Neutropenia endpoints and its effect on Cancer Patients

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Agenda

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- Introduction
- Signs and Symptoms
- Causes and Complications

Endpoints

- Safety
- Efficacy

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- Risk Models

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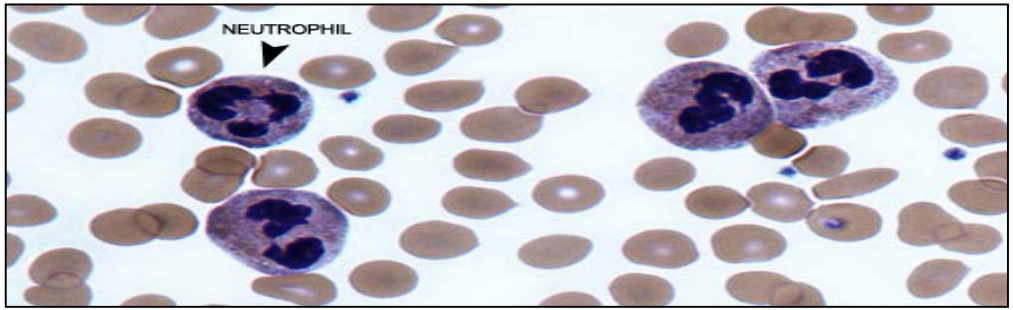
Overview

Neutropenia

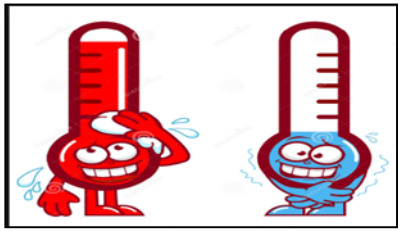
- Neutropenia is an abnormally low concentration of neutrophils (a type of white blood cell) in the blood.
- Neutrophils make up the majority of circulating white blood cells and serve as the primary defense against infection causing agents.
- Patients with neutropenia are more susceptible to bacterial infections and, without prompt medical attention, the condition may become life-threatening.
- Neutropenia occurs in about half of people with cancer who receive chemotherapy.



Signs and Symptoms:

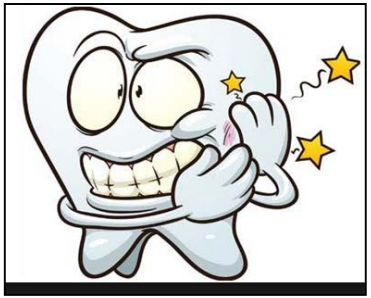
- Prone to infections
- Signs of infection:

1. A fever, which is a temperature of 100.5°F or higher



2. Chills or sweating

3. Abdominal pain



4. Sore throat, sores in the mouth, or a toothache

5. Redness, swelling, or pain, particularly around a cut, wound, or catheter placement

6. A cough or shortness of breath

Causes:

- Infections (more commonly viral infections, but also bacterial or parasitic infections).
- Medications that may damage the bone marrow or neutrophils, including cancer chemotherapy.
- Vitamin deficiencies
- Diseases of the bone marrow
- Radiation therapy.
- Congenital (inborn) disorders of bone marrow function or of neutrophil production
- Autoimmune destruction of neutrophils
- Hypersplenism, which refers to the destruction of blood cells by the spleen

Complications :

- Pneumonia: Infection of lungs
- Septicemia: Infection of blood
- Bacterial infections: Proliferation of a harmful strain of **bacteria** on or inside the body
- Fungal infections

Endpoints

Safety Endpoints:

- Adverse events (AEs) reports throughout the study.
- Clinical laboratory test results.
- Vital signs measurements
- Concomitant medication
- Number of red blood cell (RBC) and platelet transfusions.
- Immunogenicity (development of antibodies against study drug).
- ECG.
- Physical examination results

Primary Efficacy Endpoint:

- The primary efficacy variable is the ANC (Absolute Neutrophil Count), and the primary endpoint for this study is the DSN (Duration of Severe Neutropenia) in days in the first cycle of chemotherapy.

Secondary Efficacy Endpoints:

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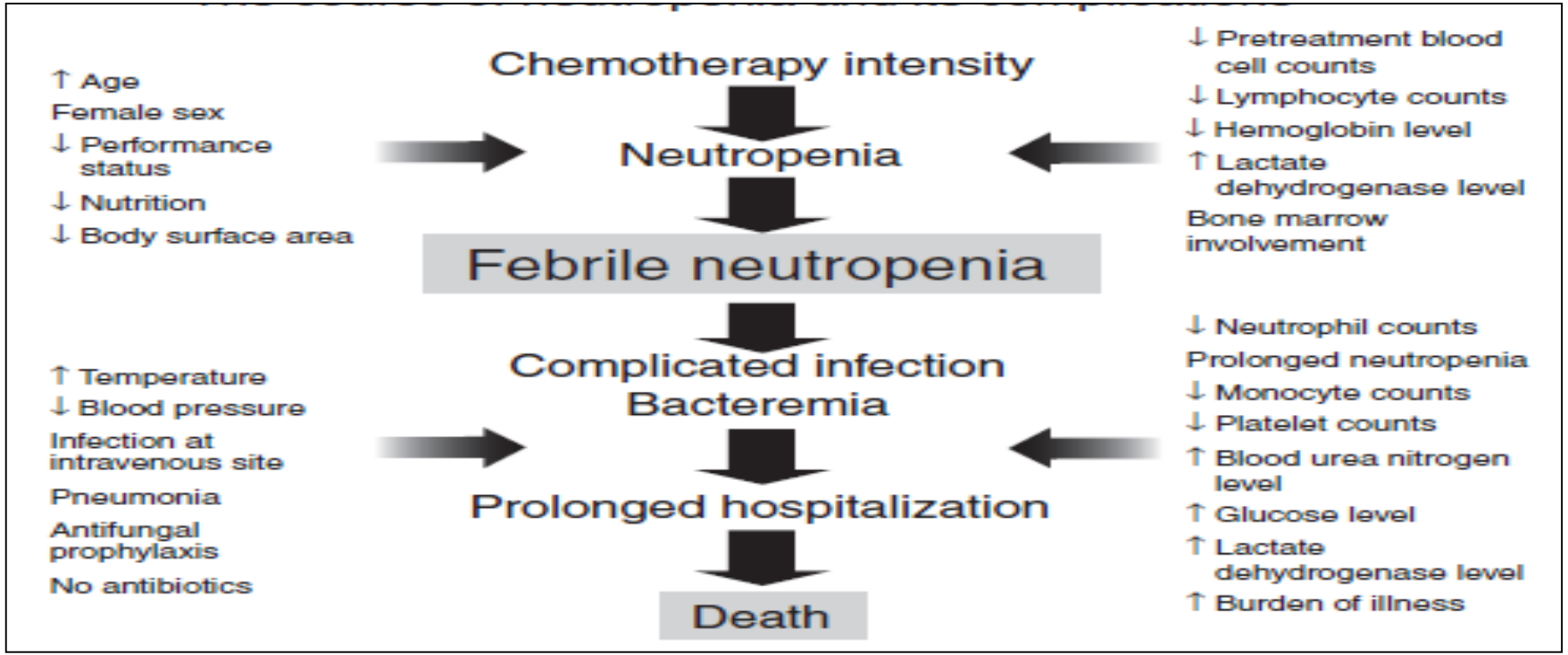
- Incidence of febrile neutropenia, FN defined as body temperature of >38.5°C
- Neutropenia-related quality of life as measured by the Functional Assessment of Cancer Therapy-Neutropenia (FACT-N) questionnaire
- Hospitalisations due to FN

Risks

Risk factors:



Risk factors:

- **Patient Specific Risk Factors**
  - Age
  - Performance Status
  - Comorbidities
  - Lab abnormalities
  - Poor nutritional status
  - Bone marrow involvement

- **Treatment Specific Risk Factor**
  - Chemotherapy Regimen
  - CSF Use
  - Low baseline and first-cycle blood cell counts

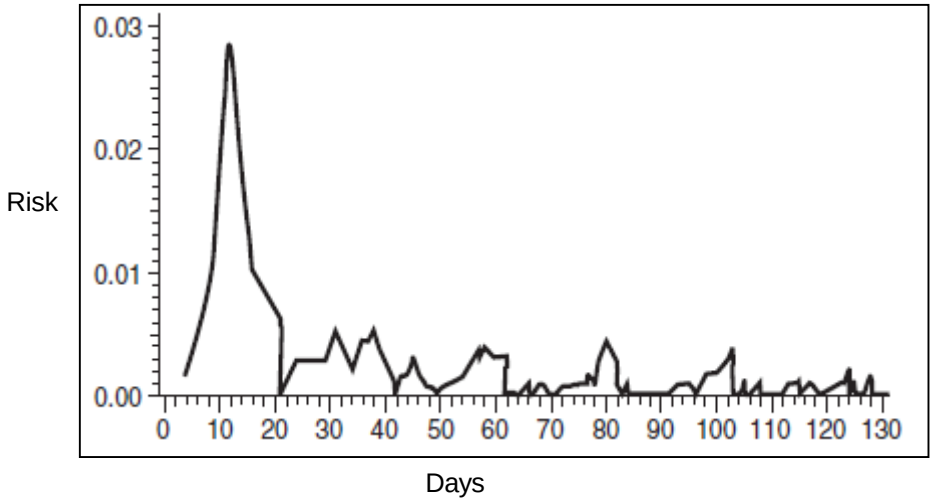
- **Disease Specific Risk Factor**
  - Tumor Type
  - Advanced disease and uncontrolled cancers

Risk Models:

CONDITIONAL MODELS

Conditional models that include the results from the initial cycle as independent variables.

Neutropenic complications are most likely to occur in the first cycle of chemotherapy



Risk Models:

UNCONDITIONAL MODELS

Unconditional models uses pre treatment information.

Advantage of identifying those patients who are likely to have neutropenic complications before they are exposed to chemotherapy

Reports

Tables: Summary of Duration of Severe Neutropenia (DSN) in Cycle 1 by Treatment Group

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Summary of Duration of Severe Neutropenia (DSN) in Cycle 1 by Treatment Group
ITT Population

Variable Statistic	A (N=xx)	B (N=xx)
Duration of severe neutropenia (DSN) (days)		
n	xx	
Mean	xx.x	
SD	xx.xx	
SE	xx.xx	
Median	xx.x	
Min, max	xx.x, xx.x	

Grades of Neutropenia[a]

Grade	Absolute neutrophil count ($\times 10^9$/L)
0	Within normal limits
1	≥ 1.5 to < 2.0
2	≥ 1.0 to < 1.5
3	≥ 0.5 to < 1.0
4	< 0.5

[a] According to the National Cancer Institute Common Toxicity Criteria, version 2.0.[3]

Tables: Summary of Incidence of Neutropenia Requiring Dose Modification

	A (N=xx) n (%)	B (N=xx) n (%)	Total (N=xx) n (%)
Any Neutropenia Event requiring dose modification	xx (xx)	xx (xx)	xx (xx)
Grade 1	xx (xx)	xx (xx)	xx (xx)
Grade 2	xx (xx)	xx (xx)	xx (xx)
Grade 3	xx (xx)	xx (xx)	xx (xx)
Grade 4	xx (xx)	xx (xx)	xx (xx)
Grade 5	xx (xx)	xx (xx)	xx (xx)
Any dose modification as a result of Neutropenia*	xx (xx)	xx (xx)	xx (xx)
Dose delayed	xx (xx)	xx (xx)	xx (xx)
Dose reduced	xx (xx)	xx (xx)	xx (xx)
Dose held	xx (xx)	xx (xx)	xx (xx)
Dose interrupted	xx (xx)	xx (xx)	xx (xx)

Dose modification includes dose held, dose interrupted, dose reduced and dose delayed.

Dose Held: The planned or scheduled dose was not given as a result of an intentional physician intervention. No drug was administered.

A A patient counts once for the highest CTCAE grade.

Preferred term of Neutropenia and Neutrophil Count Decreased are counted as Neutropenia.

Tables:

Summary of Incidence of Treatment-Emergent Infections and Infestations (SOC) for Patients with Grade 3 or 4 Neutropenia

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Number of Subjects with Grade 3 or 4 Neutropenia[a]	xx (xx)	xx (xx)	xx (xx)
Any Treatment-Emergent Infections and Infestations (SOC) Event[b]	xx (xx)	xx (xx)	xx (xx)
PT1	xx (xx)	xx (xx)	xx (xx)
PT2	xx (xx)	xx (xx)	xx (xx)
PT3	xx (xx)	xx (xx)	xx (xx)
PT4	xx (xx)	xx (xx)	xx (xx)
PT 5			

a Subjects with grade 3 or 4 treatment-emrgent neutropenia .

b Subjects with treatment-emergent infections and infestations (SOC) that started during the duration of the grade 3 or 4 neutropenia and up to 7 days after.

Preferred term of Neutropenia and Neutrophil Count Decreased are counted as Neutropenia.

A patient counts once for the highest CTCAE grade.

Tables: Summary of Grade 3 and 4 Neutropenia

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Treatment-Emergent	454 (69)	361 (55)	815 (62)
Grade 3	117 (18)	139 (21)	256 (19)
Grade 4	313 (47)	178 (27)	491 (37)
Drug-Related	438 (66)	334 (51)	772 (58)
Grade 3	110 (17)	132 (20)	242 (18)
Grade 4	306 (46)	164 (25)	470 (36)
Serious Adverse Events	22 (3)	5 (< 1)	27 (2)
Grade 3	2 (< 1)	1 (< 1)	3 (< 1)
Grade 4	19 (3)	4 (< 1)	23 (2)

Preferred term of Neutropenia and Neutrophil Count Decreased are counted as Neutropenia.
A patient counts once for the highest CTCAE grade.

Tables: Summary of Febrile Neutropenia by Cycle

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	(N=xx) n (%)	n (%)
Overall	xx (xx)	xx (xx)
Treatment -Emergent	xx (xx)	xx (xx)
		xx (xx)
		xx (xx)
Grade 1	xx (xx)	xx (xx)
		xx (xx)
Grade 2	xx (xx)	xx (xx)
		xx (xx)
Repeat for group 3, 4, 5.		
Drug- Related		
	xx (xx)	xx (xx)
		xx (xx)
Grade 1	xx (xx)	xx (xx)
		xx (xx)
Grade 2	xx (xx)	xx (xx)
		xx (xx)
Repeat for group 3, 4, 5.		
Serious Adverse Events		
	xx (xx)	xx (xx)
		xx (xx)
Drug related	xx (xx)	xx (xx)
		xx (xx)
Cycle 1, etc		
Repeat above overall summaries for Cycle 1 and all other cycles.		

Percentages are based on the number of subjects in the safety population.
Maximum CTCAE grade by patient is summarized.
~~Preferred term of Neutropenia and Neutrophil Count Decreased are counted as Neutropenia.~~
A patient counts once for the highest CTCAE grade.

Tables: Febrile Neutropenia Summary by Potential Risk Factors

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Incidence of febrile neutropenia	xx (xx)	xx (xx)	xx (xx)
Break down in age groups			
18 – <30			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
30 – <40			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
40 – <50			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
50 – <60			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
60 – <70			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
70 – <80			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
80 and above			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
Break down by gender			
Male			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
Female			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)

Tables: Febrile Neutropenia Summary by Potential Risk Factors (Contd.)

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Break down by stage			
Stage III			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
Stage IV			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
Break down by bone marrow involvement			
No bone marrow involvement			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
Bone marrow involvement			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
Break down by Extranodal Involvement at Initial Diagnosis			
Yes			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
No			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
Break down by anemia			
Hgb < 120 g/L			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)
Hgb >= 120 g/L			
n (%)	xx (xx)	xx (xx)	xx (xx)
FN (%)	xx (xx)	xx (xx)	xx (xx)

Abbreviations: FN=Febrile Neutropenia
The percentage of FN is based on the number of patients in each category of risk factors.

Tables: Summary of Observed Absolute Neutrophil Count (ANC) (x10^9/L) by Treatment Group

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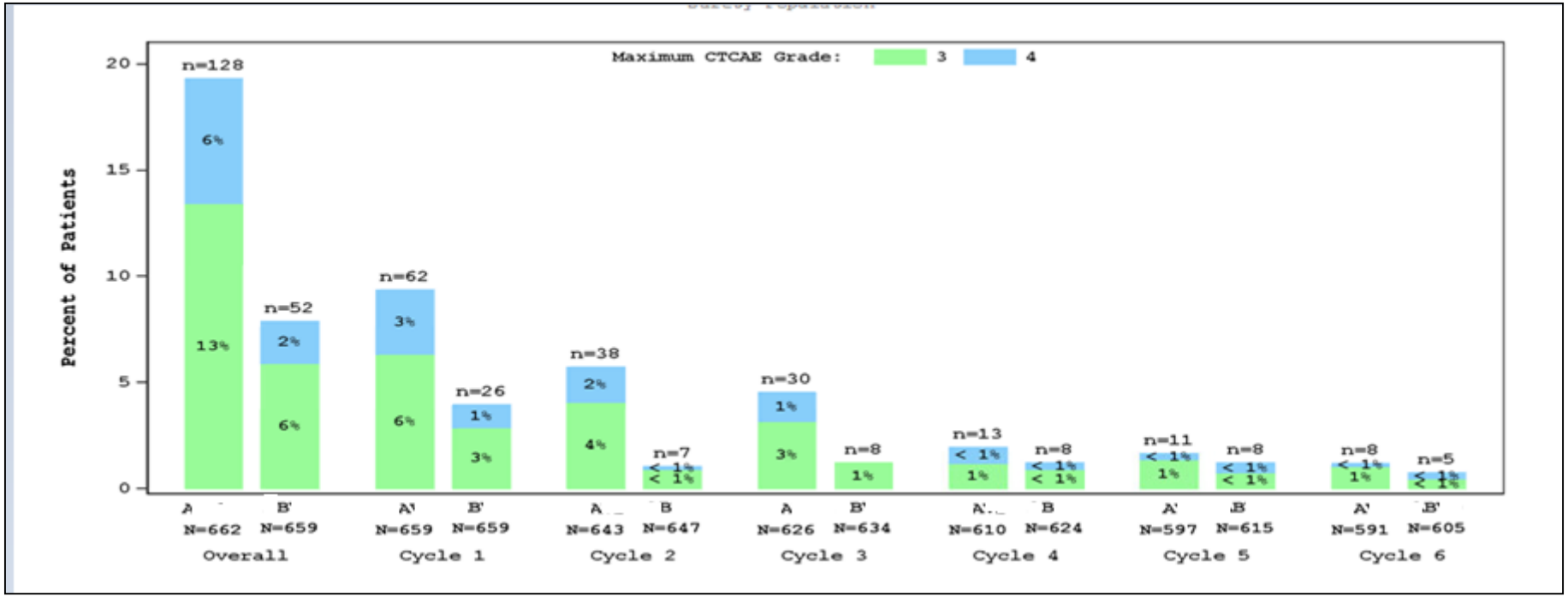
Time point Statistic	A (N=xx)	B (N=xx)
Baseline*		
N	xx	xx
Mean	xx.x	xx.x
SD	xx.xx	xx.xx
SE	xx.xx	xx.xx
Median	xx.x	xx.x
Min, max	xx.x, xx.x	xx.x, xx.x
Cycle 1, Day 1		
N	xx	xx
Mean	xx.x	xx.x
SD	xx.xx	xx.xx
SE	xx.xx	xx.xx
Median	xx.x	xx.x
Min, max	xx.x, xx.x	xx.x, xx.x
Cycle 1, Day 3		
N	xx	xx
Mean	xx.x	xx.x
SD	xx.xx	xx.xx
SE	xx.xx	xx.xx
Median	xx.x	xx.x
Min, max	xx.x, xx.x	xx.x, xx.x

[Programming note: time points include: Days 1, 3, 5, 8, 10, 12, 15 for cycle 1, days 1, 8 15 for cycles 2- 6, and EOV/ET.]

Figure: Febrile Neutropenia by Cycle and Grade



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