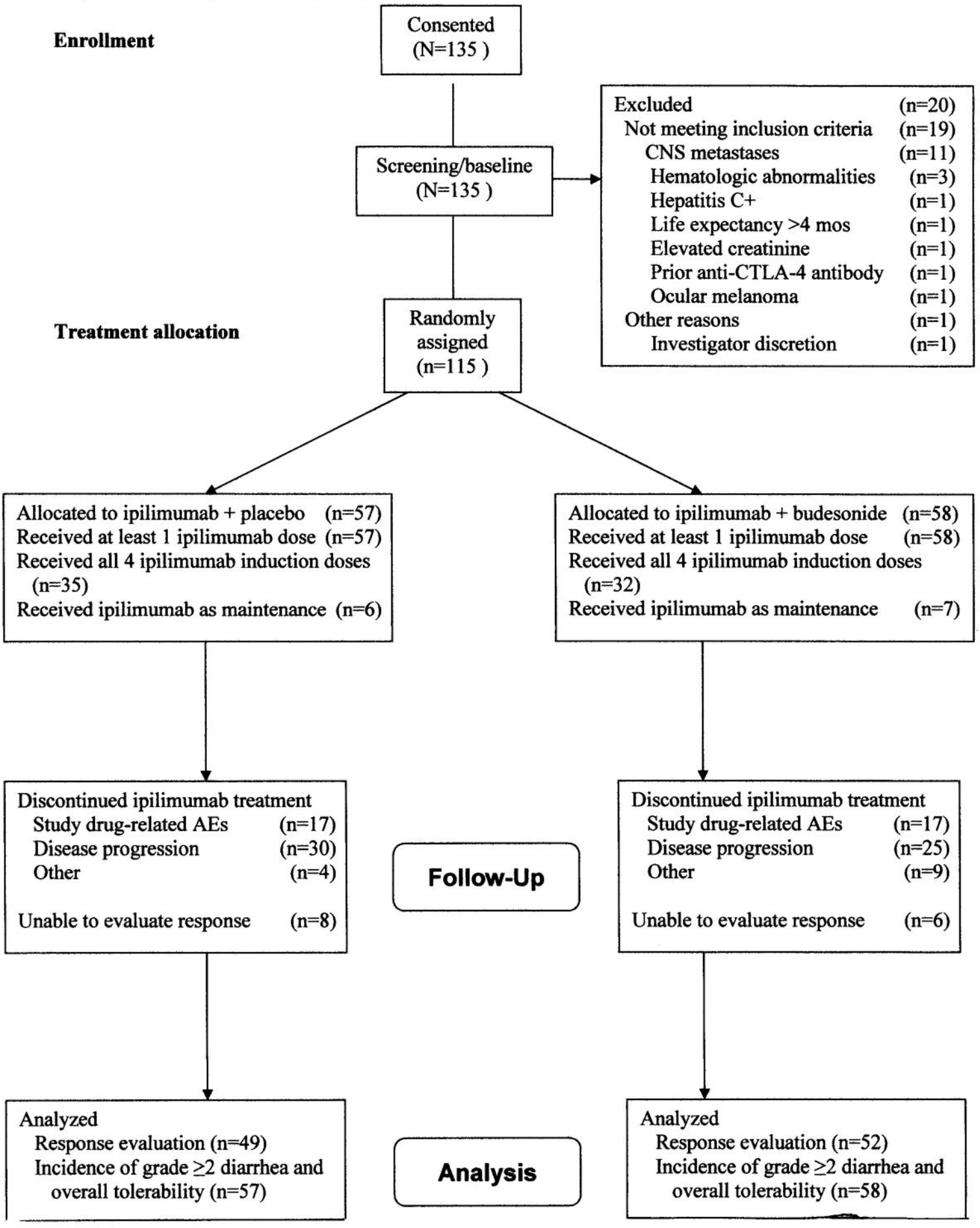
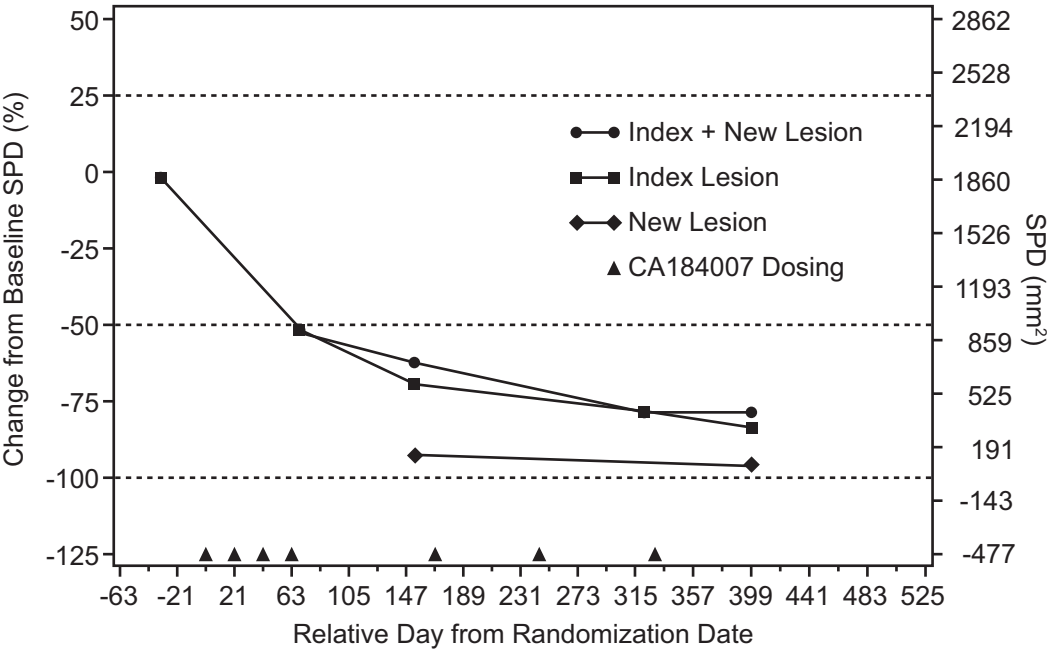
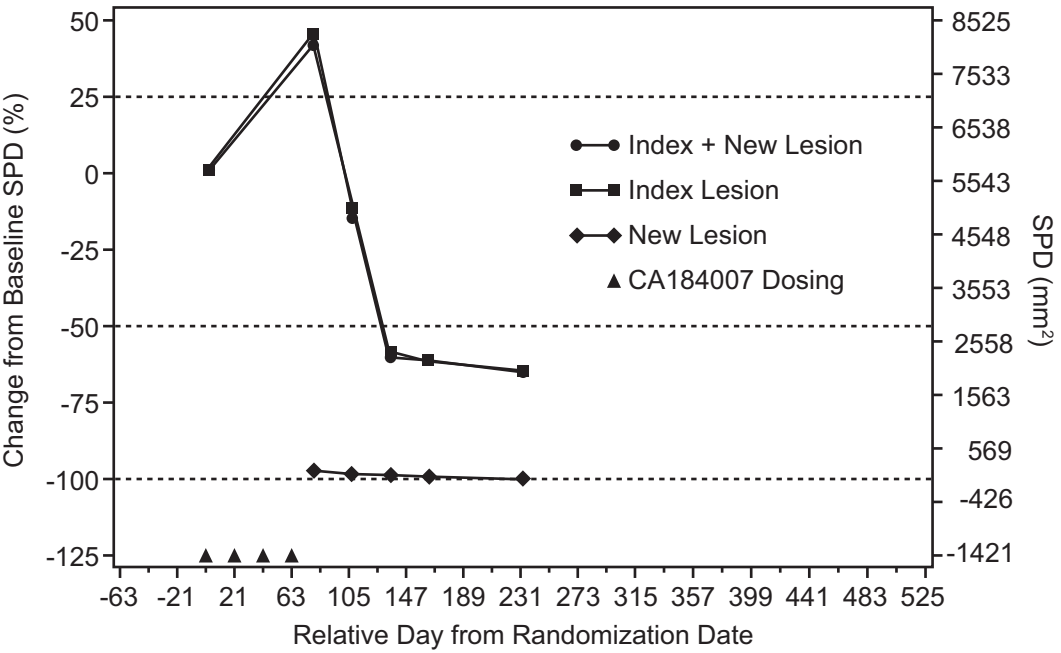
Supplemental Figure 1. Study design



NOTE: PD was the most common reason for death; no treatment-related deaths were reported. Two deaths in each group were reported as due to 'other' (budesonide group, possible cardiac arrhythmia and pneumonia; placebo group, cardiac arrest and pneumonia. One death in the budesonide group was reported as due to 'unknown', and one death in the placebo group was reported as due to Grade 5 hepatic failure.


Change from Baseline SPD (%)
50
25
0
-25
-50
-75
-100
-125
SPD (mm²)
2862
2528
2194
1860
1526
1193
859
525
191
-143
-477
Index + New Lesion
Index Lesion
New Lesion
CA184007 Dosing
-63 -21 21 63 105 147 189 231 273 315 357 399 441 483 525
Relative Day from Randomization Date


Change from Baseline SPD (%)
50
25
0
-25
-50
-75
-100
-125
SPD (mm²)
8525
7533
6538
5543
4548
3553
2558
1563
569
-426
-1421
Index + New Lesion
Index Lesion
New Lesion
CA184007 Dosing
-63 -21 21 63 105 147 189 231 273 315 357 399 441 483 525
Relative Day from Randomization Date

Supplementary Figure Legends

Supplementary Figure S1. Study design (CONSORT diagram)

Supplementary Figure S2. Reduction in total tumor burden after the appearance of new lesions (a) and/or response after initial increase in total tumor burden (b) in patients treated with ipilimumab.

Supplementary Appendix

Additional study objectives

In addition to protocol-specified endpoints, novel efficacy criteria were considered that captured changes in overall tumor burden over time (measurable [index] lesions and new lesions), both before and after progression by modified WHO criteria.[42]

Rollover study CA184-025

Non-progressors at Week 12 were, after subsequent WHO progression, eligible to receive additional ipilimumab (at the investigator's discretion) on a separate companion study. [b] All other patients were also able to enter CA184-025 for further ipilimumab maintenance, additional tumor assessments, and/or follow-up after parent study closure. Tumor assessments in study CA184025 were included in the primary IRC evaluation if prior to additional companion-study ipilimumab treatment, and were included in the novel criteria evaluation if prior to subsequent anti-cancer therapy.

Additional inclusion criteria

At least 4 weeks needed to have elapsed since the last chemotherapy, immunotherapy, hormonal therapy, radiotherapy, or major surgery prior to starting protocol induction therapy (at least 6 weeks for nitrosoureas, mitomycin C, and liposomal doxorubicin). Toxicity related to prior therapy needed to have returned to baseline or to no higher than grade 1, or to have been deemed irreversible.

Additional exclusion criteria

Patients were excluded if they had systemic lupus erythematosus, vasculitis, and infiltrating lung disease. Use of cyclosporine, mycophenolate mofetil (CellCept®), non-steroidal antiinflammatories, chemotherapy, or radiotherapy within 4 weeks of starting protocol therapy was not allowed. Concomitant therapy with IL-2 or interferon or chronic use of systemic corticosteroids (except patients on stable doses of HRT) was prohibited. Women of childbearing potential (WOCBP) who were unwilling or unable to use an acceptable method of contraception for the entire study period and for up to 12 weeks after the study were excluded, as were pregnant or breastfeeding women, and sexually active, fertile men unwilling or unable to use a barrier contraceptive or whose partners were WOCBP not using a method of birth control.

[b] ClinicalTrials.gov. A companion study for patients enrolled in prior/parent ipilimumab studies. http://clinicaltrials.gov/show/NCT00162123

Additional trial design

The trial was divided into four periods, comprising a screening period, an induction period (Week 1 dose visit through Week 24 tumor assessment visit, or until documentation of PD between Weeks 12 and 24), a maintenance period (Week 24 dose visit until PD, drug intolerance, withdrawal of consent, or study closure), and a follow-up period. Randomization was determined in the screening period using a telephone interactive voice response system (IVRS) using a permuted block procedure.

Patients without PD in the induction period through Week 24, but with poor performance status (>1) or with toxicity requiring discontinuation of study therapy, continued to receive tumor assessments until PD. Patients with PD who were ineligible for the companion study CA184-025 (or who elected not to enroll) entered the follow-up period, with no further dosing. During follow-up, it was recommended that at least two additional tumor assessments be performed (see below).

Tumor assessments

Tumor assessment (by WHO criteria) were scheduled and assessed by the Independent Review Committee (IRC) at Week 12, with additional assessments (in patients with complete response [CR], partial response [PR], or stable disease [SD]) at Weeks 16, 20, and 24 of the induction period, Weeks 30, 36, 42, and 48 of the maintenance period, and every 12 weeks thereafter. The IRC independently selected up to 10 index lesions (up to five per organ); skin lesions could not be selected as IRC index lesions. Patients were required to have at least one index lesion (measurable disease) as determined by the investigator. The sum of the product of the two perpendicular dimensions (SPD) of the index lesions was calculated. All other lesions were identified as non-index lesions (evaluable disease) and evaluated qualitatively.

The investigator selected up to 15 index lesions, no more than five per organ and no more than five skin lesions. Index lesions were required to have at least one diameter of 20 mm or greater, and another perpendicular diameter of 10 mm or greater (or 10

x 10 mm if measured by helical computed tomography). Bone lesions and certain other lesion types could not be selected as index lesions.

Definitions of overall responses and SD for index and non-index lesions

CR at each timepoint was defined as complete disappearance of all lesions. PR was defined as a decrease compared with baseline of at least 50% in the largest SPD of all index lesions, and with no evidence of PD. SD was defined as failure to meet criteria for CR or PR in the absence of PD. PD included any increase of at least 25% in the SPD of all index lesions, unequivocal progression of non-index lesions, or the appearance of a new lesion.

Best overall response (BOR) was calculated from timepoint assessments as follows: a BOR of CR required at least two consecutive timepoint assessments of CR at per-protocol assessment dates or at least 4 weeks apart. PR required at least two timepoint assessments of PR (or CR following PR) at per-protocol assessment dates or at least 4 weeks apart, with no intervening PD. Patients with a timepoint assessment of PD and who did not have SD or better at the Week-12 assessment were classified as PD. A BOR of SD required a timepoint assessment of SD or better at the Week-12 assessment in the absence of a BOR of CR or PR.

Additional assessments

Novel efficacy criteria based on measurements of both index and new lesions were evaluated that considered tumor assessments subsequent to PD; total tumor burden was calculated as the SPD of index and measurable new lesions, and underwent IRC review.

Additional methods

Multiple investigator-reported episodes of the same AE which were consecutive, overlapping, or occurred within 10 weeks following the same ipilimumab dose and prior to the next dose, were collapsed into a single event of combined duration for purposes of calculating irAE duration and number of events.