defined as the time from randomization to death or date last known alive.
Time Frame	Assessed every 3 months for 2 years, then every 6 months for years 3-5
Analysis Population Description	Concurrently randomized patients on Arms A and B

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
Arm/Group Description	Patients receive induction high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 21 days for a total of 4 courses in the absence of disease progression or unacceptable toxicity. Beginning on week 24, patients receive maintenance high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 12 weeks for a maximum of 4 courses in the absence of disease progression or unacceptable toxicity.	Patients receive high-dose recombinant interferon alpha-2b days 1-5, 8-12, 15-19, and 22-26 absence of disease progression unacceptable toxicity. Patients t receive maintenance high-dose recombinant interferon alpha-2b on days 1, 3, and 5. Treatment re every week for 48 weeks in the absence of disease progression unacceptable toxicity.
Overall Number of Participants Analyzed	511	478
Measure Type: Number (95% Confidence Interval) | Unit of Measure: proportion of participants	0.70 (0.65 to 0.74)	0.65 (0.60 to 0.70)

Statistical Analysis 1

Statistical Analysis Overview

Comparison Group Selection	Arm A (HIP), Arm B (HDI)
Comments	This study has a two-step hierarchical approach. In the first step, the low-dose Ipi (LIP) will be compared with HDI. If the low-dose Ipi is significantly better than HDI, then the high-dose Ipi will be compared with HDI as a second step. When comparing the two investigational treatment groups, the primary comparison will be an intent to treat analysis of recurrence free survival (RFS; First Co-primary Endpoint) and overall survival (OS; Second Co-primary Endpoint).
Type of Statistical Test	Superiority
Comments	[Not Specified]

Statistical Test of Hypothesis

P-Value	0.289
Comments	If low dose Ipi (LIP) vs. HDI is significant for OS at the 2.2% level, then we will compare high dose Ipi (HIP) vs. HDI at the 2.2% level.
Method	Log Rank
Comments	Stratified logrank test

5. Change in FACT-G (Functional Assessment of Cancer Therapy - General) Total Score From Baseline to 3 Months

Type: Secondary | Time Frame: Assessed at baseline and 3 months

Description	The Functional Assessment of Cancer Therapy - General (FACT-G) is a 27-item questionnaire that has four areas of measurements (physical well-being, social/family well-being, emotional well-being and functional well-being) with a scale of 0-4. The FACT-G total score ranges between 0 and 108. The higher the score, the better the quality of life. Change in FACT-G total score from baseline to 3 months was calculated as month 3 score - baseline score.
Time Frame	Assessed at baseline and 3 months
Analysis Population Description	Patients with baseline and 3-month FACT-G assessments were included in this analysis. Pediatric patients did not participate in the quality of life part of the study.

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
Arm/Group Description	Patients receive induction high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 21 days for a total of 4 courses in the absence of disease progression or unacceptable toxicity. Beginning on week 24, patients receive maintenance high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 12 weeks for a maximum of 4 courses in the absence of disease progression or unacceptable toxicity.	Patients receive high-dose recombinant interferon alpha-2b days 1-5, 8-12, 15-19, and 22-26 absence of disease progression unacceptable toxicity. Patients t receive maintenance high-dose recombinant interferon alpha-2b on days 1, 3, and 5. Treatment re every week for 48 weeks in the absence of disease progression unacceptable toxicity.
Overall Number of Participants Analyzed	110	114
Mean (Standard Deviation) | Unit of Measure: score on a scale	-4.9 (14.1)	-12.9 (14.1)

6. Change in FACIT-D (Functional Assessment of Cancer Therapy - Diarrhea) Diarrhea Subscale Score From Baseline to 3 Months

Type: Secondary | Time Frame: Assessed at baseline and 3 months

Description	The diarrhea subscale of The Functional Assessment of Chronic Illness Therapy - Diarrhea (FACIT-D) is an 11-item questionnaire with a scale of 0-4. The FACIT-D diarrhea subscale score ranges between 0 and 44. The higher the score, the better the quality of life. Change in FACIT-D diarrhea subscale score from baseline to 3 months was calculated as month 3 score - baseline score.
Time Frame	Assessed at baseline and 3 months
Analysis Population Description	Patients with baseline and 3-month FACIT-D diarrhea subscale assessments were included in this analysis. Pediatric patients did not participate in the quality of life part of the study.

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
Arm/Group Description	Patients receive induction high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 21 days for a total of 4 courses in the absence of disease progression or unacceptable toxicity. Beginning on week 24, patients receive maintenance high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 12 weeks for a maximum of 4 courses in the absence of disease progression or unacceptable toxicity.	Patients receive high-dose recombinant interferon alpha-2b days 1-5, 8-12, 15-19, and 22-26 absence of disease progression unacceptable toxicity. Patients t receive maintenance high-dose recombinant interferon alpha-2b on days 1, 3, and 5. Treatment re every week for 48 weeks in the absence of disease progression unacceptable toxicity.
Overall Number of Participants Analyzed	109	114
Mean (Standard Deviation) | Unit of Measure: score on a scale	-3.7 (6.9)	-0.7 (2.7)

7. Change in FACT-BRM (Functional Assessment of Cancer Therapy - Biologic Response Modifiers) Total Score From Baseline to 3 Months

Type: Secondary | Time Frame: Assessed at baseline and 3 months

Description	The Functional Assessment of Cancer Therapy - Biologic Response Modifiers (FACT-BRM) is a questionnaire including FACT-G (The Functional Assessment of Cancer Therapy - General) and additional sections addressing physical and mental quality of life aspects. It is a 40-item questionnaire with a scale of 0-4. The FACT-BRM total score ranges between 0 and 160. The higher the score, the better the quality of life. Change in FACT-BRM total score from baseline to 3 months is calculated as month 3 score - baseline score.
Time Frame	Assessed at baseline and 3 months
Analysis Population Description	Patients with baseline and 3-month FACT-BRM assessments were included in this analysis. Pediatric patients did not participate in the quality of life part of the study.

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
Arm/Group Description	Patients receive induction high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 21 days for a total of 4 courses in the absence of disease progression or unacceptable toxicity. Beginning on week 24, patients receive maintenance high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 12 weeks for a maximum of 4 courses in the absence of disease progression or unacceptable toxicity.	Patients receive high-dose recombinant interferon alpha-2b days 1-5, 8-12, 15-19, and 22-26 absence of disease progression unacceptable toxicity. Patients t receive maintenance high-dose recombinant interferon alpha-2b on days 1, 3, and 5. Treatment re every week for 48 weeks in the absence of disease progression unacceptable toxicity.
Overall Number of Participants Analyzed	110	114
Mean (Standard Deviation) | Unit of Measure: score on a scale	-8.3 (19.7)	-22.7 (20.4)

Adverse Events

Time Frame
Assessed every 4 weeks while on treatment and for 30 days after the end of treatment, up to 20 years

Adverse Event Reporting Description
Only patients who started protocol therapy are included in the analysis of adverse events. All registered patients are included in the analysis of all-cause mortality.

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
Arm/Group Description	Patients receive induction high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 21 days for a total of 4 courses in the absence of disease progression or unacceptable toxicity. Beginning on week 24, patients receive maintenance high-dose ipilimumab IV over 90 minutes on day 1. Treatment repeats every 12 weeks for a maximum of 4 courses in the absence of disease progression or unacceptable toxicity.	Patients receive high-dose recombinant interferon alpha-2b days 1-5, 8-12, 15-19, and 22-26 absence of disease progression unacceptable toxicity. Patients t receive maintenance high-dose recombinant interferon alpha-2b on days 1, 3, and 5. Treatment re every week for 48 weeks in the absence of disease progression unacceptable toxicity.

All-Cause Mortality

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
	Affected / at Risk (%)	Affected / at Risk (%)
Total	153/511 (29.94%)	168/636 (26.42%)

Serious Adverse Events

Arm/Group Title	Arm A (HIP)	Arm B (HDI)
	Affected / at Risk (%)	Affected / at Risk (%)
Total	292/503 (58.05%)	410/520 (78.85%)
Blood and lymphatic system disorders		
Anemia †1	3/503 (0.60%)	4/520 (0.77%)
Febrile neutropenia †1	0/503 (0.00%)	1/520 (0.19%)
Leukocytosis †1	1/503 (0.20%)	1/520 (0.19%)
Blood and lymphatic disorders - Other †1	0/503 (0.00%)	0/520 (0.00%)
Cardiac disorders		

Acute coronary syndrome †1	0/503 (0.00%)	1/520 (0.19%)
Atrial fibrillation †1	2/503 (0.40%)	1/520 (0.19%)
Cardiac arrest †1	0/503 (0.00%)	0/520 (0.00%)
Chest pain - cardiac †1	1/503 (0.20%)	1/520 (0.19%)
Heart failure †1	0/503 (0.00%)	2/520 (0.38%)
Left ventricular systolic dysfunction †1	2/503 (0.40%)	0/520 (0.00%)
Myocardial infarction †1	1/503 (0.20%)	0/520 (0.00%)
Myocarditis †1	1/503 (0.20%)	0/520 (0.00%)
Restrictive cardiomyopathy †1	1/503 (0.20%)	0/520 (0.00%)
Sinus tachycardia †1	3/503 (0.60%)	0/520 (0.00%)
Supraventricular tachycardia †1	1/503 (0.20%)	0/520 (0.00%)
Ventricular arrhythmia †1	0/503 (0.00%)	1/520 (0.19%)

Ear and labyrinth disorders

Hearing impaired †1	2/503 (0.40%)	1/520 (0.19%)
Vertigo †1	0/503 (0.00%)	1/520 (0.19%)
Vestibular disorder †1	1/503 (0.20%)	0/520 (0.00%)

Endocrine disorders

Adrenal insufficiency †1	18/503 (3.58%)	0/520 (0.00%)
Hyperthyroidism †1	1/503 (0.20%)	0/520 (0.00%)

Hypothyroidism †1	5/503 (0.99%)	1/520 (0.19%)
Endocrine disorders - Other, specify †1	43/503 (8.55%)	0/520 (0.00%)

Eye disorders

Cataract †1	1/503 (0.20%)	0/520 (0.00%)
Conjunctivitis †1	1/503 (0.20%)	0/520 (0.00%)
Uveitis †1	1/503 (0.20%)	0/520 (0.00%)
Eye disorders - Other, specify †1	2/503 (0.40%)	0/520 (0.00%)

Gastrointestinal disorders

Abdominal distension †1	1/503 (0.20%)	0/520 (0.00%)
Abdominal pain †1	4/503 (0.80%)	2/520 (0.38%)
Anal fistula †1	0/503 (0.00%)	0/520 (0.00%)
Colitis †1	52/503 (10.34%)	1/520 (0.19%)
Colonic perforation †1	6/503 (1.19%)	0/520 (0.00%)
Colonic ulcer †1	1/503 (0.20%)	0/520 (0.00%)
Constipation †1	2/503 (0.40%)	2/520 (0.38%)
Diarrhea †1	73/503 (14.51%)	4/520 (0.77%)
Dysphagia †1	2/503 (0.40%)	0/520 (0.00%)
Enterocolitis †1	3/503 (0.60%)	0/520 (0.00%)
Esophagitis †1	0/503 (0.00%)	0/520 (0.00%)
Gastric perforation †1	0/503 (0.00%)	0/520 (0.00%)
Gastric ulcer †1	1/503 (0.20%)	0/520 (0.00%)

Gastritis †1	1/503 (0.20%)	0/520 (0.00%)
Gastrointestinal pain †1	0/503 (0.00%)	0/520 (0.00%)
Ileal perforation †1	1/503 (0.20%)	0/520 (0.00%)
Ileus †1	1/503 (0.20%)	0/520 (0.00%)
Intra-abdominal hemorrhage †1	1/503 (0.20%)	0/520 (0.00%)
Lower gastrointestinal hemorrhage †1	1/503 (0.20%)	0/520 (0.00%)
Mucositis oral †1	3/503 (0.60%)	1/520 (0.19%)
Nausea †1	19/503 (3.78%)	25/520 (4.81%)
Oral pain †1	1/503 (0.20%)	0/520 (0.00%)
Pancreatitis †1	5/503 (0.99%)	2/520 (0.38%)
Peritoneal necrosis †1	1/503 (0.20%)	0/520 (0.00%)
Proctitis †1	0/503 (0.00%)	0/520 (0.00%)
Rectal fistula †1	1/503 (0.20%)	0/520 (0.00%)
Rectal hemorrhage †1	1/503 (0.20%)	0/520 (0.00%)
Rectal pain †1	0/503 (0.00%)	0/520 (0.00%)
Small intestinal obstruction †1	1/503 (0.20%)	0/520 (0.00%)
Vomiting †1	13/503 (2.58%)	12/520 (2.31%)
Gastrointestinal disorders - Other †1	3/503 (0.60%)	0/520 (0.00%)
General disorders		
Chills †1	1/503 (0.20%)	2/520 (0.38%)

Death NOS † 1	1/503 (0.20%)	0/520 (0.00%)
Fatigue † 1	26/503 (5.17%)	120/520 (23.08%)
Fever † 1	6/503 (1.19%)	4/520 (0.77%)
Flu like symptoms † 1	1/503 (0.20%)	14/520 (2.69%)
Injection site reaction † 1	0/503 (0.00%)	2/520 (0.38%)
Non-cardiac chest pain † 1	0/503 (0.00%)	0/520 (0.00%)
Pain † 1	1/503 (0.20%)	0/520 (0.00%)
Hepatobiliary disorders		
Hepatobiliary disorders - Other, specify † 1	1/503 (0.20%)	0/520 (0.00%)
Immune system disorders		
Autoimmune disorder † 1	16/503 (3.18%)	2/520 (0.38%)
Immune system disorders - Other, specify † 1	5/503 (0.99%)	0/520 (0.00%)
Infections and infestations		
Abdominal infection † 1	1/503 (0.20%)	0/520 (0.00%)
Enterocolitis infectious † 1	3/503 (0.60%)	0/520 (0.00%)
Lung infection † 1	5/503 (0.99%)	2/520 (0.38%)
Meningitis † 1	4/503 (0.80%)	0/520 (0.00%)
Peritoneal infection † 1	0/503 (0.00%)	0/520 (0.00%)
Sepsis † 1	2/503 (0.40%)	1/520 (0.19%)

Skin infection †1	3/503 (0.60%)	1/520 (0.19%)
Soft tissue infection †1	1/503 (0.20%)	0/520 (0.00%)
Urinary tract infection †1	0/503 (0.00%)	1/520 (0.19%)
Infections and infestations - Other †1	3/503 (0.60%)	0/520 (0.00%)

Investigations

Alanine aminotransferase increased †1	40/503 (7.95%)	78/520 (15.00%)
Alkaline phosphatase increased †1	4/503 (0.80%)	1/520 (0.19%)
Aspartate aminotransferase increased †1	32/503 (6.36%)	61/520 (11.73%)
Blood bilirubin increased †1	6/503 (1.19%)	2/520 (0.38%)
Cholesterol high †1	0/503 (0.00%)	1/520 (0.19%)
CPK increased †1	1/503 (0.20%)	31/520 (5.96%)
Creatinine increased †1	1/503 (0.20%)	0/520 (0.00%)
Ejection fraction decreased †1	1/503 (0.20%)	1/520 (0.19%)
Lipase increased †1	23/503 (4.57%)	4/520 (0.77%)
Lymphocyte count decreased †1	4/503 (0.80%)	65/520 (12.50%)
Neutrophil count decreased †1	4/503 (0.80%)	206/520 (39.62%)

Platelet count decreased † 1	0/503 (0.00%)	4/520 (0.77%)
Serum amylase increased † 1	2/503 (0.40%)	0/520 (0.00%)
Weight loss † 1	1/503 (0.20%)	6/520 (1.15%)
White blood cell decreased † 1	1/503 (0.20%)	70/520 (13.46%)
Investigations - Other, specify † 1	3/503 (0.60%)	0/520 (0.00%)

Metabolism and nutrition disorders

Alkalosis † 1	0/503 (0.00%)	0/520 (0.00%)
Anorexia † 1	2/503 (0.40%)	13/520 (2.50%)
Dehydration † 1	19/503 (3.78%)	8/520 (1.54%)
Hypercalcemia † 1	0/503 (0.00%)	0/520 (0.00%)
Hyperglycemia † 1	5/503 (0.99%)	1/520 (0.19%)
Hypertriglyceridemia † 1	0/503 (0.00%)	10/520 (1.92%)
Hyperuricemia † 1	1/503 (0.20%)	0/520 (0.00%)
Hypoalbuminemia † 1	2/503 (0.40%)	0/520 (0.00%)
Hypocalcemia † 1	2/503 (0.40%)	2/520 (0.38%)
Hypokalemia † 1	9/503 (1.79%)	6/520 (1.15%)
Hyponatremia † 1	17/503 (3.38%)	6/520 (1.15%)
Hypophosphatemia † 1	7/503 (1.39%)	29/520 (5.58%)
Metabolism and nutrition - Other † 1	1/503 (0.20%)	0/520 (0.00%)

Musculoskeletal and connective tissue

disorders

Arthralgia †1	4/503 (0.80%)	4/520 (0.77%)
Arthritis †1	2/503 (0.40%)	0/520 (0.00%)
Back pain †1	0/503 (0.00%)	1/520 (0.19%)
Bone pain †1	0/503 (0.00%)	1/520 (0.19%)
Flank pain †1	1/503 (0.20%)	0/520 (0.00%)
Generalized muscle weakness †1	5/503 (0.99%)	1/520 (0.19%)
Muscle weakness left-sided †1	1/503 (0.20%)	0/520 (0.00%)
Muscle weakness lower limb †1	1/503 (0.20%)	0/520 (0.00%)
Muscle weakness right-sided †1	0/503 (0.00%)	1/520 (0.19%)
Myalgia †1	6/503 (1.19%)	11/520 (2.12%)
Neck pain †1	0/503 (0.00%)	1/520 (0.19%)
Osteonecrosis of jaw †1	0/503 (0.00%)	1/520 (0.19%)
Pain in extremity †1	1/503 (0.20%)	1/520 (0.19%)
Musculoskeletal and connective - Other †1	1/503 (0.20%)	0/520 (0.00%)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Treatment related secondary malignancy †1	1/503 (0.20%)	0/520 (0.00%)

Nervous system disorders

Cognitive disturbance †1	2/503 (0.40%)	2/520 (0.38%)
Dizziness †1	0/503 (0.00%)	4/520 (0.77%)
Encephalopathy †1	1/503 (0.20%)	0/520 (0.00%)
Facial nerve disorder †1	1/503 (0.20%)	0/520 (0.00%)
Headache †1	16/503 (3.18%)	15/520 (2.88%)
Intracranial hemorrhage †1	0/503 (0.00%)	1/520 (0.19%)
Peripheral motor neuropathy †1	3/503 (0.60%)	3/520 (0.58%)
Peripheral sensory neuropathy †1	1/503 (0.20%)	0/520 (0.00%)
Syncope †1	6/503 (1.19%)	9/520 (1.73%)
Nervous system disorders - Other †1	3/503 (0.60%)	0/520 (0.00%)
Psychiatric disorders		
Anxiety †1	0/503 (0.00%)	7/520 (1.35%)
Confusion †1	2/503 (0.40%)	0/520 (0.00%)
Delirium †1	0/503 (0.00%)	1/520 (0.19%)
Depression †1	0/503 (0.00%)	17/520 (3.27%)
Insomnia †1	0/503 (0.00%)	4/520 (0.77%)
Mania †1	0/503 (0.00%)	1/520 (0.19%)
Psychosis †1	0/503 (0.00%)	2/520 (0.38%)
Suicide attempt †1	0/503 (0.00%)	2/520 (0.38%)

Psychiatric disorders - Other, specify † 1	0/503 (0.00%)	0/520 (0.00%)
Renal and urinary disorders		
Acute kidney injury † 1	3/503 (0.60%)	1/520 (0.19%)
Chronic kidney disease † 1	1/503 (0.20%)	0/520 (0.00%)
Renal calculi † 1	1/503 (0.20%)	0/520 (0.00%)
Renal and urinary disorders - Other † 1	0/503 (0.00%)	0/520 (0.00%)
Respiratory, thoracic and mediastinal disorders		
Adult respiratory distress syndrome † 1	0/503 (0.00%)	1/520 (0.19%)
Dyspnea † 1	3/503 (0.60%)	3/520 (0.58%)
Hypoxia † 1	2/503 (0.40%)	1/520 (0.19%)
Pleural effusion † 1	1/503 (0.20%)	0/520 (0.00%)
Pneumonitis † 1	7/503 (1.39%)	0/520 (0.00%)
Pulmonary edema † 1	0/503 (0.00%)	1/520 (0.19%)
Respiratory failure † 1	2/503 (0.40%)	0/520 (0.00%)
Respiratory thoracic mediastinal - Other † 1	0/503 (0.00%)	0/520 (0.00%)
Skin and subcutaneous tissue disorders		
Dry skin † 1	0/503 (0.00%)	1/520 (0.19%)
Pruritus † 1	11/503 (2.19%)	0/520 (0.00%)
Rash acneiform † 1	2/503 (0.40%)	0/520 (0.00%)

Rash maculo-papular †1	40/503 (7.95%)	5/520 (0.96%)
Skin ulceration †1	0/503 (0.00%)	1/520 (0.19%)

Vascular disorders

Hypertension †1	3/503 (0.60%)	9/520 (1.73%)
Hypotension †1	5/503 (0.99%)	6/520 (1.15%)
Thromboembolic event †1	3/503 (0.60%)	0/520 (0.00%)
Vascular disorders - Other, specify †1	0/503 (0.00%)	1/520 (0.19%)

† Indicates events were collected by systematic assessment

1 Term from vocabulary, CTCAE 4.0

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events	5%	
Arm/Group Title	Arm A (HIP)	Arm B (HDI)
	Affected / at Risk (%)	Affected / at Risk (%)
Total	495/503 (98.41%)	510/520 (98.08%)

Blood and lymphatic system disorders

Anemia †1	90/503 (17.89%)	209/520 (40.19%)

Endocrine disorders

Adrenal insufficiency †1	61/503 (12.13%)	3/520 (0.58%)
Hyperthyroidism †1	31/503 (6.16%)	17/520 (3.27%)
Hypothyroidism †1	103/503 (20.48%)	50/520 (9.62%)

Endocrine disorders - Other, specify †1	94/503 (18.69%)	12/520 (2.31%)
Eye disorders		
Blurred vision †1	37/503 (7.36%)	29/520 (5.58%)
Gastrointestinal disorders		
Abdominal pain †1	103/503 (20.48%)	39/520 (7.50%)
Colitis †1	29/503 (5.77%)	0/520 (0.00%)
Constipation †1	44/503 (8.75%)	110/520 (21.15%)
Diarrhea †1	234/503 (46.52%)	176/520 (33.85%)
Dry mouth †1	20/503 (3.98%)	88/520 (16.92%)
Mucositis oral †1	16/503 (3.18%)	35/520 (6.73%)
Nausea †1	182/503 (36.18%)	361/520 (69.42%)
Vomiting †1	83/503 (16.50%)	133/520 (25.58%)
General disorders		
Chills †1	61/503 (12.13%)	178/520 (34.23%)
Fatigue †1	328/503 (65.21%)	456/520 (87.69%)
Fever †1	98/503 (19.48%)	174/520 (33.46%)
Flu like symptoms †1	39/503 (7.75%)	254/520 (48.85%)
Malaise †1	10/503 (1.99%)	31/520 (5.96%)
Pain †1	6/503 (1.19%)	31/520 (5.96%)
Investigations		
Alanine aminotransferase increased †1	140/503 (27.83%)	342/520 (65.77%)

Alkaline phosphatase increased †1	53/503 (10.54%)	42/520 (8.08%)
Aspartate aminotransferase increased †1	125/503 (24.85%)	367/520 (70.58%)
Blood bilirubin increased †1	24/503 (4.77%)	48/520 (9.23%)
CPK increased †1	3/503 (0.60%)	176/520 (33.85%)
Lipase increased †1	48/503 (9.54%)	9/520 (1.73%)
Lymphocyte count decreased †1	32/503 (6.36%)	169/520 (32.50%)
Neutrophil count decreased †1	13/503 (2.58%)	317/520 (60.96%)
Platelet count decreased †1	32/503 (6.36%)	278/520 (53.46%)
Serum amylase increased †1	26/503 (5.17%)	9/520 (1.73%)
Weight loss †1	57/503 (11.33%)	214/520 (41.15%)
White blood cell decreased †1	12/503 (2.39%)	273/520 (52.50%)
Investigations - Other, specify †1	107/503 (21.27%)	95/520 (18.27%)
Metabolism and nutrition disorders		
Anorexia †1	102/503 (20.28%)	288/520 (55.38%)
Dehydration †1	20/503 (3.98%)	34/520 (6.54%)
Hyperglycemia †1	27/503 (5.37%)	39/520 (7.50%)
Hypoalbuminemia †1	31/503 (6.16%)	51/520 (9.81%)
Hypocalcemia †1	25/503 (4.97%)	90/520 (17.31%)

Hypokalemia †1	32/503 (6.36%)	52/520 (10.00%)
Hyponatremia †1	36/503 (7.16%)	24/520 (4.62%)
Hypophosphatemia †1	17/503 (3.38%)	93/520 (17.88%)
Musculoskeletal and connective tissue disorders		
Arthralgia †1	58/503 (11.53%)	102/520 (19.62%)
Back pain †1	7/503 (1.39%)	27/520 (5.19%)
Generalized muscle weakness †1	20/503 (3.98%)	31/520 (5.96%)
Myalgia †1	34/503 (6.76%)	154/520 (29.62%)
Nervous system disorders		
Dizziness †1	45/503 (8.95%)	109/520 (20.96%)
Dysgeusia †1	21/503 (4.17%)	165/520 (31.73%)
Headache †1	152/503 (30.22%)	238/520 (45.77%)
Peripheral sensory neuropathy †1	27/503 (5.37%)	43/520 (8.27%)
Psychiatric disorders		
Anxiety †1	15/503 (2.98%)	93/520 (17.88%)
Depression †1	20/503 (3.98%)	160/520 (30.77%)
Insomnia †1	28/503 (5.57%)	92/520 (17.69%)
Respiratory, thoracic and mediastinal disorders		
Cough †1	26/503 (5.17%)	42/520 (8.08%)
Dyspnea †1	28/503 (5.57%)	69/520 (13.27%)
Skin and subcutaneous tissue disorders		

Alopecia †1	11/503 (2.19%)	115/520 (22.12%)
Dry skin †1	23/503 (4.57%)	51/520 (9.81%)
Pruritus †1	226/503 (44.93%)	84/520 (16.15%)
Rash maculo-papular †1	281/503 (55.86%)	98/520 (18.85%)
Skin and subcutaneous tissue - Other †1	27/503 (5.37%)	35/520 (6.73%)

† Indicates events were collected by systematic assessment

1 Term from vocabulary, CTCAE 4.0

Limitations and Caveats

[Not Specified]

Collaborators and Investigators

This is where you will find people and organizations involved with this study.

Sponsor

National Cancer Institute (NCI)

Investigators

- Principal Investigator: Ahmad Tarhini, ECOG-ACRIN Cancer Research Group

Publications

From PubMed

These publications come from PubMed, a public database of scientific and medical articles. This list is automatically created by ClinicalTrials.gov Identifier (NCT Number), and these articles may or

may not be about the study.

- McLouth LE, Zheng Y, Smith S, Hodi FS, Rao UN, Cohen GI, Amatruda TT, Dakhil SR, Curti BD, Nakhoul I, Chandana SR, Bane CL, Marinier DE, Lee SJ, Sondak VK, Kirkwood JM, Tarhini AA, Wagner LI. Patient-reported tolerability of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk stage III-IV melanoma in phase III trial E1609. Qual Life Res. 2023 Jan;32(1):183-196. doi: 10.1007/s11136-022-03226-8. Epub 2022 Aug 27. (https://pubmed.ncbi.nlm.nih.gov/36029412)

- Saad M, Lee SJ, Tan AC, El Naqa IM, Hodi FS, Butterfield LH, LaFramboise WA, Storkus W, Karunamurthy AD, Conejo-Garcia J, Hwu P, Streicher H, Sondak VK, Kirkwood JM, Tarhini AA. Enhanced immune activation within the tumor microenvironment and circulation of female high-risk melanoma patients and improved survival with adjuvant CTLA4 blockade compared to males. J Transl Med. 2022 Jun 3;20(1):253. doi: 10.1186/s12967-022-03450-3. (https://pubmed.ncbi.nlm.nih.gov/35659704)

- Johnson DB, Friedman DL, Berry E, Decker I, Ye F, Zhao S, Morgans AK, Puzanov I, Sosman JA, Lovly CM. Survivorship in Immune Therapy: Assessing Chronic Immune Toxicities, Health Outcomes, and Functional Status among Long-term Ipilimumab Survivors at a Single Referral Center. Cancer Immunol Res. 2015 May;3(5):464-9. doi: 10.1158/2326-6066.CIR-14-0217. Epub 2015 Feb 3. (https://pubmed.ncbi.nlm.nih.gov/25649350)

More Information

Record History

Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed

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Patient-reported Tolerability of Adjuvant Ipilimumab (3 or 10 mg/kg) versus High-Dose Interferon Alfa-2b for Resected High-Risk Stage III-IV Melanoma in Phase III Trial E1609

Laurie E. McLouth[1], **Yue Zheng**[2], **Stephanie Smith**[3], **F. Stephen Hodi**[2,4], **Uma N. Rao**[5,*], **Gary I. Cohen**[6], **Thomas T. Amatruda**[7], **Shaker R. Dakhil**[8], **Brendan D. Curti**[9], **Ibrahim Nakhoul**[10], **Sreenivasa R. Chandana**[11], **Charles L. Bane**[12], **David E. Marinier**[13], **Sandra J. Lee**[2], **Vernon K. Sondak**[14], **John M. Kirkwood**[5], **Ahmad A. Tarhini**[14], **Lynne I. Wagner**[15]

[1]University of Kentucky, College of Medicine, Markey Cancer Center, Lexington, KY, USA

[2]Dana-Farber Cancer Institute—ECOG-ACRIN Biostatistics Center, Boston, MA, USA

Corresponding Author: Laurie McLouth, PhD, Department of Behavioral Science, University of Kentucky College of Medicine, 371 Healthy Kentucky Research Building, 760 Press Avenue, Lexington, KY 40508, Laurie.mclouth@uky.edu, 859-562-2526.

*Deceased prior to manuscript submission

Authors contributions: LEM: Manuscript drafting, data interpretation, final version approval; YZ: Data analysis, manuscript drafting, final version approval; SS: Data collection, manuscript drafting; FSH: Study design, data collection, manuscript drafting; UNR: Study design, data collection; GIC: Study design, data collection, manuscript drafting; TTA: Study design, data collection, manuscript drafting; SRD: Study design, data collection, manuscript drafting; BDC: Study design, data collection, manuscript drafting; IN: Study design, data collection, manuscript drafting; SRC: Study design, data collection, manuscript drafting; CLB: Study design, data collection, manuscript drafting; DEM: Study design, data collection, manuscript drafting; SJL: Study design, data analysis, manuscript drafting; VKS: Study design, administrative support, data collection, manuscript drafting; JMK: Study design, administrative support, data collection, manuscript drafting; AAT: Study design, administrative support, data collection, data interpretation, manuscript drafting, final version approval; LIW: Study design, administrative support, manuscript drafting, data interpretation, final version approval. All authors read and approved the manuscript.

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Competing interests: *FSH*: **Stock and Other Ownership Interests:** Apricity, Torque **Consulting or Advisory Role:** Merck Sharp & Dohme, Novartis, Genentech/Roche, EMD Serono, Sanofi, Bayer, Aduro Biotech, Pfizer, Verastem, Bristol-Myers Squibb, Takeda Pharmaceuticals, Surface, Compass Therapeutics, Partners Therapeutics, Pionyr, 7Hills Pharma, Torque, Rheos **Research Funding:** Bristol-Myers Squibb (Inst), Merck Sharp & Dohme (Inst), Genentech/Roche (Inst), Novartis (Inst) **Patents, Royalties, Other Intellectual Property:** Patent pending as per institutional policy; patent-pending royalties received on MICA-related disorder application to institution per institutional IP policy; angiopoietin-2 biomarkers predictive of anti-immune checkpoint response (Inst); compositions and methods for identification, assessment, prevention, and treatment of melanoma using PD-L1 isoforms; methods of using pembrolizumab and trebananib (Inst) **Travel, Accommodations, Expenses:** Novartis, Bristol-Myers Squibb**Other Relationship:** Bristol-Myers Squibb, Genentech/Roche; *GIC*: **Stock and Other Ownership Interests:** Nymox, Celgene, AbbVie **Honoraria:** Amgen; *SJL*: **Stock and Other Ownership Interests:** NantKwest (I) **Consulting or Advisory Role:** Roche/Genentech; *VKJ*: **Consulting or Advisory Role:** Merck/Schering Plough, Novartis, Bristol-Myers Squibb, Array BioPharma, Genentech/Roche, Pfizer, Polynoma, Regeneron, Replimune; *JMK*: **Consulting or Advisory Role:** Bristol-Myers Squibb, Novartis, Array BioPharma, Immunocore, Iovance, Elsevier, Checkmate Pharmaceuticals (Inst), Bristol-Myers Squibb (Inst), Immunocore (Inst), Merck (Inst) **Research Funding:** Merck (Inst), Prometheus Laboratories (Inst), Immunocore (Inst); *AAT*: **Consulting or Advisory Role:** Bristol-Myers Squibb, Merck, Genentech/Roche, Incyte, Newlink Genetics, Array BioPharma, Novartis, OncoSec, HUYA Bioscience International, Immunocore, Pfizer/EMD Serono, Sanofi/Regeneron, BioNTech **Research Funding:** Incyte (Inst), Prometheus Laboratories (Inst), Bristol-Myers Squibb (Inst), Amgen (Inst), Incyte (Inst), Novartis (Inst), GreenPeptide (Inst), Merck (Inst). No other potential conflicts of interest were reported.

Ethics approval and consent to participate: The protocol was approved by the Institutional Review Boards at each registering institution. Written informed consent was obtained from all patients.

Consent for publication: Not applicable.

Availability of data and materials: Data may be made available upon request as per the ECOG-ACRIN Data Sharing Policy.

Trial Registration: NCT01274338, January 11, 2011 (first posted date) https://clinicaltrials.gov/ct2/show/NCT01274338?term=NCT01274338&draw=2&rank=1;

[3]Nancy N. and J.C. Lewis Cancer and Research Pavilion, St. Joseph's/Candler, Savannah, GA, USA

[4]Harvard Cancer Center, Boston, MA, USA

[5]University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA

[6]Greater Baltimore Medical Center, Baltimore, MD, USA

[7]Minnesota Oncology, Fridley, MN, USA

[8]Ascension Via Christi Hospitals, Wichita, KS, USA

[9]Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR, USA

[10]Regional Cancer Center at Indian Path Community Hospital, Kingsport, TN, USA

[11]Cancer and Hematology Centers of Western Michigan/Cancer Research Consortium of West Michigan NCORP, Grand Rapids, MI, USA

[12]Good Samaritan Hospital-Dayton, Dayton, OH, USA

[13]Gundersen Health System, La Crosse, WI, USA

[14]Moffitt Cancer Center, Tampa, FL, USA

[15]Wake Forest Baptist Comprehensive Cancer Center, Winston-Salem, NC, USA

Abstract

Purpose: Trial E1609 demonstrated superior overall survival with ipilimumab-3mg/kg (ipi3) compared to high dose interferon (HDI) for patients with resected high-risk melanoma. To inform treatment tolerability, we compared health-related quality of life (HRQoL), gastrointestinal (GI), and treatment-specific physical and cognitive/emotional symptoms. We also compared treatment-specific concerns between all arms.

Methods: We assessed HRQoL using the Functional Assessment of Cancer Therapy-General, physical and cognitive/emotional concerns using the FACT-Biologic Response Modifier subscale, and GI symptoms with the Functional Assessment of Chronic Illness Therapy-Diarrhea subscale pre-treatment and every 3-months. The primary outcome was the difference in HRQoL at 3-months between ipi3/ipi10 vs. HDI.

Results: 549 patients (n=158 ipi3; n=191 ipi10; n=200 HDI) were analyzed. 3-month completion was 58.7%. Compared to HDI, ipilimumab patients reported better HRQoL (ipi3 = 87.5 ±14.6 vs. HDI = 74.7 ±15.4, p <.001; ipi10 = 84.9 ±16.5 vs. HDI, p <.001) and fewer physical (ipi3 = 22.3 ±4.6 vs. HDI=17.1 ±5.4, p <.001; ipi10=21.8 ±5.0 vs. HDI p <.001) and cognitive/emotional (ipi3=18.6 ±4.4 vs. HDI=15.0 ±5.3, p <.001; ipi10=17.7 ±4.8 vs. HDI p<.001) concerns, but worse GI symptoms (ipi3=40.8 ±5.0 vs. HDI = 42.2 ±2.9, p = .011; ipi10=39.5 ±7.0 vs. HDI, p <.001). Fewer ipilimumab patients reported worsening treatment-specific concerns (e.g., 52% of ipi3 and 58% of ipi10 reported worsening fatigue vs. 82% HDI, p's < .001).

Conclusion: PROs demonstrated less toxicity of ipi3 compared to HDI and ipi10. Priorities for symptom management among patients receiving ipilimumab include GI toxicities, fatigue, weakness, appetite loss, arthralgia, and depression.

Keywords

ipilimumab; melanoma; adjuvant therapy; interferon; patient-reported outcomes; quality of life

Background

Each year, over 100,000 people are diagnosed with melanoma in the United States [1]. Five-year survival for patients diagnosed with stage III melanoma ranges from 32–93% depending on the stage group, being most favorable for stage IIIA and worst for stage IIID [2, 3]. For patients with stage IV disease, five-year survival rates are approximately 34–50% based on recently updated phase III trial results testing targeted therapy for BRAF-mutant melanoma and immunotherapy, although real-world clinical outcomes (outside of clinical trials) are expected to be worse [2–4]. Patients with resectable high risk stage III disease (lymph node involvement) and resected stage IV disease are at high risk for recurrence, poor disease-free survival, and low overall survival (OS). For these high-risk melanoma patients, systemic adjuvant treatment is warranted.

The ECOG-ACRIN E1609 phase III trial evaluated the efficacy and tolerability of ipilimumab at 3 (ipi3) or 10mg/kg (ipi10) compared to high-dose interferon alfa-2b (HDI) as adjuvant treatment for high risk resected melanoma, stages IIIB, IIIC, M1a, M1b [5]. At study design, HDI was the standard adjuvant therapy for resected stage III and IV melanoma based on prior ECOG-ACRIN trials E1684, E1690, E1694 (that included stage III melanoma) and E2696 included stage IV melanoma) [6–9]. Phase II trials had shown benefit of ipi10 in unresectable stage III and IV melanoma patients [10, 11] and this was the basis of the initial design of E1609 as activated in 2011 testing ipi10 versus HDI as a 2-arm study. After a phase III trial of ipi3 in inoperable stage III and IV melanoma patients and the subsequent FDA approval of ipi3 for metastatic melanoma [12], E1609 was amended to include ipi3 as a third trial arm compared to HDI. E1609 trial results showed superior overall survival of ipi3 compared to HDI, with no significant differences in overall or relapse free survival between ipi3 and ipi10 [5]. Ipi3 was also significantly less toxic than ipi10.

Tolerability was a key study question of E1609, as both HDI and ipilimumab had previously demonstrated significant grade 3/4 toxicities [6–11]. E1609 results showed grade 3 or higher adverse events (AEs) occurred most often in HDI, followed by ipi10 [5]. Occurrence of grade 3 or higher AEs was significantly worse in ipi10 compared to ipi3. As AEs reflect only one aspect of tolerability, a second aim of E1609 was to assess tolerability through patient-reported outcome (PRO) data.

The purpose of the E1609 PRO correlative study was to assess overall health-related quality of life (HRQoL), gastrointestinal (GI) symptoms, and physical and cognitive/emotional concerns associated with interferon therapy and to examine differences between treatment arms on these domains to obtain a complete understanding of ipilimumab-related symptoms from the patient's perspective. GI symptoms were selected due to high incidence of GI toxicities from ipilimumab [10, 11]. Biologic response modifier-associated symptoms (BRM; e.g., mood disruption, cognitive concerns; joint pain) were selected due to HDI's associated neuro-cognitive and physical deficiencies [6–9]. The PRO correlative for this trial

was designed to test the a priori hypothesis that patients assigned to ipilimumab would experience superior HRQoL at the end of induction therapy compared to those assigned to HDI. An additional objective was to compare treatment-specific concerns between all arms.

Methods

Study Design

E1609 was conducted through the National Clinical Trials Network and was coordinated by the ECOG-ACRIN Cancer Research Group (ClinicalTrials.gov Identifier: NCT01274338). E1609 was a phase III double-blinded randomized controlled trial comparing overall and relapse free survival between patients with resected high-risk melanoma randomly assigned to ipi3, ipi10 and HDI. The trial was activated on May 25, 2011, amended to add PROs in February 2012, and reached target accrual and closure on August 15, 2014. Primary trial results are published [5]. The protocol was approved by the Institutional Review Boards at each registering institution. Written informed consent was obtained from all patients.

Participants

The full eligibility criteria are published [5]. Patients were eligible if they were at least 18 years old with histologically confirmed stage IIIB, IIIC, M1a or M1b (AJCC 7th edition staging) melanoma, ECOG performance status 0 or 1, within 84 days of last surgery, and no prior systemic adjuvant therapy for melanoma.

Data Collection

PRO assessments were administered on paper pre-randomization (i.e., baseline), at completion of induction therapy (3-months; primary endpoint), and every 3-months thereafter during maintenance treatment. Maintenance treatment ended at 15-months for ipilimumab patients and at 12-months for HDI patients.

Measures

Health-related Quality of Life (FACT-G)—The 27-item Functional Assessment of Cancer Therapy-General (FACT-G; version 4) was administered via paper to assess patient-reported HRQoL [13]. The FACT-G includes subscales that assess physical, functional, social/family, and emotional wellbeing. Items are responded to on a 5-point Likert-type scale from 0 (not at all) to 4 (very much), with some items reverse-scored. Total scores range from 0–108, with higher scores indicating better HRQoL. Estimates of minimally important differences on FACT-G total scores suggest a difference of 3–7 points [14]. Cronbach's alpha for total FACT-G scores in this sample ranged from 0.89 to 0.92 (baseline, 3-months).

Physical and Cognitive/Emotional Concerns associated with Biologic Response Modifiers (FACT-BRM)—The FACT-Biologic Response Modifiers subscale includes 7 physical (e.g., "I have pain in my joints") and 6 cognitive/emotional (e.g., "I get depressed easily") concern items [15, 16]. Items are rated on a 5-point Likert-type scale (0=not at all to 4=very much), with some items reverse-scored. BRM subscales were validated in patients undergoing HDI for melanoma [15]. Scores range from 0–28 (physical concerns) and 0–24 (cognitive/emotional), with higher scores indicating less symptom

bother. Cronbach's alphas in the current sample were 0.73 and 0.82 (physical; baseline, 3-months) and 0.84 and 0.86 (cognitive/emotional; baseline, 3-months).

Gastrointestinal Symptoms (FACIT-D)—The Functional Assessment of Chronic Illness Therapy-Diarrhea (FACIT-D) Subscale of the FACIT-D includes 11 items to assess GI concerns. Items are responded to on a 5-point Likert-type scale (0=not at all to 4=very much), with some items reverse scored. Scores range from 0–44 with higher scores indicating fewer GI concerns. Cronbach's alphas in the current sample were 0.57 (baseline) and 0.89 (3-months).

Selected Individual PRO Items—Individual items from the FACT-G, FACT-BRM, and FACIT-D Diarrhea Subscale were examined for worsening from baseline to 3-months. Worsening was defined as a change in score of one category or more on the individual item in the direction that would indicate worsening (e.g., a change from "not at all" to "a little bit," "somewhat," "quite a bit," or "very much"). Items were selected based on clinical relevance [17, 18]. Items included: treatment bother ("I am bothered by side effects of treatment"; FACT-G); FACT-BRM: "I get tired easily," "I feel weak all over," "I have a good appetite," "I have pain in my joints," "I have trouble concentrating," "I get depressed easily"; and FACIT-D: "I have control of my bowels," "I move my bowels more frequently than usual," I have to limit my social activity because of diarrhea", and "I have to limit my physical activity because of diarrhea."

Analyses

The difference in FACT-G scores between HDI vs. ipi3 and ipi10 at 3-months, adjusting for baseline FACT-G, was the primary endpoint for PROs, as this was the end of induction therapy. Additional planned comparisons included the difference in physical and cognitive/emotional concerns associated with BRM therapy (FACT-BRM subscales) and the difference in GI symptoms (FACIT-D subscale) between HDI vs. ipi3 and ipi10 at 3-months, adjusting for baseline scores. A secondary aim was to compare PROs between ipi3 and ipi10. Although differences at 3-months (i.e., end of induction therapy) were the primary endpoints, we also examined differences throughout maintenance therapy to inform future research and clinical practice. All analyses were conducted in the eligible and treated patient population. Two-sample t-tests were used to examine treatment arm differences. Fisher exact tests were used to compare categorical measurements. Linear regression models of 3-month outcomes comparing ipilimumab arms to HDI adjusting for baseline PRO scores were conducted as a sensitivity analyses. We selected linear regression models adjusting for baseline over mixed effect models with repeated measures because our hypothesis was specific to the difference in treatment arms at the end of induction therapy (i.e., 3-months) and not differences throughout the duration of therapy (for which a mixed effect model with repeated measures might have been preferred). No adjustment was made for multiple comparisons. All significance tests were 2-sided with a type I error of 5%. Analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC). Sample size was based on the trial's primary outcome analysis for progression free survival.

Results

Study Population

A total of 1,670 patients were enrolled, of whom 549 were enrolled after the trial was amended to include PROs. Patient and disease characteristics were similar between the three treatment arms at baseline [5]. The 549 patients with PRO data in the sample analyzed were similar to the 1121 patients without PRO data with respect to age, sex, race and ethnicity, and clinical characteristics, and all characteristics were comparable across arms (Supplemental Table 1). Patients in the analyzed sample were an average of 52 years of age (SD = 13; Table 1). The sample was 62% male and predominantly non-Hispanic White. Most had an ECOG performance status of 0 at baseline (Table 1). Sociodemographic and clinical characteristics in the analyzed sample were not significantly different between treatment arms (Table 1).

PRO Completion Rates

Figure 1 (CONSORT) shows the number of assessments completed and reasons for non-completion.

To calculate PRO completion rates, all patients who had completed the baseline PRO and were alive at the scheduled assessment were expected to complete the PROs and used as the denominator. If a patient completed any of the PROs sufficiently to calculate a valid score, they were included in the numerator. The PRO completion rate was 58.7 % (322/549) at 3-months. A substantial number of 3-month assessments were not completed for unknown reasons, meaning the site did not document a reason for non-completion; known reasons for non-completion (e.g., institutional factors, patient too ill) were comparable between arms. Patients with only baseline PRO data were not included in the PRO data analysis but were comparable to the PRO analysis sample on demographic and clinical characteristics (Supplemental Table 1). Compliance with PRO completion was the same between the three arms at baseline (100%) and similar at 3-month assessment (ipi3 = 62.0%; ipi10 = 57.6%; HDI = 57.0%; **see** Supplemental Table 2 for compliance across assessments).

Primary Objective

Comparison of HRQoL (FACT-G) between Ipilimumab and HDI

Total HRQoL Scores on FACT-G.: Patients reported similar HRQoL on the FACT-G at baseline in the ipilimumab arms compared to the HDI (Table 2) with a mean score of 89.2 (SD = 13.1) for the overall sample. At 3-months, patients in the ipilimumab arms reported better overall HRQoL compared to HDI (ipi10 = 84.9, 95% CI = 81.8, 88.0 vs. HDI = 74.7, 95% CI = 71.9, 77.5, p <.001; ipi3 = 87.5, 95% CI =84.7, 90.4 vs. HDI = 74.7, 95% CI = 71.9, 77.5, p <.001; Table 2). These differences were both statistically and clinically significant based on a minimally important difference of 3–7 points [14]. This pattern continued throughout all assessments (Figure 2a). Scores were not significantly different between ipi arms, though scores among patients receiving ipi10 appeared to be improving from 9-months onward.

Change in HRQoL on FACT-G from Baseline to 3-months.: Patients in the ipilimumab arms reported less decline in HRQoL compared to HDI (ipi10 mean change = −4.9, 95% CI = −7.6, −2.2 vs. HDI mean change −12.9, 95% CI = −15.5 −10.3, p <.001; ipi3 mean change = −3.4, 95% CI = −6.0, −0.7 vs. HDI mean change, p <.001; Table 2). A linear regression model showed similar results (Supplemental Table 3). This pattern continued throughout all assessments (Figure 2b). Changes in total HRQoL were not significantly different between ipi arms.

Secondary Objectives

Comparison of Physical and Cognitive/Emotional Concerns associated with Biological Response Modifying Treatments between Treatment Arms (FACT-BRM Physical and Mental Concerns)

Total Physical Concerns.: Scores on the FACT-BRM Physical concerns subscale were comparable at baseline (Table 2) with a mean score of 24.0, SD = 3.9 for the overall sample. At 3-months, patients in the ipilimumab arms reported fewer physical concerns compared to those in the HDI arm (ipi10 = 21.8, 95% CI = 20.9, 22.8 vs. HDI = 17.1, 95% CI = 16.1, 18.1, p <.001; ipi3 = 22.3, 95% CI = 21.4, 23.3 vs. HDI = 17.1, 95% CI = 16.1, 18.1, p <.001; Table 2). This pattern continued throughout all assessments (Figure 3a).

Change in Physical Concerns from Baseline to 3-months.: Patients in the ipilimumab arms reported less change in physical concerns at 3-months compared to those in the HDI arm (ipi10 mean change = −2.7; 95% CI = −3.6, −1.8 vs. HDI mean change −6.6, 95% CI = −7.6, −5.6, p <.001; ipi3 mean change = −1.8, 95% CI = −2.6, −1.0 vs. HDI mean change −6.6, 95% CI = −7.5, −5.6, p <.001; Table 2). A linear regression model showed similar results (Supplemental Table 3).

Total Cognitive/Emotional Concerns.: Scores on the FACT-BRM Cognitive/Emotional Subscale were comparable at baseline (Table 2) with a mean score of 18.8, SD = 4.4 for the overall sample. At 3-months, patients in the ipilimumab arms reported fewer cognitive/emotional compared to HDI patients (ipi10 = 17.7, 95% CI = 16.8, 18.6 vs. HDI = 15.0, 95% CI = 14.1, 16.0, p <.001; ipi3 = 18.6, 95% CI = 17.8, 19.5 vs. HDI = 15.0, 95% CI = 14.1, 16.0, p <.001; Table 2). This pattern continued throughout all assessments (Figure 3b).

Change in Cognitive/Emotional Concerns from Baseline to 3-months.: Patients in the ipilimumab arms reported less change in cognitive/emotional concerns at 3-months compared to those in the HDI arm (ipi10 mean change = −0.7; 95% CI = −1.4, 0.1 vs. HDI mean change −3.3, 95% CI = −4.2, −2.4, p <.001; ipi3 mean change = −1.0, 95% CI = −1.9, −0.2 vs. HDI mean change −3.3, 95% CI = −4.2, −2.4, p <.001; Table 2). A linear regression model showed similar results (Supplemental Table 3).

Comparison of Gastrointestinal Symptoms between Treatment Arms (FACIT-D Diarrhea Subscale; DS)

Total GI Symptoms.: Scores on the FACIT-D diarrhea subscale indicated comparable GI symptoms at baseline (Table 2) with a mean score of 42.9, SD = 2.1 for the overall sample. At 3-months, patients in the ipilimumab arms reported worse GI symptoms compared to

those in HDI (ipi10 = 39.5, 95% CI = 38.2, 40.8 vs. HDI 42.2, 95% CI = 41.7, 42.8, p <.001; ipi3 = 40.8, 95% CI = 39.8, 41.8 vs. HDI, p = .011; Table 2). This difference was not consistently observed across all assessments (Figure 3c).

Change in Total GI Symptoms from Baseline to 3-months.: Patients in the ipilimumab arms reported greater change in GI symptoms at 3-months compared to those in the HDI arm (ipi10 mean change = −3.7, 95% CI = −5.0, −2.3 vs. HDI mean change = −0.7, 95% CI = −1.2, −0.2, p <.001; ipi3 mean change = −2.2, 95% CI = −3.3, −1.2 vs. HDI mean change = −0.7, 95% CI = 01.2, −0.2, p = .009; Table 2). A linear regression model showed similar results (Supplemental Table 3). The difference in changes from baseline to 3-months was marginal between the two ipi arms (p = .088).

Worsening on Selected Items from All PROs.: Figure 4 shows the percentage of patients in each treatment arm who reported worsening on selected individual PRO items from baseline to 3-months. A higher proportion of patients assigned to HDI and ipi10 reported worsening treatment bother at 3-months compared to patients assigned to ipi3 (ipi3 = 53.3% vs. HDI = 79.6%, p <0.001; ipi3 vs. ipi10 = 70.8%, p = .013), whereas ipi10 and HDI were not significantly different (p = .15). A higher proportion of patients assigned to HDI reported worsening fatigue, weakness, appetite loss, arthralgia, concentration problems, and depression compared to patients assigned to both ipilimumab arms. Whereas more ipi10 patients reported worsening GI symptoms compared to HDI, ipi3 patients only reported worsening GI symptoms compared to HDI for the item, ‘limiting social activities due to diarrhea.’

Discussion

E1609 was the first trial to demonstrate significant improvement in overall survival with adjuvant therapy for patients with resected high risk melanoma using ipilimumab against an active control that was standard of care, HDI. It was also the first to compare both the currently approved adjuvant dose of ipilimumab (10mg/kg) and a new dose of ipilimumab (3mg/kg) against HDI for the melanoma adjuvant setting. Given significant grade 3 or higher toxicities in all treatment arms [5], a critical secondary aim of the study was to examine patient-reported tolerability of ipi10, ipi3, and HDI. Overall, PRO data from this trial align with the toxicity data to support the use of ipi3 over HDI and highlight several toxicities that should be monitored in future trials as well as clinical practice.

Overall HRQoL was worse for patients who received HDI compared to both ipilimumab arms. Differences in HRQoL on the FACT-G exceeded the threshold for minimally important differences, suggesting meaningful clinical differences. Further, patients on HDI reported significantly more physical and cognitive/emotional concerns compared to patients in both ipilimumab arms. Although minimally important differences for the FACT-BRM subscales have not been well-described, the observed difference of 3–4 points in ipi vs. HDI arms is likely clinically meaningful [14, 19]. More patients who received HDI also reported worsening fatigue, weakness, arthralgia, concentration problems, and depression symptoms from baseline to 3-months compared to ipilimumab arms. Nearly 80% reported worsening treatment tolerability on the FACT GP5 item at 3-months. The only PROs on

which patients in ipilimumab arms fared worse were gastrointestinal concerns, which was expected. Further, HRQoL appeared superior in the ipilimumab arms compared to HDI throughout all remaining assessment points. This is consistent with the intermittent, transient nature of immune-related adverse events experienced with immune checkpoint inhibitors compared to the persistent and chronic nature of the main toxicities with cytokine therapies such as fatigue and nausea. PRO data clearly support the use of ipilimumab over HDI.

Ipilimumab 3mg/kg was added as a second comparator to HDI after FDA approval for its use in unresectable stage IV melanoma in 2011. The addition of ipi3 to E1609 was critical, as it had not yet been tested in the adjuvant melanoma setting and phase II trials of ipilimumab 10mg/kg identified significant toxicities. E1609 was not designed to test ipi10 vs. ipi3; however, as described below, the PRO data, combined with the trial's toxicity data and OS findings in favor of ipi3, support the use of ipi3 for systemic adjuvant therapy for melanoma over the currently approved dose of ipi10.

Although FACT-G and FACT-BRM scores were not significantly different between ipi3 and ipi10, scores were in the direction of favoring ipi3, and the FACT-G difference between ipi3 and ipi10 at 3-months may be clinically meaningful [14]. The fact that the ipi10 arm crossed the ipi3 arm on the FACT-G at 9-months could suggest they experienced better quality of life later into maintenance therapy. However, confidence intervals overlapped, and small sample sizes after the primary 3-month outcome assessment preclude conclusions. Higher FACT-G scores among ipi10 patients at the 9-month assessment and beyond could be due to sample bias and need to be replicated. Scores on the FACT measures at 3-months- and the proportion of patients with worsening symptoms clearly favored ipi3 over ipi10. Specifically, whereas ipi10 patients reported worsening GI symptoms compared to HDI on all selected symptoms, ipi3 patients only reported worsening GI symptoms compared to HDI on one. Finally, more patients (almost 20% more) in the ipi10 cohort reported worsening treatment tolerability (FACT GP5 item) and weakness compared to ipi3 patients. A 20% difference in worsening on the FACT GP5 item is noteworthy, as worsening on this item has predicted adherence to cancer therapy [17, 18]. The higher rates of worsening weakness in ipi10 vs. ipi3 could reflect greater endocrine and gastrointestinal toxicities. The differences observed in patient-reported treatment tolerability in ipi3 vs. ipi10 are consistent with differences in physician-rated AEs and proportions of patients completing planned treatments, initiating maintenance therapy, requiring corticosteroids to manage toxicities, and requiring hormone replacement therapy – all of which indicated the higher dosage of ipilimumab was less tolerable [5].

Since E1609 was completed, other agents have been tested as systemic adjuvant therapy in melanoma, including nivolumab, pembrolizumab [20], and combination dabrafenib-trametinib (BRAF mutant melanoma) leading to the regulatory approval of these agents in the first line adjuvant setting. At this time based on E1609 data, ipi3 (rather than ipi10) can be recommended as adjuvant therapy for patients in whom PD1 blockade and BRAF-MEK inhibition is not an option or after failure of adjuvant therapy with these new regimens. This is supported by E1609 OS and PRO results [5]. In addition, this is an option for patients who fail prior adjuvant anti-PD1 therapy and continue to have resectable disease.

Our examination of the proportion of patients in each arm who experienced worsening on selected symptoms suggests concentration problems and depression symptoms should be monitored among patients receiving ipilimumab as part of future clinical trials and in routine practice. Over 20% of patients receiving ipi3 reported worsening concentration problems and depression three months into treatment. In contrast to gastrointestinal concerns, which are a well-known toxicity of immunotherapies and which, by their acute nature, are likely to be reported by patients to their cancer care team, difficulty concentrating and depression may be less likely to be identified. Single item measures of these toxicities are available through the FACIT.org system and the PRO-CTCAE™ and could be administered. Future research could also study the utility of administering and monitoring the FACT GP5 item ("I am bothered by the side effects of treatment") in clinical practice. Over 50% of patients reported worsening on this item at 3-months. This item has demonstrated convergent and known groups validity across several cancer types, including melanoma [21]. We have also demonstrated its predictive value prior to treatment or at transition from induction to maintenance in identifying patients at risk for early treatment discontinuation [22, 23]. A high score pre-treatment or worsening on this item during treatment could be discussed in routine oncology visits, perhaps leading patients to identify bothersome toxicities that if better managed, could prevent early discontinuation.

Limitations

This study was limited by a small sample size and attrition at 3-months, which could have introduced sample bias. Reasons for PRO non-completion were not well documented by participating sites; however, PRO completion rates were comparable between arms and documentation of reasons for PRO non-completion was not different by site (i.e., academic medical center vs. community). Patients with 3-month PRO data had significantly longer relapse-free survival (RFS) compared to those with only baseline PRO data, suggesting the 3-month PRO sample had better overall health status. However, the RFS for both groups was well beyond 3-months, precluding conclusions that RFS contributed to PRO dropout. Importantly, patients with 3-month PRO data had comparable RFS to the primary trial sample; thus PRO results presented generalize to the larger trial sample. Still, increasing institutional adherence to PRO collection is important for future trials. Toward that end, investigators should educate staff on importance of PRO aims in therapeutic trials and the potential for misinterpreting PRO data if protocol adherence is poor; monitor PRO adherence and intervene early on non-adherence; and leverage electronic PRO administration to facilitate data collection [24]. The growing evidence-base for PRO monitoring in clinical practice may further encourage and normalize PRO data collection in therapeutic trials. A final limitation is that we did not adjust for multiple comparisons, which may increase type I error.

Conclusion

This study suggests patients find ipilimumab more tolerable compared to HDI and provides further support for ipilimumab 3mg/kg over ipilimumab 10mg/kg as systemic adjuvant therapy for unresectable melanoma. Patient-rated treatment tolerability, fatigue, weakness, gastrointestinal concerns, depression, and arthralgia are important to monitor in future

clinical trials and clinical practice. Future checkpoint inhibitor trials should also include immunotherapy-specific PROs [25] to evaluate other potential toxicities not yet well-defined by PROs in past studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AEs	adverse events
FACIT-D	Functional Assessment of Chronic Illness Therapy-Diarrhea
FACT-BRM	Biologic Response Modifier
FACT-G	Functional Assessment Of Cancer Therapy-General
GI	gastrointestinal
HDI	high dose interferon
HRQoL	health-related quality of life
ipi3/ipi10	ipilimumab 3 mg/kg or ipilimumab 10 mg/kg
irAEs	immune-related adverse events
OS	overall survival
PD-L1	program death ligand 1
PROs	patient-reported outcomes
RFS	relapse-free survival

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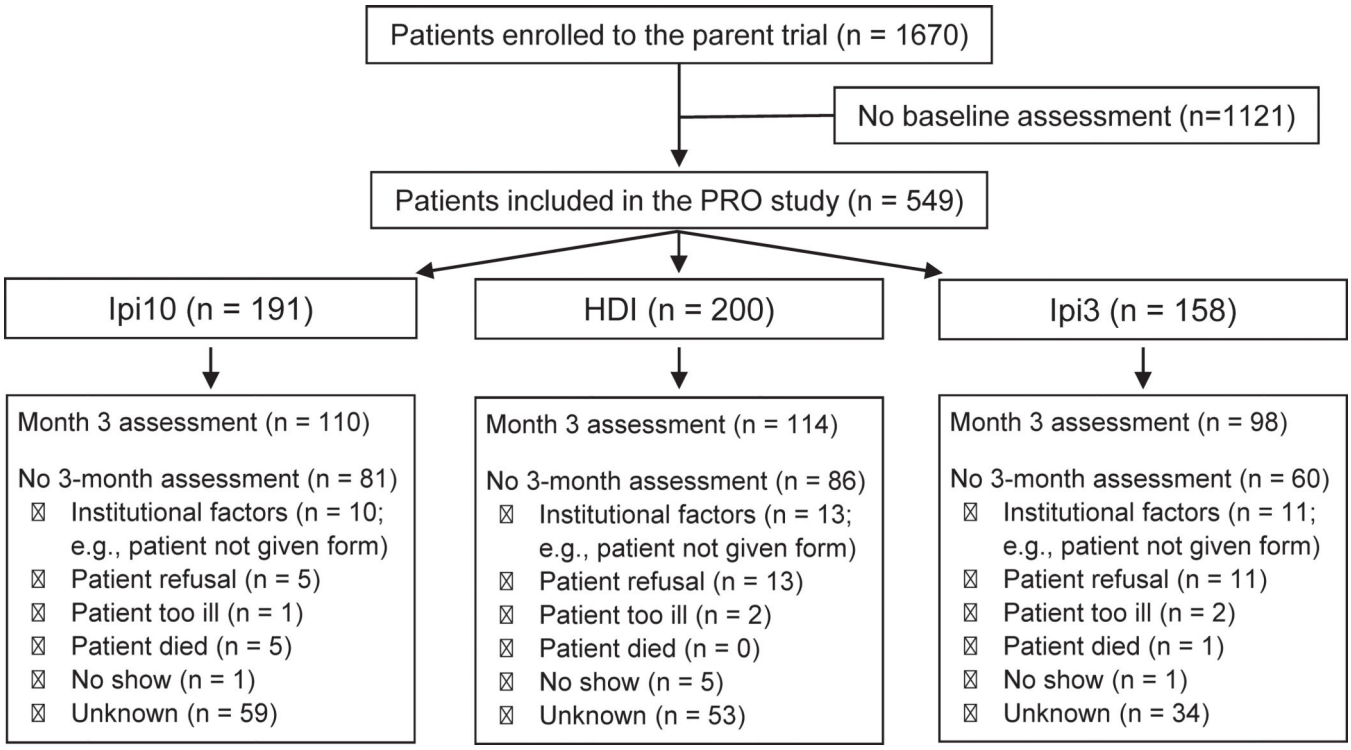

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) Flowchart. PRO = Patient-reported outcome.

CONSORT flow diagram depicting study recruitment and retention.

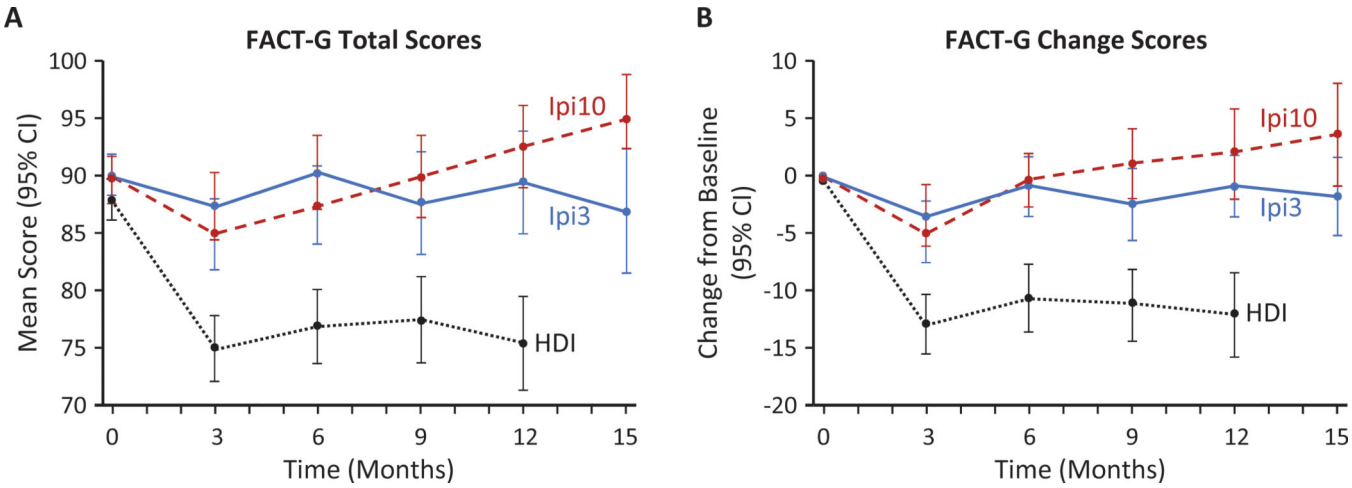

Figure 2. Mean and 95% CI of FACT-G total score and total change score from baseline.

FACT-G = Functional Assessment of Cancer Therapy-General (25-items). PRO = Patient-reported outcome. Higher scores on the FACT-G indicate better health-related quality of life.

Note: PROs were not collected for HDI at 15 months, as maintenance therapy ended at 12 months.

Patients in the ipilimumab arms reported better health-related quality of life at 3-months compared to HDI. All patients reported worsening health-related quality of life at 3-months, however patients in the ipilimumab arms reported less decline compared to HDI.

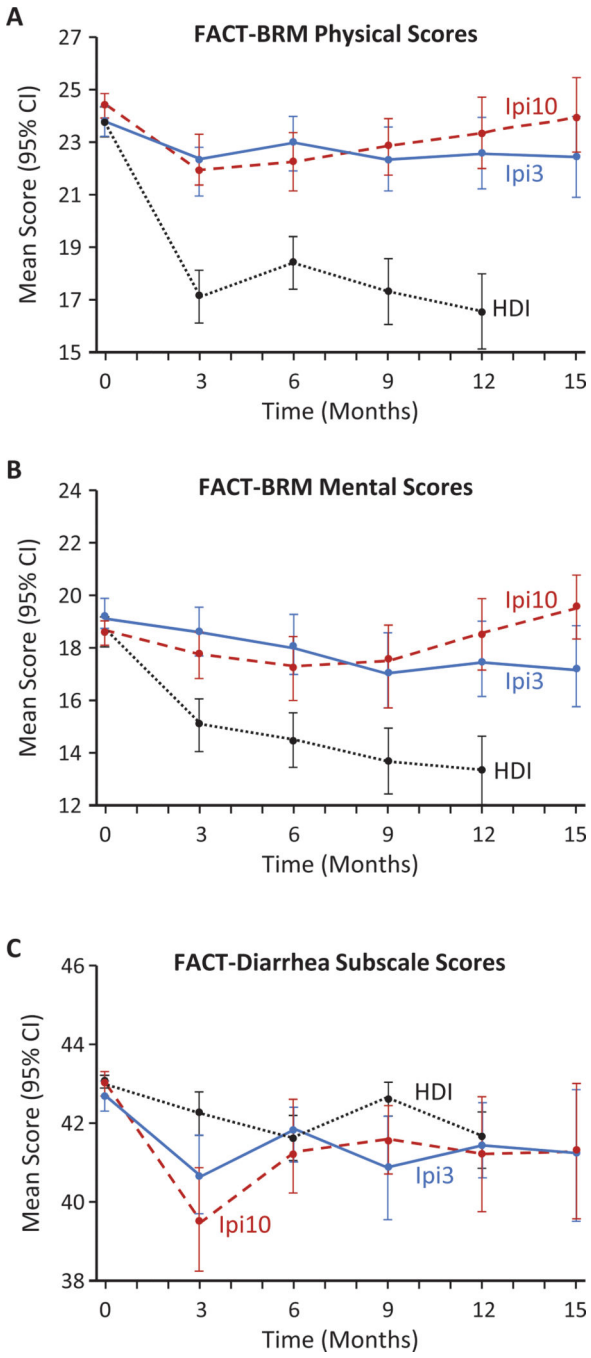

Figure 3. Mean and 95% CI of FACT-BRM Physical and Mental Scores and FACIT-D Diarrhea Subscale.

FACT-BRM = Functional Assessment of Cancer Therapy Biologic Response Modifier. FACIT-D = Functional Assessment of Chronic Illness Therapy Diarrhea. Higher scores on the FACT-BRM and FACIT-D Diarrhea Subscale indicate fewer concerns. Note: Patient-reported outcomes were not collected for HDI at 15 months, as maintenance therapy ended at 12 months.

Patients in the HDI arm reported more physical and cognitive/emotional concerns compared to the ipilimumab arms at 3-months. Patients in the ipilimumab arms reported worse gastrointestinal symptoms at 3-months compared to the HDI arm.

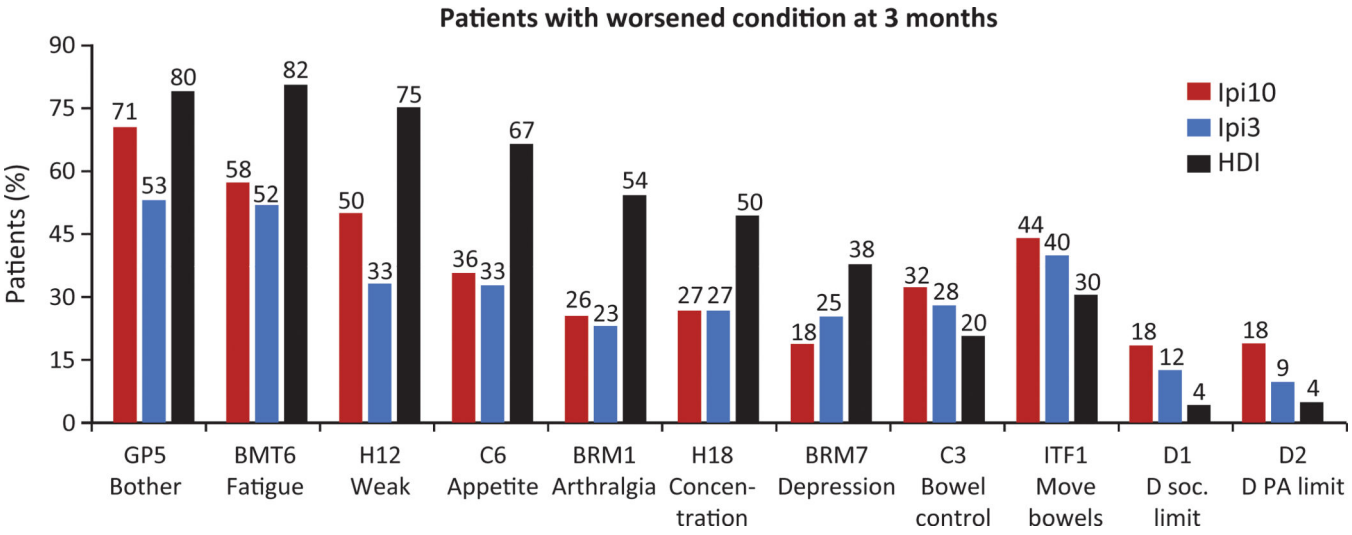

Figure 4. Percentage of Patient Condition Worsened at 3-months on Selected PRO Items by Treatment Arm.

PRO = Patient-reported outcome. GP5: I am bothered by side effects of treatment; BMT6: I get tired easily; HI12: I feel weak all over; C6: I have a good appetite; BRM1: I have pain in my joints; HI8: I have trouble concentrating; BRM7: I get depressed easily; C3: I have control of my bowels; ITF1: I move my bowels more frequently than usual; D1: I have to limit my social activity because of diarrhea; D2: I have to limit my physical activity because of diarrhea.

More patients assigned to HDI reported worsening fatigue, weakness, appetite loss, arthralgia, concentration, and depression symptoms compared to ipilimumab arms (all *p's* <.001 except $p = .054$ for depression ipi3 vs. HDI). More patients assigned to HDI and ipi10 reported worsening treatment bother compared to ipi3 (HDI vs. ipi3 $p<.001$; ipi10 vs. ipi3 $p = .013$). More patients assigned to ipi10 reported worsening gastrointestinal symptoms compared to HDI (*p's* <.001 to .048).

Table 1.

Demographic and Clinical Characteristics for E1609 PRO Cohort and Treatment Arms.

Characteristic or Demographic	Arm A: Ipi10 n=191	Arm B: HDI n=200	Arm C: Ipi3 n=158	Overall PRO n-549
Mean age (SD), years	53 (14)	52 (13)	50 (13)	52 (13)
RFS (month), median (95%CI) *	43.2 (29.7, 69.8)	29.9 (16.4, 40.0)	26.8 (16.3, 46.9)	33.9 (26.4, 40.9)
Age group, years – n (%)				
≤ 50	80 (41.9)	91 (45.5)	72 (45.6)	243 (44.3)
51 – 65	79 (41.4)	83 (41.5)	70 (44.3)	232 (42.2)
> 65	32 (16.7)	26 (13.0)	16 (10.1)	74 (13.5)
Sex				
Male	117 (61.3)	128 (64.0)	93 (58.9)	338 (61.6)
Female	74 (38.7)	72 (36.0)	65 (41.1)	211 (38.4)
Race				
White	189 (99.0)	197 (98.5)	157 (99.4)	543 (99.0)
Black	0 (0)	0 (0)	0 (0)	0 (0)
Asian	2 (1.0)	1 (0.5)	0 (0)	3 (0.5)
Other/Unknown	0 (0)	2 (1.0)	1 (0.6)	3 (0.5)
Ethnic group				
Hispanic	2 (1.0)	8 (4.0)	6 (3.8)	16 (2.9)
Not Hispanic	186 (97.4)	188 (94.0)	150 (94.9)	524 (95.5)
Unknown	3 (1.6)	4 (2.0)	2 (1.3)	9 (1.6)
Tumor size, cm				
≤ 1.00	25 (13.1)	27 (13.5)	15 (9.5)	67 (12.2)
1.01 – 2.00	33 (17.2)	39 (19.5)	35 (22.2)	107 (19.5)
2.01 – 4.00	62 (32.5)	46 (23.0)	40 (25.3)	148 (27.0)
> 4.00	47 (24.6)	59 (29.5)	48 (30.4)	154 (28.0)
Unknown	24 (12.6)	29 (14.5)	20 (12.6)	73 (13.3)
ECOG Performance Status				
0	160 (83.8)	173 (86.5)	136 (86.1)	469 (85.4)
1	31 (16.2)	27 (13.5)	22 (13.9)	80 (14.6)
Surgically resected AJCC stage				
IIIB	106 (55.5)	100 (50.0)	82 (51.9)	288 (52.5)
IIIC	72 (37.7)	86 (43.0)	65 (41.1)	223 (40.6)
M1a	9 (4.7)	8 (4.0)	9 (5.7)	26 (4.7)
M1b	4 (2.1)	6 (3.0)	2 (1.3)	12 (2.2)
Ulceration				
No	81 (42.4)	86 (43.0)	54 (34.2)	221 (40.3)
Yes	89 (46.6)	86 (43.0)	89 (56.3)	264 (48.1)
Unknown	21 (11.0)	28 (14.0)	15 (9.5)	64 (12.6)
Lactate Dehydrogenase				
Normal	170 (89.0)	180 (90.0)	149 (94.3)	499 (90.9)

Characteristic or Demographic	Arm A: Ipi10 n=191	Arm B: HDI n=200	Arm C: Ipi3 n=158	Overall PRO n-549
Elevated	15 (7.9)	14 (7.0)	5 (3.2)	34 (6.2)
Unknown	6 (3.1)	6 (3.0)	4 (2.5)	16 (2.9)
C-reactive protein				
Normal	99 (51.8)	120 (60.0)	99 (62.7)	318 (57.9)
Elevated	46 (24.1)	49 (24.5)	39 (24.7)	134 (24.4)
Unknown	46 (24.1)	31 (15.5)	20 (12.6)	97 (17.7)

* Overall survival (OS) was not presented because median OS was not reached for either of the treatment groups. Note: Ipi10 = ipilimumab 10mg/kg; Ipi3 = ipilimumab 3mg/kg; HDI = high dose interferon; PRO = patient-reported outcomes; RFS = relapse-free survival; CI = confidence interval; AJCC = American Joint Committee on Cancer.

Table 2.

Patient-reported Outcome Variable Descriptive Statistics and Change Scores by Arm and Overall

	Ipi 10	HDI	Ipi 3	Overall
FACT-G Total Scores				
Baseline				
n	191	200	157	548
Mean ± SD	90.0±12.2	87.9±13.2	89.8±13.9	89.2 ± 13.1
95% CI	88.3, 91.8	86.1, 89.8	87.6, 92.0	88.1, 90.3
Median (IQR)	92.0 (83.0, 99.0)	90.9 (78.0, 98.0)	93.0 (84.0, 100.0)	92.0 (82.0, 99.0)
P-value (vs. HDI)	0.100		0.201	
3-months				
n	113	119	102	334
Mean ± SD	84.9±16.5	74.7±15.4	87.5±14.6	82.1 ± 16.5
95% CI	81.8, 88.0	71.9, 77.5	84.7, 90.4	80.3, 83.9
Median (IQR)	87.7 (74.0, 99.0)	74.0 (64.0, 87.0)	90.0 (78.0, 99.0)	84.0 (70.0, 96.0)
P-value (vs. HDI)	<.001		<.001	
3-month Change				
n	110	114	97	321
Mean Change ± SD	-4.9±14.1	-12.9±14.1	-3.4±13.2	-7.3 ± 14.4
95% CI	-7.6, −2.2	-15.5, −10.3	-6.0, −0.7	-8.9, −5.7
P-value (vs. HDI)	<.001		<.001	
FACT-BRM Physical				
Baseline				
n	191	200	158	549
Mean ± SD	24.4±3.5	23.8±4.1	23.8±3.9	24.0 ± 3.9
95% CI	23.9, 24.9	23.2, 24.4	23.2, 24.4	23.7, 24.3
Median (IQR)	25.0 (23.0, 27.0)	25.0 (21.0, 27.0)	24.0 (22.0, 26.0)	25.0 (22.0, 27.0)
P-value (vs. HDI)	0.109		0.992	
3-months				
n	112	119	102	333
Mean ± SD	21.8±5.0	17.1±5.4	22.3±4.6	20.3 ± 5.6
95% CI	20.9, 22.8	16.1, 18.1	21.4, 23.3	19.7, 20.9
Median (IQR)	23.0 (19.0, 26.0)	18.0 (13.0, 21.0)	23.0 (19.0, 26.0)	21.0 (17.0, 25.0)
P-value (vs. HDI)	<.001		<.001	
3-month Change				
n	110	114	97	321
Mean ± SD	-2.7±4.7	-6.6±5.3	-1.8±3.9	-3.8 ± 5.2
95% CI	-3.6, −1.8	-7.6, −5.6	-2.6, −1.0	-4.4, −3.2
Median (IQR)	-2.0 (−6.0, 0.0)	-7.0 (−9.0, −3.0)	-1.0 (−4.0, 1.0)	-3.0 (−7.0, 0.0)
P-value (vs. HDI)	<.001		<.001	

	Ipi 10	HDI	Ipi 3	Overall
FACT-BRM Cognitive/Emotional				
Baseline				
n	191	200	158	549
Mean ± SD	18.7±4.5	18.6±4.4	19.2±4.2	18.8 ± 4.4
95% CI	18.0, 19.3	17.9, 19.2	18.6, 19.9	18.4, 19.2
Median (IQR)	20.0 (16.0, 22.0)	19.5 (16.0, 22.0)	21.0 (17.0, 22.0)	20.0 (16.0, 22.0)
P-value (vs. HDI)	0.823		0.133	
3-months				
n	112	119	102	333
Mean ± SD	17.7±4.8	15.0±5.3	18.6±4.4	17.0 ± 5.1
95% CI	16.8, 18.6	14.1, 16.0	17.8, 19.5	16.5, 17.6
Median (IQR)	18.5 (15.0, 21.0)	16.0 (11.0, 20.0)	19.5 (17.0, 22.0)	18.0 (14.0, 21.0)
P-value (vs. HDI)	<.001		<.001	
3-month Change				
n	110	114	97	321
Mean ± SD	-0.7±3.9	-3.3±4.9	-1.0±4.1	-1.7 ± 4.5
95% CI	-1.4, 0.1	-4.2, −2.4	-1.9, −0.2	-2.2, −1.2
Median (IQR)	0.0 (−2.0, 1.0)	-3.0 (−6.0, 0.0)	0.0 (−3.0, 1.0)	-1.0 (−4.0, 1.0)
P-value (vs. HDI)	<.001		<.001	
FACIT-D Subscale				
Baseline				
n	190	199	158	547
Mean ± SD	43.0±2.1	43.0±1.9	42.7±2.5	42.9 ± 2.1
95% CI	42.7, 43.3	42.7, 43.2	42.3, 43.1	42.7, 43.1
Median (IQR)	44.0 (43.0, 44.0)	44.0 (42.9, 44.0)	44.0 (42.0, 44.0)	44.0 (42.9, 44.0)
P-value (vs. HDI)	0.792		0.211	
3-months				
n	113	119	102	334
Mean ± SD	39.5±7.0	42.2±2.9	40.8±5.0	40.9 ± 5.3
95% CI	38.2, 40.8	41.7, 42.8	39.8, 41.8	40.3, 41.5
Median (IQR)	43.0 (37.0, 44.0)	43.0 (42.0, 44.0)	43.0 (39.0, 44.0)	43.0 (40.0, 44.0)
P-value (vs. HDI)	<.001		0.011	
3-month change				
n	109	114	97	320
Mean ± SD	-3.7±6.9	-0.7±2.7	-2.2±5.1	-2.2 ± 5.3
95% CI	-5.0, −2.3	-1.2, −0.2	-3.3, −1.2	-2.7, −1.6
Median (IQR)	-1.0 (−4.0, 0.0)	0.0 (−2.0, 0.0)	-1.0 (−3.0, 0.0)	0.0 (−3.0, 0.0)
P-value (vs. HDI)	<.001		0.009	

Note. P-values are calculated by two-sample t-test. Note: Ipi10/Ipi3, ipilimumab 10 mg/kg /ipilimumab 3 mg/kg; HDI, high dose interferon; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-BRM, Functional Assessment of Cancer Therapy-Biologic Response Modifier; FACIT-D, Functional Assessment of Chronic Illness Therapy-Diarrhea

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RESEARCH

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Enhanced immune activation within the tumor microenvironment and circulation of female high-risk melanoma patients and improved survival with adjuvant CTLA4 blockade compared to males

Mariam Saad[1], Sandra J. Lee[2], Aik Choon Tan[9], Issam M. El Naqa[10], F. Stephen Hodi[3], Lisa H. Butterfield[4], William A. LaFramboise[5], Walter Storkus[6], Arivarasan D. Karunamurthy[6], Jose Conejo-Garcia[12], Patrick Hwu[13], Howard Streicher[7], Vernon K. Sondak[11], John M. Kirkwood[6,8] and Ahmad A. Tarhini[1*]

Abstract

Background: We hypothesized that a gender difference in clinical response may exist to adjuvant CTLA4 blockade with ipilimumab versus high-dose IFNα (HDI). We investigated differences in candidate immune biomarkers in the circulation and tumor microenvironment (TME).

Patients and methods: This gender-based analysis was nested within the E1609 trial that tested adjuvant therapy with ipilimumab 3 mg/kg (ipi3) and 10 mg/kg (ipi10) versus HDI in high risk resected melanoma. We investigated gender differences in treatment efficacy with ipi3 and ipi10 versus HDI while adjusting for age, stage, ECOG performance (PS), ulceration, primary tumor status and lymph node number. Forest plots were created to compare overall survival (OS) and relapse free survival (RFS) between ipi and HDI. Gene expression profiling (GEP) was performed on tumors of 718 (454 male, 264 female) patients. Similarly, serum and peripheral blood mononuclear cells (PBMC) samples were tested for soluble and cellular biomarkers (N = 321 patients; 109 female and 212 male).

Results: The subgroups of female, stage IIIC, PS = 1, ulcerated primary, in-transit metastasis demonstrated significant improvement in RFS and/or OS with ipi3 versus HDI. Female gender was significant for both OS and RFS and was further explored. In the RFS comparison, a multivariate Cox regression model including significant variables indicated a significant interaction between gender and treatment ($P = 0.024$). In peripheral blood, percentages of CD3+ T cells ($P = 0.024$) and CD3+ CD4+ helper T cells ($P = 0.0001$) were higher in females compared to males. Trends toward higher circulating levels of IL1β ($P = 0.07$) and IL6 ($P = 0.06$) were also found in females. Males had higher percentages of monocytes ($P = 0.03$) with trends toward higher percentages of regulatory T cells (T-reg). Tumor GEP analysis supported enhanced infiltration with immune cells including gammadelta T cells ($P = 0.005$), NK cells ($P = 0.01$), dendritic

*Correspondence: Ahmad.Tarhini@moffitt.org

[1] Departments of Cutaneous Oncology and Immunology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA, 10920 McKinley Dr.
Full list of author information is available at the end of the article

cells ($P=0.01$), CD4+T cells ($P=0.03$), CD8+T cells ($P=0.03$) and T-reg ($P=0.008$) in the tumors of females compared to males and a higher T-effector and IFNγ gene signature score ($P=0.0244$).

Conclusion: Female gender was associated with adjuvant CTLA4 blockade clinical benefits and female patients were more likely to have evidence of type1 immune activation within the TME and the circulation.

Trial registration ClinicalTrials.gov NCT01274338. Registered 11 January 2011, https://www.clinicaltrials.gov/ct2/show/NCT01274338

Keywords: Melanoma, Adjuvant, Female, Male, Ipilimumab, Interferon

Introduction

Melanoma accounts for the majority of skin cancer deaths in the United States. An estimated total of 7650 deaths will be attributed to melanoma in 2022 [1]. While early-stage resectable low-risk melanoma can be cured by surgical excision alone, later high-risk stages are managed with the postoperative addition of systemic adjuvant therapy that can reduce the risks of recurrence and death [2]. In 2015, ipilimumab 10 mg/kg (ipi10) received regulatory approval in the U.S. as the first immune checkpoint inhibitor (ICI) adjuvant therapy for high-risk resected melanoma, almost 10 years after the approval of adjuvant high-dose interferon-alpha (HDI) [3]. The North American Intergroup Phase III adjuvant trial E1609 tested ipilimumab 3 mg/kg (ipi3) versus HDI (primary comparison) or ipi10 versus HDI and demonstrated significant overall survival (OS) improvement with ipi3 versus HDI (hazard ratio [HR], 0.78; 95.6% repeated CI 0.61 to 0.99; $P=0.044$) and no significant differences in survival between ipi10 and HDI [4]. Comparing ipi3 and ipi10, there were significant differences in toxicity rates in favor of ipi3 while recurrence and survival rates were similar.

While sexual dimorphism in immunity is acknowledged, sex-based responses to immunotherapies continue to be poorly understood [5]. Gender-based differences in cancer survival are well established in melanoma, with females having a significant survival advantage when compared to males. Cancer-specific survival differences in favor of females appear to decrease, however with increasing age [6], and with increasing metastatic tumor load [7]. While non-biological factors could be associated with this variance, such as a proposed more protective health-seeking behavior in women as well as improved reporting and access to health care, similar trends in cancer-related survival in favor of women were reported when these factors are accounted for [7]. Furthermore, sex hormonal differences have been hypothesized to differentially affect immune responses to immunotherapies [5]. Hormonal studies in murine models have demonstrated gender differences in melanoma outcomes that may be hormonally driven [9]. This is in addition to reported associations between the levels of estrogen and estrogen receptor expression in melanoma with patient survival in women [8]. When it comes to response to ICIs, gender-based differences have not been consistent in recent analyses of immunotherapy clinical trials. While one meta-analysis of recent immunotherapy clinical trials found significant gender-based differences in clinical benefits from ICIs in patients with metastatic melanoma [9], another metaanalysis found no significant association between gender and ICI survival benefits [10].

Therefore, there is a need to further investigate the contribution of sex to patient immunity and clinical benefits from ICIs in well-conducted randomized clinical trials such as E1609 with available biospecimens for correlative scientific testing. Here, based on our observations and literature reports we hypothesized that there is a gender difference in response to adjuvant immunotherapy with ipilimumab (ipi3 or ipi10) versus HDI as tested in the E1609 trial and investigated treatment efficacy between ipi and HDI in the subgroup of gender while controlling for other prognostic factors in a multivariate model. In addition, we hypothesized that male–female disparities in clinical benefits from ICIs are supported by differences in candidate immune biomarkers in the circulation and the tumor microenvironment (TME) of female and male patients.

Patients and methods

Patients

E1609 was a phase III study that enrolled patients with high-risk melanoma of cutaneous or unknown primary origin. Eligibility criteria included histological confirmation of melanoma. Patients were randomized and were rendered disease-free surgically within 12 weeks of randomization on the trial and were required to have AJCC 7th edition stages IIIB, IIIC, M1a or M1b [4]. Other criteria included ECOG performance status (PS) of 0 or 1 and passing screening safety laboratory testing criteria. Autoimmune disorders and conditions of immunosuppression that necessitated the use of systemic corticosteroids or other immunosuppressants were not permitted.

Trial design and treatments

E1609 was an open-label phase III trial that randomized melanoma patients to systemic adjuvant therapy with ipi10, HDI or ipi3. Patients were stratified by the AJCC 7th edition stage groups of IIIB, IIIC, M1a and M1b [4]. Clinical trial design details and additional information related to the clinical trial endpoint points, treatment regimens, randomization specifics, and trial oversight were previously published [4]. Patient disposition is described in the consort diagram included in Additional file 1: Fig. S1. All patients provided an IRB-approved written informed consent.

Methods and statistical analysis

E1609 demonstrated significant OS benefit with ipi3 versus HDI. We investigated treatment efficacy between ipi and HDI in the subgroups by gender (female, male), age (<55 or ≥ 55), stage at study entry (AJCC 7th edition IIIB, IIIC, M1a/1b), ECOG performance status (PS 0, 1), primary tumor ulceration (yes, no), primary tumor identification (known, unknown), number of lymph nodes involved (0, 1, 2–3, 4+). Forest plots were created to compare OS and RFS with ipi3 versus HDI and ipi10 versus HDI using the concurrently randomized ITT populations. For the estimated HRs, 95% confidence intervals were created for all subgroups. Univariate and Multivariate analyses were conducted with the multivariate Cox regression analysis used to adjust for confounders.

Gene expression profiling (GEP)

GEP was performed on the tumor biopsies of 718 (454 male, 264 female) melanoma patients. Only metastatic tumors were included that were resected to render patients disease free prior to clinical trial enrollment. Microdissection of Formalin-Fixed Paraffin-Embedded (FFPE) tumor specimens was performed manually using an inverted microscope (Nikon Eclipse TE200) as needed to obtain a minimum of 90% tumor cells for RNA purification. Dissection involved scraping cells from unstained sections of 5 micron thickness on slides aligned in register with serially cut hematoxylin and eosin stained specimens including tumor domains demarcated by a surgical pathologist (A. K.). RNA purification was performed using the Qiagen miRNeasy FFPE Kit and protocol (Qiagen, Valencia, CA) with isolated RNA suspended in nuclease-free water. Inclusion in subsequent in vitro amplification (IVT) assays was determined both by spectrophotometric absorption ratio [260/280 > 1.8 (NanoDrop, Wilmington, DE)] and RIN values (RNA Integrity Index) determined via microchip electrophoretic analysis (Agilent Bioanalyzer 2100, Agilent Technologies, Santa Clara, CA). We previously established that RIN values ranging from 5.0 to 8.0 in RNA from FFPE specimens can undergo successful in vitro transcription and amplification using a multiplex primer approach. Amplification was performed using the NuGen whole transcription method comprising the Ovation FFPE WTA assay (NuGEN, San Carlos, CA) employing random and 3′ primers to eliminate amplification bias beginning with 100 ng total RNA. Confirmation of cDNA diversity was obtained using the Bioanalyzer 2100 to generate an electrophoretogram for each amplification reaction regarding sample yield, integrity and size diversity compared to a laboratory human RNA standard and a Universal Human Reference RNA (Stratagene, La Jolla, CA). 5 µg of purified cDNA were incubated with fragmentation buffer (NuGEN, San Carlos, CA) at 37 °C for 30 min, then 95 °C for 2 min. The cDNA samples were hybridized on Affymetrix GeneChip HG U133A 2.0 arrays which comprehensively represent the functionally characterized human genome with overlapping probe sets for transcripts.

Data analysis of gene expression profiles

Robust Multi-array Average (RMA) method was used to normalize raw microarray data as previously described [11, 12]. Genes with multiple probe sets were collapsed by using the probe with maximum gene expression. Gene set enrichment analysis (GSEA) was performed by comparing the female and male tumor samples [13]. In this study, KEGG pathways gene sets were obtained from MSigDB to interrogate the enrichment of pathways in the female and male samples [14]. In order to further deconvolute the cell types in the bulk transcriptomics, we used gene sets obtained from CIBERSORT [15, 16], and TIMEx [17], in comparing the female versus male samples. Gene sets with a false discovery rate (FDR) q-value <0.15 were deemed as significant. We also tested previously published prognostic gene signatures of immunotheraphy in comparing female versus male tumors including IFNγ 6-gene signature (IDO1, CXCL10, CXCL9, HLA-DRA, IFNG, STAT1) [18], and T-effector and IFNγ gene signature (CD8A, GZMA, GZMB, IFNG, EOMES, CXCL9, CXCL10, TBX21) [19]. For each sample, we computed a gene signature score by averaging the standardized z-score for the genes in the signature. For each of these gene signatures [20]. Mann–Whitney U test was performed by comparing female and male and $p<0.05$ was deemed as statistically significant.

Serum and peripheral blood mononuclear cells (PBMC) data analysis

Peripheral blood samples were tested for soluble (Luminex) and cellular (multicolor flow cytometry) prognostic biomarkers in a subset of patients (N = 321; 109 female and 212 male). Mann–Whitney U test was

performed by comparing between female and male and $p < 0.05$ was deemed as statistically significant.

Peripheral blood

Red top vacutainer tubes (BD, no anticoagulant) were used for serum collection and all samples were processed within 24 h of collection (samples received before 5 pm were processed upon receipt, those arriving after 5 pm were processed the following morning). Serum samples were centrifuged at 2500 rpm for 10 min at 4 °C according to laboratory standard operating procedures (SOPs) and single use aliquots of each patient's sera were then stored at − 80 °C. For PBMC, blood was drawn into heparin tubes and processed by the Immunologic Monitoring Laboratory upon receipt. PBMCs were obtained from the blood samples by ficol density-gradient centrifugation and stored frozen. The laboratory freezers were monitored continuously for any temperature fluctuations and maintained the samples at -80 °C.

Multiplex serum cytokine analysis

21 serum cytokines were selected for analysis based on function. These included Th1 type cytokines (IL-12p70, IL-17, IL-2, IP-10), proinflammatory (IL-1α, IL-1β, IL-6, TNF-α, TNF-RII, IL-2R, IL-8, CRP, IL-17, IFN-α), immunoregulatory (TGF-α, IL-10, TIMP1), growth factor (VEGF-A), and other/chemokines (CCL3/MIP-1α, CCL4/MIP-1β, CXCL9/MIG, CXCL11/I-TAC). The xMAP Luminex serum assay for these cytokines was performed according to the manufacturer's protocol (BioSource International (Camarillo, CA) as previously described [21], and laboratory SOPs, and analyzed on the Bio-Plex suspension array system (Bio-Rad Laboratories, Hercules, CA). Experimental data was analyzed using five-parametric curve fitting and assay controls included kit standards and multiplex QC controls (R & D Systems). Inter-assay variabilities for individual cytokines were 1.0 to 9.8% and intra-assay variabilities were 3.6 to 12.6% (information provided by Biosource International and validation performed in our laboratory). C-reactive Protein (CRP) was run singly as it requires different dilutions.

Multicolor flow cytometry

Multicolor flow cytometry was used to compare cell subset phenotypes on thawed patient peripheral blood mononuclear cells (PBMC), with healthy donor controls, run according to laboratory SOPs. Regulatory T cells (Treg) were defined as CD4+ CD25+ FOXP3+ or CD4+ CD25hi+ CD39+ cells, to incorporate the candidate functional marker CD39 as previously described [22]. Myeloid-derived-suppressor cells (MDSC) were defined as cells expressing Lin-neg/HLA-DR−/CD33+/CD11b+ in either a "lymphocyte" (small FSCxSSC) gate, or in a "monocyte" (larger FSCxSSC) gate, and as HLA-DR+/lo CD14+ cells in a large gate as previoulsy described [22]. We also tested the frequencies of CD4+ and CD8+ T cells specific to shared tumor-associated antigens (gp100, MART-1, NY-ESO-1) utilizing overlapping peptide libraries (15-mer peptides overlapping by 4) and a short (4–5 h) in vitro culture to identify activated (CD69+) and cytokine producing (intracellular IFNγ+) T cells. Detailed methods were described previously [22].

Results

The characteristics of patients enrolled in E1609 and the treatment details as well as the incidence rate of irAEs were previously published [4]. Table 1 summarizes the baseline and disease characteristics of the E1609 study population included in this analysis.

Using the concurrently randomized ITT populations in the subgroup analyses, forest plots were created to compare ipi3 versus HDI in terms of RFS and OS (Fig. 1) and to compare ipi10 versus HDI in terms of RFS and OS (Additional file 2: Fig. S2).

In investigating RFS with ipi3 versus HDI, the subgroups of female, stage IIIC, PS = 1, ulcerated, in-transit without lymph node involvement demonstrated significant improvement in OS and/or RFS with ipi3 versus HDI as summarized in Table 2. Female gender was significant for both OS and RFS and was further explored. A multivariate Cox regression model including gender, treatment and interaction term of gender*treatment, indicated a significant interaction between gender and treatment ($P = 0.026$). Including gender, PS (0 versus 1), age (< 55 versus ≥ 55), ulceration (yes versus no), stage (IIIB, IIIC, M1a, M1b), treatment and interaction term of gender*treatment, indicated a significant interaction between gender and treatment ($P = 0.024$).

When exploring age further in the univariate analyses in the ipi3 versus HDI comparison, older women appeared to drive most of the difference (age ≥ 55: OS, $P = 0.02$ and RFS, $P = 0.08$; differences non-significant for age < 55).

While similar trends were clearly seen, no significant interactions between gender and treatment effect were found in the OS multivariate analysis for ipi3 versus HDI or in the comparison of ipi10 versus HDI.

Among the subset of patients (N = 321) tested for circulating biomarkers, females were significantly younger than males ($P = 0.03$). Testing PBMCs, the percentages of CD3+ T cells ($P = 0.04$) and CD3+ CD4+ helper T cells ($P = 0.001$) were significantly higher in female patients compared to males (Fig. 2). Also, there were trends toward higher levels of proinflammatory cytokines IL-1β

Table 1 Patient demographics and baseline disease characteristics

	Ipilimumab 10 mg/kg (ipi10) (n = 511)	**HDI (n = 636)**	**Ipilimumab 3 mg/kg (ipi3) (n = 523)**
Age Median (range)	52 years (18–80)	54 years (18–83)	54 years (19–80)
Stage (AJCC7)			
IIIB	268 (52.5%)	331 (52.0%)	280 (53.5%)
IIIC	205 (40.1%)	253 (39.8%)	205 (39.2%)
M1a	28(5.5%)	34 (5.4%)	28 (5.4%)
M1b	10 (1.9%)	18(2.8%)	10 (1.9%)
Sex			
Male	342 (66.9%)	395 (62.1%)	328 (62.7%)
Female	169 (33.1%)	241 (37.9%)	195 (37.3%)
PS			
0	426 (83.5%)	533 (83.8%)	439 (84.7%)
1	85(16.5%)	102 (16.0%)	82 (15%)
Unknown/Missing	0	1 (.2%)	2 (.3%)
Primary tumor status			
Unknown	56 (11.0%)	103 (16.2%)	84 (16.1%)
Ulceration			
No	216 (42.3%)	263 (41.4%)	187 (35.4%)
Yes	227 (44.4%)	260 (41.5%)	252 (46.9%)
Unknown (most due to unknown primary)	68 (13.3%)	113 (18.1%)	84 (17.7%)
Microscopic LN Involvement			
Yes (among IIIB/IIIC)	233 (49.2%)	285 (50.5%)	247 (50.9%)

($P = 0.07$) and IL6 ($P = 0.06$) in females (Additional file 3: Fig. S3). Conversely, males had significantly higher percentages of circulating monocytes ($P = 0.03$). Importantly, there were trends toward higher percentages of CD3+/CD4+/CD25hi+/Foxp3+ ($P = 0.1$) and CD3+/CD4+/CD25+/CD127low+ ($P = 0.1$) T-reg in male patients compared to females (Fig. 3).

Among the cohort of patients (N = 718) with tumor GEP data, females were significantly younger than males ($P = 0.0009$, U-test). As expected, when comparing the differentially expressed genes and pathways between female and male patient tumors, the top ranked genes were related to the sex chromosomes. To investigate the underlying immunologic differences related to female and male in response to immunotherapy, we performed GSEA using CIBERSORT gene signatures which are related to immune cell infiltration and activation. Interestingly, female patients' tumors were significantly enriched in immune related pathways and genes compared to the tumors of male patients, with estimated enhanced immune cell infiltration including CD4+ T cells, CD8+ T cells, γδ T cells, NK cells, dendritic cells, Tregs and M1 macrophages (Table 3). Furthermore, we performed TIMEx analysis and male patients' tumors were estimated to be enriched in tumor stromal endothelial cells as compared to female patients' tumors (p = 0.0429, U-test).

To further explore gender-related differences in response to adjuvant immunotherapy, we evaluated published gene signatures that may be associated with immunotherapy benefits in female versus male tumors in this study. The T-effector and IFNγ gene signature was found to have a higher score in female tumors as compared to male tumors ($P = 0.0244$, U-test) and there was a trend toward a higher score for the IFNγ 6-gene signature in favor of female tumors ($P = 0.07$, U-test) (Fig. 4).

Discussion

When exploring differences in gender response to immune-checkpoint inhibitors, results from the E1609 trial suggest superior clinical benefits from CTLA4 blockade in the subgroup of female patients. Particularly when accounting for potential confounders, females were shown to have significantly higher relapse-free survival rate as compared to males in the study comparison of ipi3 versus HDI with similar trends observed in the OS comparison and in investigating RFS and OS with ipi10 versus HDI. Overall, in melanoma, female patients have generally been reported to have improved survival including a lower risk of regional and systemic disease progression, and a higher likelihood of survival

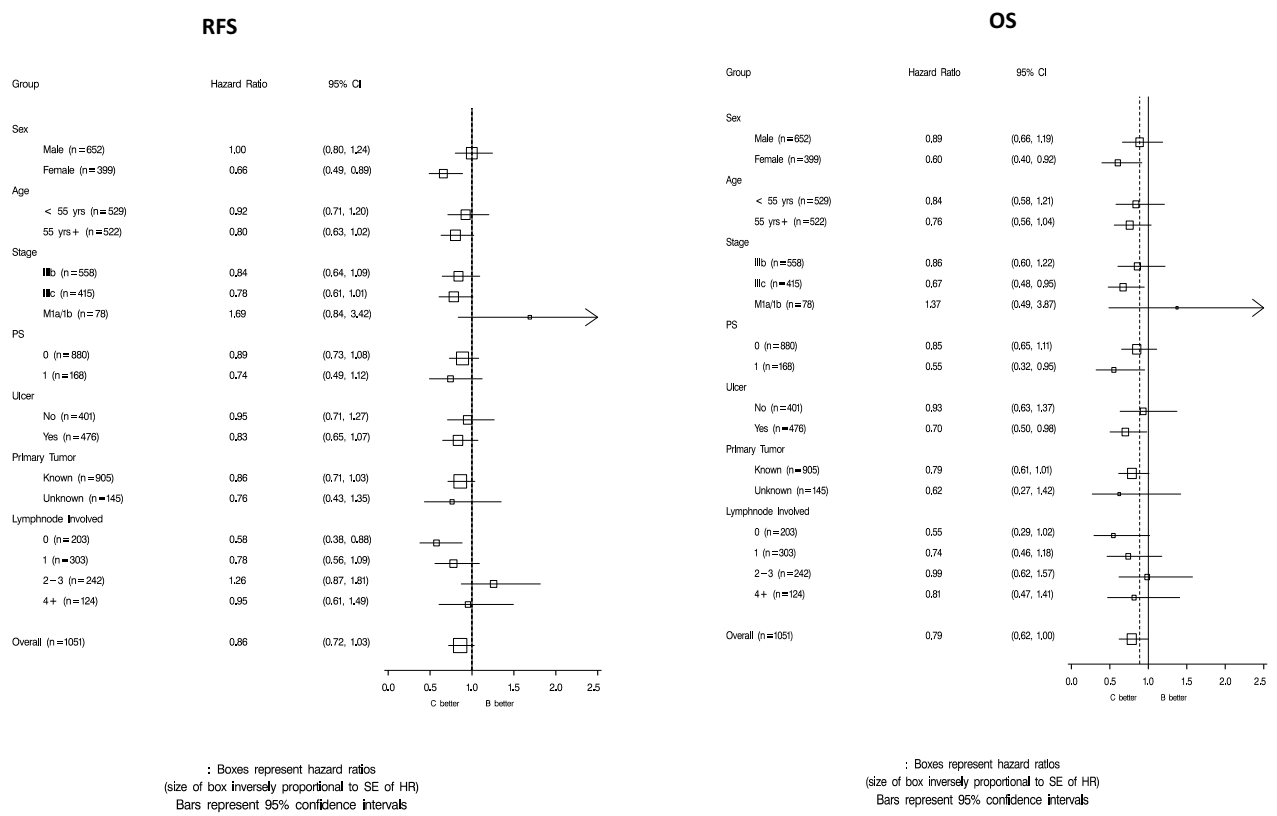

Fig. 1 Forest plots comparing relapse free survival (RFS) and overall survival (OS) for ipilimumab 3 mg/kg versus high dose interferon-alfa

Table 2 Treatment efficacy between ipi3 and HDI by subgroup

Group	HR, 95% CI	
	OS	RFS
Female gender	0.60 (0.40, 0.92)	0.66 (0.49, 0.89)
In-transit, LN-ve	0.55 (0.29, 1.02)	0.58 (0.38, 0.88)
Ulceration	0.70 (0.50, 0.98)	0.83 (0.65, 1.07)
Stage IIIC	0.67 (0.48, 0.95)	0.78 (0.61, 1.01)
PS = 1	0.55 (0.32, 0.95)	0.74 (0.49, 1.12)

Estimated hazard ratios (HR) with 95% confidence intervals (CI) are provided. The subgroups of female, stage IIIC, PS = 1, ulcerated, in-transit without lymph node involvement demonstrated significant improvement in OS and/or RFS with ipi3 versus HDI. Female gender was significant for both OS and RFS

following disease progression [7, 23]. While the results of this study support the gender disparity in terms of benefit from adjuvant CTLA4 blockade, analyses of other ICI trials have not been consistent. Yang et al. reported no significant differences in gender-based benefits from ICIs therapy in a meta-analysis of 37 randomized clinical trials involving patients with advanced malignancies including melanoma [10]. On the other hand, Conforti et al. conducted a meta-analysis of 20 randomized trials of ICIs in advanced cancers including melanoma and suggested that men derived more survival benefits compared to women [9]. Overall, these meta-analyses constituted pan-cancer analyses, the number of men included was significantly higher than the number of women and the control arm in the melanoma studies was most often another ICI. Furthermore, the aforementioned meta-analyses included studies of inoperable metastatic disease rather than patients in the operable adjuvant setting which is the case of E1609.

Our clinical findings of potential improvement in survival for females following ipilimumab adjuvant therapy were also supported by our immune monitoring studies. In testing candidate circulating biomarkers females were shown to have significantly higher percentages of CD3+ T cells and CD3+CD4+ helper T cells in addition to trends towards higher levels of proinflammatory cytokines IL1β and IL6 in females. Males had significantly higher percentages of monocytes with trends of higher percentages of CD3+/CD4+/CD25hi+/Foxp3+ and CD3+/CD4+/CD25+/CD127low+ regulatory T cells. Our findings are consistent with other immune monitoring reports in the literature of higher baseline numbers of CD3+CD4+ helper T cells, a higher CD4+/CD8+ cell ratio in women compared to men [24],

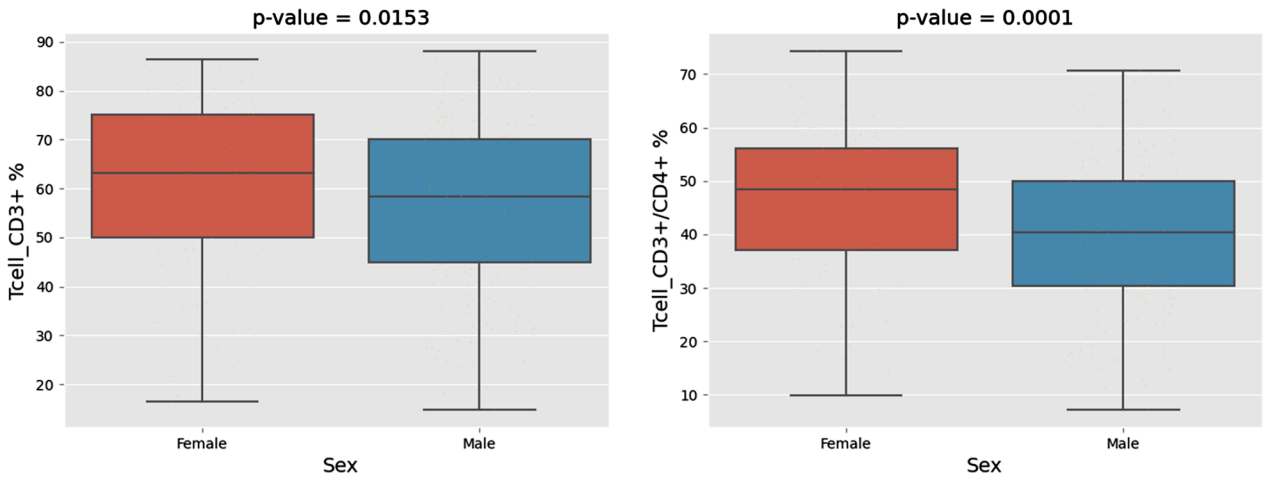

Fig. 2 Multicolor flow cytometry of peripheral blood mononuclear cells (PBMCs). The percentages of CD3+T cells ($P=0.04$) and CD3+ CD4+ helper T cells ($P=0.001$) were significantly higher in female patients compared to males

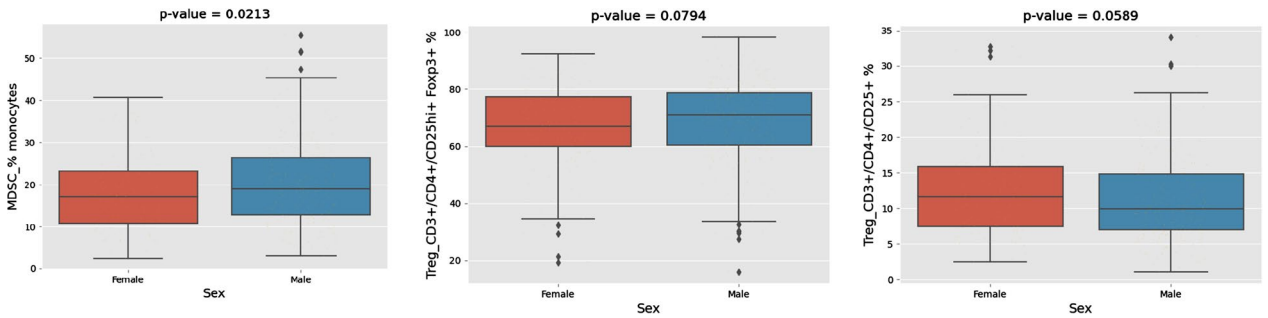

Fig. 3 Multicolor flow cytometry of peripheral blood mononuclear cells (PBMCs). Significantly higher percentages of monocytes (P = 0.03) and trends toward higher percentages of CD3+/CD4+/CD25hi+/Foxp3+ (P = 0.1) and CD3+/CD4+/CD25+/CD127low+ (P = 0.1) T-reg in male patients compared to females

Table 3 Immune related pathways found to be significantly enriched in the tumors of female patients compared to tumors of male patients as computed by gene set enrichment analysis (GSEA; utilizing CIBERSORT gene sets) (NES: Normalized enrichment score)

Name	NES	p-val	FDR q-val
T_CELLS_GAMMA_DELTA	2.16	0.0052	0.1141
NK_CELLS_ACTIVATED	1.97	0.0102	0.0607
NK_CELLS_RESTING	1.77	0.0118	0.0552
DENDRITIC_CELLS_ACTIVATED	1.73	0.0106	0.0465
T_CELLS_REGULATORY_(TREGS)	1.65	0.0085	0.0503
DENDRITIC_CELLS_RESTING	1.59	0.0140	0.0636
T_CELLS_CD8	1.52	0.0270	0.0830
MACROPHAGES_M1	1.50	0.0164	0.0824
T_CELLS_CD4_NAIVE	1.46	0.0294	0.0932

and lower regulatory T cell percentage in females than in males [25]. The monocyte frequency is a new finding and should be investigated further for the M1/M2 profile of those cells, and absolute counts in addition to frequencies. Because ipilimumab blockade of CTL4 induces immune-mediated tumoricidal actions by fortifying effector T cell activation [26], our findings support potential more pronounced immune effects with CTLA4 blockade in the peripheral blood of females as compared to males.

Immune escape in melanoma includes, and certainly is not limited to, altering immune cell functions such as impairing NK cell cytolytic activity, reducing stimulatory effects of dendritic cells upon effector T cells, promoting cytotoxic T cell anergy and stimulating Treg [27]. This is in addition to the ability of the tumor cells

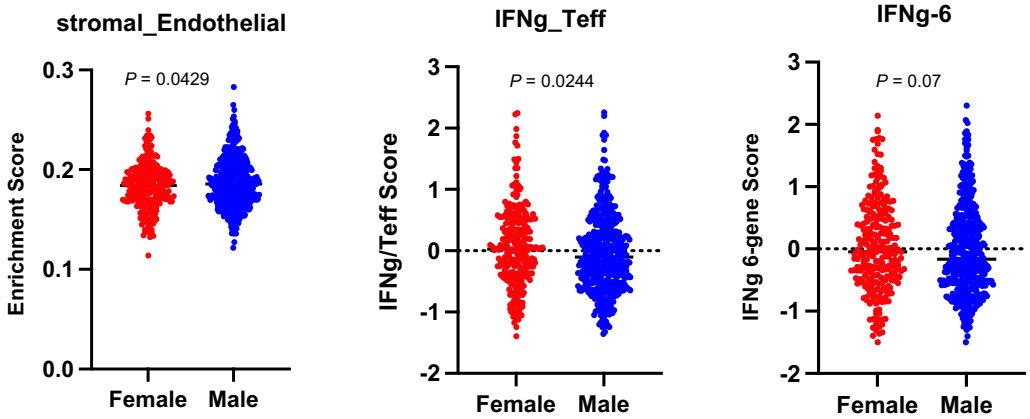

Fig. 4 Gene expression changes in female versus male patients. T-effector and IFNγ gene signature was higher in female tumors as compared to male tumors ($P = 0.0244$) There was a trend towards a higher score for the IFNγ 6-gene signature in favor of female ($P = 0.07$). On the otherhand, endothelial cells were estimated to be enriched in the tumors of male patients as estimated by TIMEx ($P = 0.0429$)

themselves to directly evade T cell surveillance and destruction. The nature of the TME transcriptome provides important clues that reflect the immunogenicity of the TME and its susceptibility to immunotherapy interventions. In this study we identified pathways and genes related to immune cell infiltration and activation that were significantly enriched in the tumors of females compared to males. We estimated enhanced immune cell infiltration in female tumors including CD4+ T cells, CD8+ T cells, γδT cells, NK cells and dendritic cells that support a more immunogenic TME and are prognostic or improved survival [28]. Similarly, the T-effector and IFNγ gene signature was found to have a higher score in female tumors and there was a trend towards a higher score for the of IFNγ 6-gene signature in favor of female tumors. These gene expression profiles were shown to be prognostic of improved survival in patients treated with ICIs [18, 19]. Our findings that these signatures were more pronounced in the tumors of females support our original hypothesis of a higher susciptibility to ICI induced immune responses in females with high-risk resected melanoma. Interestingly, we observed that genes related to stromal endothelial cells were significantly more expressed in the tumors of males. Cancer growth and metastasis are regulated in part by stromal cells such as fibroblasts and endothelial cells that imacpt the immune cell repertoire within the TME. Increased endothelial cell density may reflect a more angiogenic tumor where neoangiogenesis is a recognized hallmark of cancer that drives cancer progression and growth and confers poorer prognosis [29–31]. In terms of the tumor types tested and potential differences between males and females, all tumors were metastases. The types of metastases were cutaneous/subcutaneous, nodal or lung metastasis as reflected by the patients' stage groups (IIIB, IIIC, M1a or M1b). We analyzed our cohort of 718 patients and have found no significant differences between females and males in terms of stage groups. Therefore, it is unlikely that there are significant differences between females and males in terms of the types of tumor tissue samples analyzed that may explain the difference in endothelial cell density.

Finally, we observed that females were significantly younger than males in our cohorts. This observation is consistent with the incidence of melanoma in the general population. Furthermore, in our investigation of gender differences in treatment efficacy we adjusted for age and other prognostic factors including stage, ECOG PS, ulceration, primary tumor status and lymph node number. In addition, when exploring age further in the univariate analyses in the ipi3 versus HDI comparison, older women appeared to drive most of the differences in survival (age ≥ 55: OS, $P = 0.02$ and a trend in RFS, $P = 0.08$; differences were non-significant for age < 55). Therefore, it is unlikely that the younger age of females is a major contributing factor to the outcomes seen in our analysis.

Conclusions

Female gender was associated with adjuvant immunotherapeutic benefit and female patients were more likely to have evidence of immune activation within the TME and the circulation, supporting a potentially important role for factors related to female gender in

the immune response against melanoma. These warrant further investigation.

Abbreviations

AJCC: American Joint Committee on Cancer; CTLA-4: Cytotoxic T lymphocyte antigen 4; ECOG-ACRIN: Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; FFPE: Formalin fixed paraffin embedded; GSEA: Gene set enrichment analysis; GI: Gastrointestinal; MHC: Major histocompatibility complex; HDI: High-dose interferon-α; HR: Hazard ratio; ICI: Immune checkpoint inhibitor; irAE: Immune-related adverse event; Ipi3: Ipilimumab at 3 mg/kg; Ipi10: Ipilimumab at 10 mg/kg; KEGG: Kyoto Encyclopedia of Genes and Genomes; MUP: Melanoma of unknown primary; NES: Normalized enrichment score; PBMC: Peripheral blood mononuclear cells; PD-1: Programmed cell death protein 1; PS: Performance status; OS: Overall survival; RFS: Relapse free survival; TME: Tumor microenvironment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-022-03450-3.

Additional file 1: Figure S1. E1609 Consolidated Standards of Reporting Trials diagram (adult patient populationa). aE1609 included a pediatric component (ages 12–17 years) consisting of three separate cohorts randomized to the three treatment regimens and analyzed separately for safety per study protocol. Total pediatric accrual was three subjects; bthese overlap with but are not limited to treatment-related grade 5 events previously reported; cconcurrently randomized cases. HDI, high-dose interferon alpha-2b; Ipi3, ipilimumab 3 mg/kg; Ipi10, ipilimumab 10 mg/kg; ITT, Intent to Treat.

Additional file 2: Figure S2. Forest plots comparing relapse free survival (RFS) and overall survival (OS) for ipilimumab 10 mg/kg versus high dose interferon-alfa.

Additional file 3: Figure S3. Serum cytokine analysis utilizing the xMAP Luminex serum assay. Trends toward higher levels of proinflammatory cytokines IL1beta ($P = 0.07$) and IL6 ($P = 0.06$) in females compared to males.

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Author contributions

Conception and design: AT, SL, ACT, IE, LB, WL. Provision of study material or patients: AT, JK, FSH, VS, ECOG-ACRIN E1609 study investigators. Collection and assembly of data: AT, JK, SL, FSH, VS, ECOG-ACRIN E1609 study investigators. Data analysis: AT, SL, ACT, IE, MS. Data interpretation: AT, SL, ACT, IE, LB, WL, WS, FSH, JK, VS, ADK, JCG, PH, HS, MS. Manuscript writing: All authors. Final approval of manuscript: All authors. Accountable for all aspects of the work: All authors. All authors read and approved the final manuscript.

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Data availability

The data sets generated, analyzed and reported in the present paper will be made available in the NCTN/NCORP Data Archive (https://nctn-data-archive.nci.nih.gov).

Declarations

Ethics approval and consent to participate

The study protocol was approved by the institutional review board of each participating institution and conducted in accordance with Good Clinical Practice guidelines as defined by the International Conference on Harmonization. All patients provided an IRB-approved written informed consent. This study was monitored by the ECOG-ACRIN Data Safety Monitoring Committee and the NCI.

Consent for publication

Yes.

Competing interests

MS has nothing to disclose. AAT reports grants from National Cancer Institute, National Institute of Health, ECOG-ACRIN, grants from Bristol Myers Squibb, during the conduct of the study; grants from Bristol Myers Squibb, personal fees from Bristol Myers Squibb, grants from Merck, personal fees from Merck, personal fees from Novartis, personal fees from Genentech-Roche, grants from Genentech-Roche, personal fees from Array Biopharma, grants from Incyte, personal fees from Incyte, personal fees from NEWLINK Genetics, personal fees from HUYA, personal fees from BioNTech, grants from Prometheus, personal fees from Prometheus, personal fees from Immunocore, grants from Greenpeptide, grants from Amgen, grants from Clinigen, personal fees from Clinigen, personal fees from Partners Therapeutics, personal fees and grants from Regeneron, personal fees and grants from Sanofi-Genzyme outside the submitted work. SJL has nothing to disclose. ACT reports has nothing to disclose. IEN is a deputy editor for Medical Physics and reports relationship with Scientific Advisory Endectra, LLC. FSH reports clinical trial support from Eastern Cooperative oncology Group, during the conduct of the study; grants, personal fees and other from Bristol Myers Squibb, personal fees from Merck, personal fees from EMD Serono, grants and personal fees from Novartis, personal fees from Takeda, personal fees from Surface, personal fees from Genentech/Roche, personal fees from Compass Therapeutics, personal fees from Apricity, personal fees from Bayer, personal fees from Aduro, personal fees from Partners Therapeutics, personal fees from Sanofi, personal fees from Pfizer, personal fees from Pionyr, from 7 Hills Pharma, personal fees from Verastem, other from Torque, personal fees from Rheos, outside the submitted work; in addition, Dr. Hodi has a patent Methods for Treating MICA-Related Disorders (#20100111973) with royalties paid, a patent Tumor antigens and uses thereof (#7250291) issued, a patent Angiopoiten-2 Biomarkers Predictive of Anti-immune checkpoint response (#20170248603) pending, a patent Compositions and Methods for Identification, Assessment, Prevention, and Treatment of Melanoma using PD-L1 Isoforms (#20160340407) pending, a patent Therapeutic peptides (#20160046716) pending, a patent Therapeutic Peptides (#20140004112) pending, a patent Therapeutic Peptides (#20170022275) pending, a patent Therapeutic Peptides (#20170008962) pending, a patent THERAPEUTIC PEPTIDES Therapeutic Peptides Patent number: 9402905 issued, and a patent METHODS OF USING PEMBROLIZUMAB AND TREBANANIB pending. LHB declares the following unrelated advisory activities: StemImmune/Calidi Scientific and Medical Advisory Board, April 6, 2017-present; Western Oncolytics, Scientific Advisory Board, 2018-present; Torque Therapeutics, Scientific Advisory Board, 2018–2020; Khloris, Scientific Advisory Board, 2019-present; Pyxis, Scientific Advisory Board, 2019-present; Cytomix, Scientific Advisory Board, 2019-present; Vir, Scientific Advisory Board meeting, Feb. 2020; DCprime, Scientific Advisory Board meeting, Nov. 2020; RAPT, Scientific Advisory Board, 2020-present; Takeda, Scientific Advisor, 2020-present; EnaraBio scientific advisor, Feb. 2021. WAL has nothing to disclose. WS has nothing to disclose. ADK has nothing to disclose. JRCG has stock options with Compass

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Author details
[1]Departments of Cutaneous Oncology and Immunology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA, 10920 McKinley Dr.. [2]Dana Farber Cancer Institute and Harvard Medical School, Boston, MA, USA. [3]Dana Farber Cancer Institute, Boston, MA, USA. [4]Univ. California San Francisco and The Parker Institute for Cancer Immunotherapy, San Francisco, CA, USA. [5]Allegheny Health Network Cancer Institute, Pathology, Pittsburgh, PA, USA. [6]University of Pittsburgh School of Medicine (UPSOM), Pittsburgh, PA, USA. [7]National Cancer Institute, Rockville, MD, USA. [8]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA. [9]Department of Biostatistics and Bioinformatics, H. Lee Moffitt Cancer Center and Research Institute, Tampa, USA, Florida. [10]Department of Machine Learning, H. Lee Moffitt Cancer Center and Research Institute, Tampa, USA. [11]Department of Cutaneous Oncology, H. Lee Moffitt Cancer Center and Research Institute, Florida, Tampa, USA. [12]Department of Immunology, H. Lee Moffitt Cancer Center and Research Institute, Florida, Tampa, USA. [13]Administration, Cutaneous Oncology, Immunology, H. Lee Moffitt Cancer Center and Research Institute, Florida, Tampa, USA.

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