

4.3 Analysis

Purpose: The Analysis Section, shown on the right-hand side of the user interface, is a feature of the Redouble AI system that provides a short summary of the key points of the AI-generated response (Key Findings) and alerts the user to potential contradictions and discrepancies that the AI has spotted (Red Flags).

Appearance: Collapsible sections with color-coded headers and icons

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Sample size and power

The CA209816 study's sample size calculations were based on dual primary endpoints of pathologic complete response (pCR) and event-free survival (EFS), with specific alpha allocations and power assumptions that evolved through protocol amendments.

Original Sample Size Design

The original study design (before Revised Protocol 02) was a 2-arm study with 1:1 randomization between nivolumab+ipilimumab (Arm A) and chemotherapy (Arm B). However, Revised Protocol 02 fundamentally changed the study design by adding a third arm (nivolumab+chemotherapy, Arm C) and modifying the primary objectives from major pathologic response (MPR) to dual primary objectives of pCR and EFS.

Final Sample Size Calculation

For the primary analysis comparing concurrently randomized Arms B and C, approximately 350 subjects (175 per arm) were planned. The sample size was calculated based on the following assumptions:

For pCR endpoint:

- Alpha level: 0.01 (1%)
- Assumed pCR rate in chemotherapy arm (Arm B): 10%
- Assumed pCR rate in nivo+chemo arm (Arm C): 30%
- Expected odds ratio: 3.857
- Power: >90% with 350 subjects

For EFS endpoint:

- Initial alpha level: 0.04 (4%), or 0.05 (5%) if pCR was significant

Sources

Sample_CSR_Nivolumab_CA209816_Interim_Report

CA209816-Interim-CSR-Sep2020

CA209816_CSR_Statistical_Tables

Analysis

Key Findings

- Original 2-arm design changed to 3-arm design with Revised Protocol 02, fundamentally altering sample size calculations
- 350 subjects (175 per arm) were planned for concurrent randomization between Arms B and C
- Dual primary endpoints of pCR and EFS with alpha allocation of 0.01 and 0.04 respectively
- pCR power calculation assumed 10% rate in chemo arm and 30% in nivo+chemo arm, providing >90% power
- EFS power calculation assumed HR of 0.65 with 185 total events needed for 80% power
- Hierarchical testing with fallback method allowed alpha reallocation from pCR to EFS if pCR was significant
- OS power calculation also assumed HR of 0.65 with 185 events for 80% power
- Actual enrollment of 358 concurrently randomized subjects exceeded planned 350
- Primary analysis confirmed assumptions with pCR

Subsections

Key Findings

Purpose: Presents the most important conclusions and facts extracted from the documents, providing an executive summary of the AI analysis.

Red Flags

Purpose: Highlights potential contradictions and discrepancies that the AI has found in the documents for the user to review and verify. This critical section ensures users are made aware of inconsistencies or conflicting information found across different sources.

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Patients were enrolled from multiple countries across four main geographic regions. The regional distribution was: Asia (43.6%), North America (31.1%), Europe (17.8%), and Rest of World (7.5%). The top enrolling countries were the United States with 186 patients (24.1% of enrolled), China with 166 patients (21.5% of enrolled), and Japan with 108 patients (14.0% of enrolled).

Regarding the key trial dates, the first patient first visit (FPFV) date is not explicitly stated in the provided documents. However, the enrollment period began in March 2017, suggesting the FPFV was likely in March 2017. The pCR analysis occurred with a database lock on 16-Sep-2020. The documents indicate that the first interim analysis (EFS IA1, OS IA1) was expected approximately 54 months from FPFV when 148 events were observed. The last patient last visit date and final clinical database lock date are not explicitly provided in these documents.

The study design anticipated that 350 participants would be randomized in approximately 27 months from the start of 1:1:1 randomization. The enrollment period from March 2017 to December 2019 spans approximately 33 months, which is slightly longer than initially anticipated.

Method of assigning subjects to a treatment arm

Randomization Methods in CA209816 Trial

The CA209816 trial underwent protocol revisions that changed the randomization scheme

Key Findings

- 773 total patients enrolled in the study
- 505 patients (65.3%) were randomized
- 495 patients (98.0% of randomized) were treated
- Enrollment occurred between March 2017 and December 2019
- Three treatment arms: Arm A (N=113), Arm C (N=179), Arm (N=179)
- Geographic distribution: Asia 43.6%, North America 31.1%, Europe 17.8%, Rest of World 7.5%
- Top enrolling countries: United States (186 patients), China (166 patients), Japan (108 patients)
- Database lock for pCR analysis occurred on 16-Sep-2020
- Study anticipated 350 participants would be randomized in approximately 27 months

Red Flags

- The first patient first visit (FPFV) date is not explicitly stated in the provided documents
- The last patient first treatment date is not provided in the documents
- The last patient last visit date is not explicitly stated
- The final clinical database lock date is not clearly specified beyond the pCR analysis DBL date
- The enrollment period (33 months) exceeded the anticipated timeline of 27 months

References

CA209816 Protocol Amendment 07

References

Purpose: Lists source documents used to generate the analysis, providing traceability and enabling verification of displayed information. Each document is shown with two names:

- **Display name** (shown in the list): AI-generated descriptive name for easy identification
- **Original filename** (shown on hover in blue): The actual name of the uploaded file

After clicking on the document Display name name, the document content will appear in a separate panel. For more detailed information please view page [5.1 View Attached Documents](#) and [5.2 Edit Attached documents](#)

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Original Protocol and Early Revisions

The study initially employed a 1:1 randomization scheme across two treatment arms:

- Arm A: Nivolumab + Ipilimumab
- Arm B: Chemotherapy (Concurrent)

Revised Protocol 02

Three treatment arms: Arm A (N=113), Arm C (N=179), Arm (N=179)

Geographic distribution: Asia 43.6%, North America 31.1%, Europe 17.8%, Rest of World 7.5%

Top enrolling countries: United States (186 patients), China (166 patients), Japan (108 patients)

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References

- CA209816 Protocol Amendment 07
- CA209816_Supplemental_Tables_Demographics_Baseline

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