付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
感染症			
咽頭炎	1 (2.0)	3 (0.8)	4 (1.0)
1	0	0	0
2	1 (2.0)	1 (0.3)	2 (0.5)
3	0	2 (0.6)	2 (0.5)
4	0	0	0
5	0	0	0
>=3	0	2 (0.6)	2 (0.5)
鼻炎	0	1 (0.3)	1 (0.2)
1	0	1 (0.3)	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
感染症			
鼻炎	0	1 (0.3)	1 (0.2)
1	0	1 (0.3)	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
蜂巣炎	0	1 (0.3)	1 (0.2)
1	0	1 (0.3)	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
感染症			
蜂巣炎	0	1 (0.3)	1 (0.2)
1	0	1 (0.3)	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
毛包炎	1 (2.0)	2 (0.6)	3 (0.7)
1	1 (2.0)	2 (0.6)	3 (0.7)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
感染症			
毛包炎	1 (2.0)	2 (0.6)	3 (0.7)
1	1 (2.0)	2 (0.6)	3 (0.7)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
膀胱炎	1 (2.0)	1 (0.3)	2 (0.5)
1	0	0	0
2	1 (2.0)	0	1 (0.2)
3	0	1 (0.3)	1 (0.2)
4	0	0	0
5	0	0	0
>=3	0	1 (0.3)	1 (0.2)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
感染症			
膀胱炎	1 (2.0)	1 (0.3)	2 (0.5)
1	0	0	0
2	1 (2.0)	0	1 (0.2)
3	0	1 (0.3)	1 (0.2)
4	0	0	0
5	0	0	0
>=3	0	1 (0.3)	1 (0.2)
末梢神経障害			
Any preferred term	17 (33.3)	105 (29.7)	122 (30.2)
1	13 (25.5)	64 (18.1)	77 (19.1)
2	4 (7.8)	27 (7.6)	31 (7.7)
3	0	14 (4.0)	14 (3.5)
4	0	0	0
5	0	0	0
>=3	0	14 (4.0)	14 (3.5)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
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Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
末梢神経障害			
錯感覚	0	17 (4.8)	17 (4.2)
1	0	14 (4.0)	14 (3.5)
2	0	2 (0.6)	2 (0.5)
3	0	1 (0.3)	1 (0.2)
4	0	0	0
5	0	0	0
>=3	0	1 (0.3)	1 (0.2)
錯感覚	0	17 (4.8)	17 (4.2)
1	0	14 (4.0)	14 (3.5)
2	0	2 (0.6)	2 (0.5)
3	0	1 (0.3)	1 (0.2)
4	0	0	0
5	0	0	0
>=3	0	1 (0.3)	1 (0.2)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
末梢神経障害			
神経痛	1 (2.0)	3 (0.8)	4 (1.0)
1	1 (2.0)	3 (0.8)	4 (1.0)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
神経痛	0	3 (0.8)	3 (0.7)
1	0	3 (0.8)	3 (0.7)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
末梢神経障害			
ヘルペス後神経痛	1 (2.0)	0	1 (0.2)
1	1 (2.0)	0	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
多発ニューロパチー	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	0	0
3	0	1 (0.3)	1 (0.2)
4	0	0	0
5	0	0	0
>=3	0	1 (0.3)	1 (0.2)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
末梢神経障害			
多発ニューロパチー	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	0	0
3	0	1 (0.3)	1 (0.2)
4	0	0	0
5	0	0	0
>=3	0	1 (0.3)	1 (0.2)
末梢性ニューロパチー	15 (29.4)	1 (0.3)	16 (4.0)
1	11 (21.6)	1 (0.3)	12 (3.0)
2	4 (7.8)	0	4 (1.0)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
末梢神経障害			
末梢性ニューロパチー	15 (29.4)	1 (0.3)	16 (4.0)
1	11 (21.6)	1 (0.3)	12 (3.0)
2	4 (7.8)	0	4 (1.0)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
末梢性運動ニューロパチー	0	14 (4.0)	14 (3.5)
1	0	5 (1.4)	5 (1.2)
2	0	3 (0.8)	3 (0.7)
3	0	6 (1.7)	6 (1.5)
4	0	0	0
5	0	0	0
>=3	0	6 (1.7)	6 (1.5)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
末梢神経障害			
末梢性運動ニューロパチー	0	14 (4.0)	14 (3.5)
1	0	5 (1.4)	5 (1.2)
2	0	3 (0.8)	3 (0.7)
3	0	6 (1.7)	6 (1.5)
4	0	0	0
5	0	0	0
>=3	0	6 (1.7)	6 (1.5)
末梢性感覚ニューロパチー	2 (3.9)	87 (24.6)	89 (22.0)
1	2 (3.9)	49 (13.9)	51 (12.6)
2	0	30 (8.5)	30 (7.4)
3	0	8 (2.3)	8 (2.0)
4	0	0	0
5	0	0	0
>=3	0	8 (2.3)	8 (2.0)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
末梢神経障害			
末梢性感覚ニューロパチー	2 (3.9)	87 (24.6)	89 (22.0)
1	2 (3.9)	49 (13.9)	51 (12.6)
2	0	30 (8.5)	30 (7.4)
3	0	8 (2.3)	8 (2.0)
4	0	0	0
5	0	0	0
>=3	0	8 (2.3)	8 (2.0)
末梢性感覚運動ニューロパチー	0	2 (0.6)	2 (0.5)
1	0	2 (0.6)	2 (0.5)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
末梢神経障害			
末梢性感覚運動ニューロパチー	0	2 (0.6)	2 (0.5)
1	0	2 (0.6)	2 (0.5)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
肝機能障害			
Any preferred term	6 (11.8)	3 (0.8)	9 (2.2)
1	5 (9.8)	0	5 (1.2)
2	1 (2.0)	2 (0.6)	3 (0.7)
3	0	1 (0.3)	1 (0.2)
4	0	0	0
5	0	0	0
>=3	0	1 (0.3)	1 (0.2)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

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付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
肝機能障害			
トランスアミナーゼ上昇	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	1 (0.3)	1 (0.2)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
トランスアミナーゼ上昇	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	1 (0.3)	1 (0.2)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
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A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
肝機能障害			
黄疸	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	1 (0.3)	1 (0.2)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
黄疸	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	1 (0.3)	1 (0.2)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
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Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
肝機能障害			
肝機能異常	5 (9.8)	0	5 (1.2)
1	4 (7.8)	0	4 (1.0)
2	1 (2.0)	0	1 (0.2)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
肝機能異常	5 (9.8)	0	5 (1.2)
1	4 (7.8)	0	4 (1.0)
2	1 (2.0)	0	1 (0.2)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
肝機能障害			
肝機能検査異常	1 (2.0)	0	1 (0.2)
1	1 (2.0)	0	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
肝機能検査異常	1 (2.0)	0	1 (0.2)
1	1 (2.0)	0	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
肝機能障害			
肝細胞損傷	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	1 (0.3)	1 (0.2)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
肝細胞損傷	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	1 (0.3)	1 (0.2)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
肝機能障害			
肝毒性	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	0	0
3	0	1 (0.3)	1 (0.2)
4	0	0	0
5	0	0	0
>=3	0	1 (0.3)	1 (0.2)
肝毒性	0	1 (0.3)	1 (0.2)
1	0	0	0
2	0	0	0
3	0	1 (0.3)	1 (0.2)
4	0	0	0
5	0	0	0
>=3	0	1 (0.3)	1 (0.2)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
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Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
間質性肺炎			
Any preferred term	1 (2.0)	0	1 (0.2)
1	1 (2.0)	0	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
間質性肺炎	1 (2.0)	0	1 (0.2)
1	1 (2.0)	0	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
間質性肺炎			
間質性肺疾患	1 (2.0)	0	1 (0.2)
1	1 (2.0)	0	1 (0.2)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
無力症・疲労・倦怠感			
Any preferred term	27 (52.9)	184 (52.1)	211 (52.2)
1	26 (51.0)	87 (24.6)	113 (28.0)
2	1 (2.0)	81 (22.9)	82 (20.3)
3	0	16 (4.5)	16 (4.0)
4	0	0	0
5	0	0	0
>=3	0	16 (4.5)	16 (4.0)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
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This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
無力症・疲労・倦怠感			
倦怠感	20 (39.2)	2 (0.6)	22 (5.4)
1	19 (37.3)	0	19 (4.7)
2	1 (2.0)	2 (0.6)	3 (0.7)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
倦怠感	20 (39.2)	2 (0.6)	22 (5.4)
1	19 (37.3)	0	19 (4.7)
2	1 (2.0)	2 (0.6)	3 (0.7)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
無力症・疲労・倦怠感			
疲労	9 (17.6)	153 (43.3)	162 (40.1)
1	9 (17.6)	79 (22.4)	88 (21.8)
2	0	60 (17.0)	60 (14.9)
3	0	14 (4.0)	14 (3.5)
4	0	0	0
5	0	0	0
>=3	0	14 (4.0)	14 (3.5)
疲労	9 (17.6)	153 (43.3)	162 (40.1)
1	9 (17.6)	79 (22.4)	88 (21.8)
2	0	60 (17.0)	60 (14.9)
3	0	14 (4.0)	14 (3.5)
4	0	0	0
5	0	0	0
>=3	0	14 (4.0)	14 (3.5)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
無力症・疲労・倦怠感			
無力症	0	36 (10.2)	36 (8.9)
1	0	13 (3.7)	13 (3.2)
2	0	21 (5.9)	21 (5.2)
3	0	2 (0.6)	2 (0.5)
4	0	0	0
5	0	0	0
>=3	0	2 (0.6)	2 (0.5)
無力症	0	36 (10.2)	36 (8.9)
1	0	13 (3.7)	13 (3.2)
2	0	21 (5.9)	21 (5.2)
3	0	2 (0.6)	2 (0.5)
4	0	0	0
5	0	0	0
>=3	0	2 (0.6)	2 (0.5)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
味覚異常			
Any preferred term	12 (23.5)	34 (9.6)	46 (11.4)
1	11 (21.6)	30 (8.5)	41 (10.1)
2	1 (2.0)	4 (1.1)	5 (1.2)
味覚異常	12 (23.5)	34 (9.6)	46 (11.4)
1	11 (21.6)	30 (8.5)	41 (10.1)
2	1 (2.0)	4 (1.1)	5 (1.2)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
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A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-21
Japanese and Non-Japanese
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Studies 207+309 (N=353) n(%)	全体 Studies 217+207+309 (N=404) n(%)
味覚異常			
味覚異常	12 (23.5)	34 (9.6)	46 (11.4)
1	11 (21.6)	30 (8.5)	41 (10.1)
2	1 (2.0)	4 (1.1)	5 (1.2)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.
This table is based on adverse events data as available. Study 207 did not record laboratory abnormalities into adverse events data.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_21.sas 18JUN201513:39

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
Any preferred term	51 (100.0)	139 (61.5)	190 (68.6)
1	0	6 (2.7)	6 (2.2)
2	3 (5.9)	32 (14.2)	35 (12.6)
3	9 (17.6)	57 (25.2)	66 (23.8)
4	39 (76.5)	44 (19.5)	83 (30.0)
5	0	0	0
>=3	48 (94.1)	101 (44.7)	149 (53.8)
ヘマトクリット減少	0	1 (0.4)	1 (0.4)
1	0	1 (0.4)	1 (0.4)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22
Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
ヘマトクリット減少	0	1 (0.4)	1 (0.4)
1	0	1 (0.4)	1 (0.4)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
ヘモグロビン減少	2 (3.9)	6 (2.7)	8 (2.9)
1	2 (3.9)	2 (0.9)	4 (1.4)
2	0	4 (1.8)	4 (1.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
ヘモグロビン減少	2 (3.9)	6 (2.7)	8 (2.9)
1	2 (3.9)	2 (0.9)	4 (1.4)
2	0	4 (1.8)	4 (1.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
リンパ球減少	40 (78.4)	3 (1.3)	43 (15.5)
1	1 (2.0)	1 (0.4)	2 (0.7)
2	23 (45.1)	1 (0.4)	24 (8.7)
3	14 (27.5)	0	14 (5.1)
4	2 (3.9)	1 (0.4)	3 (1.1)
5	0	0	0
>=3	16 (31.4)	1 (0.4)	17 (6.1)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制，肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
リンパ球数減少	0	2 (0.9)	2 (0.7)
1	0	1 (0.4)	1 (0.4)
2	0	1 (0.4)	1 (0.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
リンパ球減少症	40 (78.4)	1 (0.4)	41 (14.8)
1	1 (2.0)	0	1 (0.4)
2	23 (45.1)	0	23 (8.3)
3	14 (27.5)	0	14 (5.1)
4	2 (3.9)	1 (0.4)	3 (1.1)
5	0	0	0
>=3	16 (31.4)	1 (0.4)	17 (6.1)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

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付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
血小板減少	3 (5.9)	14 (6.2)	17 (6.1)
1	2 (3.9)	7 (3.1)	9 (3.2)
2	1 (2.0)	5 (2.2)	6 (2.2)
3	0	1 (0.4)	1 (0.4)
4	0	1 (0.4)	1 (0.4)
5	0	0	0
>=3	0	2 (0.9)	2 (0.7)
血小板数減少	0	1 (0.4)	1 (0.4)
1	0	0	0
2	0	0	0
3	0	0	0
4	0	1 (0.4)	1 (0.4)
5	0	0	0
>=3	0	1 (0.4)	1 (0.4)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

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付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
血小板減少症	3 (5.9)	13 (5.8)	16 (5.8)
1	2 (3.9)	7 (3.1)	9 (3.2)
2	1 (2.0)	5 (2.2)	6 (2.2)
3	0	1 (0.4)	1 (0.4)
4	0	0	0
5	0	0	0
>=3	0	1 (0.4)	1 (0.4)
好中球減少	50 (98.0)	113 (50.0)	163 (58.8)
1	1 (2.0)	2 (0.9)	3 (1.1)
2	5 (9.8)	21 (9.3)	26 (9.4)
3	5 (9.8)	49 (21.7)	54 (19.5)
4	39 (76.5)	41 (18.1)	80 (28.9)
5	0	0	0
>=3	44 (86.3)	90 (39.8)	134 (48.4)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
好中球減少症	50 (98.0)	96 (42.5)	146 (52.7)
1	1 (2.0)	2 (0.9)	3 (1.1)
2	5 (9.8)	18 (8.0)	23 (8.3)
3	5 (9.8)	42 (18.6)	47 (17.0)
4	39 (76.5)	34 (15.0)	73 (26.4)
5	0	0	0
>=3	44 (86.3)	76 (33.6)	120 (43.3)
好中球数減少	0	18 (8.0)	18 (6.5)
1	0	0	0
2	0	3 (1.3)	3 (1.1)
3	0	7 (3.1)	7 (2.5)
4	0	8 (3.5)	8 (2.9)
5	0	0	0
>=3	0	15 (6.6)	15 (5.4)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
赤血球減少	0	2 (0.9)	2 (0.7)
1	0	2 (0.9)	2 (0.7)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
赤血球数減少	0	2 (0.9)	2 (0.7)
1	0	2 (0.9)	2 (0.7)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
白血球減少	51 (100.0)	51 (22.6)	102 (36.8)
1	0	5 (2.2)	5 (1.8)
2	13 (25.5)	17 (7.5)	30 (10.8)
3	28 (54.9)	25 (11.1)	53 (19.1)
4	10 (19.6)	4 (1.8)	14 (5.1)
5	0	0	0
>=3	38 (74.5)	29 (12.8)	67 (24.2)
白血球減少症	51 (100.0)	35 (15.5)	86 (31.0)
1	0	3 (1.3)	3 (1.1)
2	13 (25.5)	10 (4.4)	23 (8.3)
3	28 (54.9)	18 (8.0)	46 (16.6)
4	10 (19.6)	4 (1.8)	14 (5.1)
5	0	0	0
>=3	38 (74.5)	22 (9.7)	60 (21.7)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

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Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
白血球数減少	0	16 (7.1)	16 (5.8)
1	0	2 (0.9)	2 (0.7)
2	0	7 (3.1)	7 (2.5)
3	0	7 (3.1)	7 (2.5)
4	0	0	0
5	0	0	0
>=3	0	7 (3.1)	7 (2.5)
発熱性好中球減少	4 (7.8)	2 (0.9)	6 (2.2)
1	0	0	0
2	0	0	0
3	4 (7.8)	2 (0.9)	6 (2.2)
4	0	0	0
5	0	0	0
>=3	4 (7.8)	2 (0.9)	6 (2.2)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
発熱性好中球減少症	4 (7.8)	2 (0.9)	6 (2.2)
1	0	0	0
2	0	0	0
3	4 (7.8)	2 (0.9)	6 (2.2)
4	0	0	0
5	0	0	0
>=3	4 (7.8)	2 (0.9)	6 (2.2)
貧血	24 (47.1)	55 (24.3)	79 (28.5)
1	3 (5.9)	11 (4.9)	14 (5.1)
2	15 (29.4)	34 (15.0)	49 (17.7)
3	6 (11.8)	9 (4.0)	15 (5.4)
4	0	1 (0.4)	1 (0.4)
5	0	0	0
>=3	6 (11.8)	10 (4.4)	16 (5.8)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
骨髄抑制			
貧血	24 (47.1)	55 (24.3)	79 (28.5)
1	3 (5.9)	11 (4.9)	14 (5.1)
2	15 (29.4)	34 (15.0)	49 (17.7)
3	6 (11.8)	9 (4.0)	15 (5.4)
4	0	1 (0.4)	1 (0.4)
5	0	0	0
>=3	6 (11.8)	10 (4.4)	16 (5.8)
肝機能障害			
Any preferred term	6 (11.8)	3 (1.3)	9 (3.2)
1	5 (9.8)	0	5 (1.8)
2	1 (2.0)	2 (0.9)	3 (1.1)
3	0	1 (0.4)	1 (0.4)
4	0	0	0
5	0	0	0
>=3	0	1 (0.4)	1 (0.4)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22
Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制，肝機能障害
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
肝機能障害			
トランスアミナーゼ上昇	0	1 (0.4)	1 (0.4)
1	0	0	0
2	0	1 (0.4)	1 (0.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
トランスアミナーゼ上昇	0	1 (0.4)	1 (0.4)
1	0	0	0
2	0	1 (0.4)	1 (0.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制，肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
肝機能障害			
黄疸	0	1 (0.4)	1 (0.4)
1	0	0	0
2	0	1 (0.4)	1 (0.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
黄疸	0	1 (0.4)	1 (0.4)
1	0	0	0
2	0	1 (0.4)	1 (0.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制，肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
肝機能障害			
肝機能異常	5 (9.8)	0	5 (1.8)
1	4 (7.8)	0	4 (1.4)
2	1 (2.0)	0	1 (0.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
肝機能異常	5 (9.8)	0	5 (1.8)
1	4 (7.8)	0	4 (1.4)
2	1 (2.0)	0	1 (0.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22
Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制, 肝機能障害
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
肝機能障害			
肝機能検査異常	1 (2.0)	0	1 (0.4)
1	1 (2.0)	0	1 (0.4)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
肝機能検査異常	1 (2.0)	0	1 (0.4)
1	1 (2.0)	0	1 (0.4)
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22
Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制，肝機能障害
Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade
Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
肝機能障害			
肝細胞損傷	0	1 (0.4)	1 (0.4)
1	0	0	0
2	0	1 (0.4)	1 (0.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0
肝細胞損傷	0	1 (0.4)	1 (0.4)
1	0	0	0
2	0	1 (0.4)	1 (0.4)
3	0	0	0
4	0	0	0
5	0	0	0
>=3	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.
Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.
A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).
A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.
Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

付録 2.7.4-22

Japanese and Non-Japanese (Excluding Study 207)/骨髄抑制，肝機能障害

Treatment-Related Treatment-Emergent Adverse Events of Interest Specified in Japan by CTCAE Grade

Eribulin Treated Safety Population

Event class Package insert term or preferred term Preferred term CTCAE grade	日本人 Study 217 (N=51) n(%)	外国人 Study 309 (N=226) n(%)	全体 Studies 217+309 (N=277) n(%)
肝機能障害			
肝毒性	0	1 (0.4)	1 (0.4)
1	0	0	0
2	0	0	0
3	0	1 (0.4)	1 (0.4)
4	0	0	0
5	0	0	0
>=3	0	1 (0.4)	1 (0.4)
肝毒性	0	1 (0.4)	1 (0.4)
1	0	0	0
2	0	0	0
3	0	1 (0.4)	1 (0.4)
4	0	0	0
5	0	0	0
>=3	0	1 (0.4)	1 (0.4)

CTCAE = Common Terminology Criteria for Adverse Events. Adverse events of interest are presented in pre-defined event classes; each class is based on pre-specified preferred terms.

Treatment-related adverse events include adverse events that were considered by the investigator to be possibly or probably related to study drug and adverse events with missing relationship to study drug.

A subject with two or more adverse events in the same event class (or with same package insert term/preferred term) is counted only once for that event class (or package insert term/preferred term).

A subject is counted once by the highest non-missing CTCAE grade as applicable for preferred term and event class respectively.

Adverse event terms are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

Program: V:¥projects¥e7389¥iss309¥csr¥dev¥pg¥tables¥T_2_7_4_22.sas 18JUN201513:40

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目次

2.7.6 個々の試験のまとめ 4
2.7.6.1 外国 309 試験［悪性軟部腫瘍患者を対象としたダカルバジン対照オープン比較試験］ 5
2.7.6.2 外国 207 試験［悪性軟部腫瘍患者を対象としたオープン試験］ 52
2.7.6.3 国内 217 試験［悪性軟部腫瘍患者を対象としたオープン試験］ 82
2.7.6.4 付録 114

個々の試験のまとめの略号一覧表

略号	省略していない表現（英語）	省略していない表現（日本語）
ADI	adipocytic sarcoma	脂肪肉腫
ALP	alkaline phosphatase	アルカリホスファターゼ
ALT	alanine aminotransferase	アラニンアミノトランスフェラーゼ
AST	aspartate aminotransferase	アスパラギン酸アミノトランスフェラーゼ
C_{168hr}	plasma concentration at 168 hr after start of infusion	投与開始後 168 時間の血漿中濃度
CBR	clinical benefit rate	臨床的有用率
C_{end}	plasma concentration at end of infusion	投与終了直後の血漿中濃度
CR	complete response	完全奏効
CT	computed tomography	コンピュータ断層撮影
CTCAE	Common Terminology Criteria for Adverse Events	有害事象共通用語規準
DCR	disease control rate	病勢コントロール率
dSDR	durable stable disease rate	長期安定率
ECOG	Eastern Cooperative Oncology Group	–
EES	Efficacy Evaluable Set	有効性評価可能対象集団
EORTC	European Organisation for Research and Treatment of Cancer	–
EQ-5D	EuroQol 5 Dimension	–
FAS	Full Analysis Set	最大の解析対象集団
GCP	Good Clinical Practice	医薬品の臨床試験の実施の基準
G-CSF	granulocyte colony-stimulating factor	顆粒球コロニー刺激因子
GM-CSF	granulocyte macrophage colony-stimulating factor	顆粒球単球コロニー刺激因子
GIST	gastrointestinal stromal tumors	消化管間質腫瘍
GOT	glutamic oxaloacetic transaminase	グルタミン酸オキサロ酢酸トランスアミナーゼ
GPT	glutamic pyruvic transaminase	グルタミン酸ピルビン酸トランスアミナーゼ
hCG	human chorionic gonadotropin	ヒト絨毛性ゴナドトロピン
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use	医薬品規制調和国際会議
INR	international normalized ratio	国際標準比
LMS	leiomyosarcoma	平滑筋肉腫
MedDRA	Medical Dictionary for Regulatory Activities	ICH 国際医薬用語集
MFH	malignant fibrous histiocytoma	悪性線維性組織球腫
MRI	magnetic resonance imaging	磁気共鳴断層撮影
NE	not evaluable／not estimable	評価／推定不能
NYHA	New York Heart Association	ニューヨーク心臓協会
ORR	objective response rate	客観的奏効率
OS	overall survival	全生存期間
OTH	other types of eligible soft tissue sarcoma	その他の悪性軟部腫瘍

略号	省略していない表現（英語）	省略していない表現（日本語）
PD	progressive disease	進行
PFR_{12wks}	proression-free rate at 12 weeks	12 週時無増悪生存率
PFS	progression-free survival	無増悪生存期間
PMDA	Pharmaceuticals and Medical Devices Agency	医薬品医療機器総合機構
PNET	primitive neuroectodermal tumor	未熟神経外胚葉性腫瘍
PPS	Per Protocol Set	治験実施計画書に適合した解析対象集団
PR	partial response	部分奏効
PS	performance status	一般状態
PT	preferred term	基本語
QOL	quality of life	–
QT	QT interval	QT 間隔
QTc	QT interval corrected for heart rate	–
QTcF	QT interval corrected for heart rate using Fridericia's formula	Fridercia 式による補正 QT 間隔
RECIST	Response Evaluation Criteria in Solid Tumors	固形がんの効果判定基準
SD	stable disease	安定
SOC	system organ class	器官別大分類
STBSG	Soft Tissue and Bone Sarcoma Group	–
SYN	synovial sarcoma	滑膜肉腫
TNM	tumor-nodes-metastasis	TNM 分類
ULN	upper limit of normal	基準値上限
WHO	United Nations World Health Organization	世界保健機関

2.7.6 個々の試験のまとめ

臨床試験一覧表

治験の種類	治験実施計画書番号	治験報告書を添付した場所	治験の目的	試験デザイン及び対照の種類	治験薬 投与方法 用量，投与経路	被験者数 [a]	対象被験者	投与期間	治験の進行状況 報告書の種類
外国 309 試験 （評価資料）	E7389-G000-309	5.3.5.1.1	有効性， 安全性， 薬物動態	多施設共同，無作為化，オープン，並行群間比較試験（ダカルバジン対照）	エリブリン： 3 週間サイクルで第 1 及び 8 日目に 1.4 mg/m^2 を 2～5 分で静脈内投与 ダカルバジン： 3 週間サイクルで第 1 日目に被験者の臨床症状に応じて 850，1000 又は 1200 mg/m^2 を静脈内投与	450	悪性軟部腫瘍（脂肪肉腫又は平滑筋肉腫）	治験中止基準に該当しない限り投与を継続	実施中 完全な報告書
外国 207 試験 （評価資料）	E7389-E044-207	5.3.5.2.1	有効性， 安全性， 薬物動態	多施設共同，単一群，オープン試験（組織型分類による 4 層別）	エリブリン： 3 週間サイクルで第 1 及び 8 日目に 1.4 mg/m^2 を 2～5 分で静脈内投与	127	悪性軟部腫瘍 [b]	治験中止基準に該当しない限り投与を継続	完了 完全な報告書
国内 217 試験 （評価資料）	E7389-J081-217	5.3.5.2.2	有効性， 安全性， 薬物動態	多施設共同，単一群，オープン試験	エリブリン： 3 週間サイクルで第 1 及び 8 日目に 1.4 mg/m^2 を 2～5 分で静脈内投与	51	悪性軟部腫瘍 [b]	治験中止基準に該当しない限り投与を継続	実施中 完全な報告書

a: 治験薬が投与された被験者数

b: 以下の組織型を除く。ユーイング肉腫／未熟神経外胚葉性腫瘍（PNET），胎児性横紋筋肉腫，軟骨肉腫，骨肉腫，消化管間質腫瘍（GIST），隆起性皮膚線維肉腫，炎症性筋線維芽細胞腫，悪性中皮腫，子宮中胚葉性混合腫瘍，神経芽細胞腫

2.7.6.1 外国 309 試験［悪性軟部腫瘍患者を対象としたダカルバジン対照オープン比較試験］

……（添付資料 5.3.5.1.1）

2.7.6.1.1 治験方法

治験方法の概略を表 2.7.6.1-1 に示し，観察・検査項目及び実施スケジュールを表 2.7.6.1-2 に示した。

表 2.7.6.1-1　治験方法の概略（外国 309 試験）

項　　目	内　　容
治験実施計画書番号	E7389-G000-309
目的	主目的： ・脂肪肉腫（ADI）又は平滑筋肉腫（LMS）のいずれかの組織型の悪性軟部腫瘍の患者を対象として，全生存期間（OS）をエリブリン群（本薬群）とダカルバジン群で比較する。 副次目的： ・無増悪生存期間（PFS）を本薬群とダカルバジン群で比較する ・12 週時無増悪生存率（PFR_{12wks}）を本薬群とダカルバジン群で比較する ・臨床的有用率（CBR）を本薬群とダカルバジン群で比較する ・安全性と忍容性を本薬群とダカルバジン群で比較する ・悪性軟部腫瘍患者におけるエリブリンの母集団薬物動態を検討する 探索目的： ・客観的奏効率（ORR），病勢コントロール率（DCR）及び長期安定率（dSDR［durable SD の割合］）を本薬群とダカルバジン群で比較する ・エリブリンの暴露量と薬力学的効果（バイオマーカー）と有効性の相関を探索的に検討する ・エリブリンの暴露量と有害事象の関連を探索的に検討する ・安全性と有効性の指標に相関する血液中又は腫瘍バイオマーカーを特定する ・QOL スコアを本薬群とダカルバジン群で比較する
試験デザイン	多施設共同，無作為化，オープン，並行群間比較試験（ダカルバジン対照） 被験者を本薬群又はダカルバジン群のいずれかに 1:1 で無作為に割り付けた。無作為化は，以下の層別因子による層別割付とした。 (1)組織型：脂肪肉腫又は平滑筋肉腫 (2)地理学的地域：地域 1. 米国及びカナダ，地域 2. 西欧，オーストラリア及びイスラエル，地域 3. 東欧，ラテンアメリカ及びアジア (3)進行病変に対する前化学療法の数：2 レジメン又は 2 レジメン超（3 レジメン以上）
対象	前化学療法歴のある悪性軟部腫瘍の患者
選択基準	(1)組織学的に確定診断された中～高悪性度の悪性軟部腫瘍を有し，以下のいずれかの組織型に該当する患者 1)脂肪肉腫（脱分化型，粘液型，円形細胞型，多形型） 2)平滑筋肉腫 (2)手術又は放射線治療の適応とならない進行（局所再発，局所進行又は転移）脂肪肉腫（選択基準 (1) に記載されたタイプに限る）又は平滑筋肉腫であることが確認されている患者 (3)悪性軟部腫瘍に対し，少なくとも 2 レジメンの前化学療法歴を有する患

項　　目	内　　容
	者。前化学療法には，禁忌でない限りアントラサイクリン系薬剤を含む。 (4)最後に行われた抗悪性腫瘍の治療中又はその最終投与後に，画像による進行（PD）（固形がんの効果判定基準［RECIST］による）が確認された患者。ただし，PD は本治験の無作為割付け前 6 ヵ月以内でなければならない。 (5)以下の基準に合致する測定可能病変が存在する患者 1)RECIST 1.1 版に従ってコンピュータ断層撮影（CT）／磁気共鳴断層撮影（MRI）又はパノラマ接写カラー写真のいずれかで測定可能な長径 1.0 cm 以上の非リンパ節病変又は短径 1.5 cm 以上のリンパ節病変を 1 つ以上有すること。標的病変が 1 つのみであり非リンパ節病変である場合，長径で少なくとも 1.5 cm であること。 2)過去に放射線治療を受けた病変については RECIST 1.1 版に従って増悪を示すエビデンスがあり，標的病変とみなせること (6)Eastern Cooperative Oncology Group（ECOG）による一般状態（PS）（ECOG-PS）が 0，1 又は 2 の患者 (7)腎機能が十分保持されている患者（以下の Cockroft & Gault 式によるクレアチニンクリアランスが 50 mL/min 以上） 男性： ([140 –年齢] ×体重[kg]) / (血清クレアチニン[mg/dL]×72) = XX mL/min 女性： ([140 –年齢] ×体重[kg]) / (血清クレアチニン[mg/dL]×72) = XX mL/min × 0.85 (8)以下を満たす，骨髄機能が十分保持されている患者 1)絶対好中球数 ≥1500/mm^3 又は ≥1.5×10^9/L 2)血小板数 ≥100,000/mm^3 又は ≥100×10^9/L 3)ベースラインのヘモグロビン量 ≥10 g/dL（ヘモグロビン量 <10 g/dL を補正するために行われる無作為前期間中の輸血，造血成長因子及び造血剤の投与は可とする） (9)以下を満たす，肝機能が十分保持されている患者 1)ビリルビン≤ 1.5×基準値上限（ULN）。ただし，ジルベール症候群の間接型高ビリルビン血症を除く。 2)アルカリホスファターゼ（ALP），アラニンアミノトランスフェラーゼ（ALT）及びアスパラギン酸アミノトランスフェラーゼ（AST）≤ 3×ULN（総 ALP>3×ULN の場合には，ALP 肝アイソザイム≤3×ULN であること） (10)閉経後の女性（閉経期の年齢で，12 ヵ月以上連続して月経がなく，その他に無月経の原因がない），並びに手術により不妊となった女性（無作為割付け前 1 月経周期以上前に卵管結紮術を行った，若しくは，子宮摘出術又は両側卵巣摘出術を行った）を除く，全ての女性被験者を妊娠可能とみなす。妊娠可能な女性被験者は，無作為割付け前の最後の月経期間から治験薬投与中，並びに治験薬の最終投与後 3 ヵ月間，極めて有効な避妊法を 2 種類行うことに合意できること（2 種類の極めて有効な避妊法を開始して 1 月経周期以上が経過するまでは，下記の二重バリア型避妊法を行うこと）。この規定の例外となるのは禁欲を行っている女性被験者のみとする。現時点で禁欲中の被験者については，治験期間中に性交渉を開始する場合は，2 種類の極めて有効な避妊法を開始して 1 月経周期以上が経過するまでは，コンドーム+密閉キャップ（ペッサリー又は子宮頸管キャップ）を殺精子剤とともに用いる二重バリア型避妊を，治験薬投与中，並びに治験薬の最終

項　　目	内　　容
	投与後 3 ヵ月間行うことに合意できること。極めて有効な避妊法には，以下の 4 種の方法が含まれる。 1)子宮内避妊具の装着 2)バリア型避妊：コンドーム又は密閉キャップ（ペッサリー又は子宮頸管キャップ）を殺精子剤とともに使用する。 3)経口，注射又は埋め込みによるホルモン避妊法：ホルモン避妊薬を使用している女性被験者は，無作為割付け前の最後の月経期間から当該ホルモン避妊薬の種類及び用量を一定とし，治験薬投与中，並びに治験薬の最終投与後 3 ヵ月間は，変更せずに継続すること。 4)パートナーが精管切除術を行って無精子症であることが確認されていること (11)妊娠可能な女性（選択基準［10］に規定）をパートナーに持ち，禁欲を行っていない男性被験者及びその女性パートナーは，無作為割付け前の最後の月経期間から治験薬投与中，並びに治験薬の最終投与後 3 ヵ月間，極めて有効な避妊法を 2 種類行うこと（2 種類の極めて有効な避妊法を開始して 1 月経周期以上が経過するまでは，上記の二重バリア型の避妊法を行うこと）に合意できること。現時点で禁欲中の被験者が，治験期間中に性交渉を開始する場合は，上記の 2 種類の極めて有効な避妊法を行うまで，二重バリア型の避妊法を行うことに合意できること。 (12)自由意思により本治験参加に文書で同意し，治験実施計画書の全ての規定を遵守する意思と能力を有する (13)文書同意取得日の年齢が 18 歳以上の男女
除外基準	(1)無作為割付け前 21 日以内（又は半減期の 5 倍のいずれか長い方）に悪性腫瘍に対する治療歴（外科手術又は腫瘍内療法，放射線治療，化学療法，ホルモン剤，生物学的製剤［ヒト化抗体を含む］，免疫療法及び分子標的薬）を有する患者 (2)抗腫瘍前治療による急性毒性が有害事象共通用語規準（CTCAE）で Grade 1 以下に回復していない患者。ただし，末梢神経障害（除外基準 (5)参照）及び脱毛症を除く。 (3)過去にダカルバジン，又はその類似した抗癌剤，又はエリブリンの投与を受けた患者 (4)無作為割付け前 21 日以内に大手術を受けた患者 (5)CTCAE Grade 3 以上の末梢神経障害を有する患者 (6)下記の循環器系障害を有する患者 1)ニューヨーク心臓協会（NYHA）の心機能分類で III 度以上の心不全 2)本治験登録前 6 ヵ月以内の不安定狭心症又は心筋梗塞 3)重篤な生命を脅かす可能性のある心不整脈 (7)QT 延長症候群の発症リスクの高い患者又は電解質の不均衡を補正した上で少なくとも 2 回の心電図検査で 501 msec 以上の QTc 延長が認められる患者 (8)中枢神経系転移が認められる患者 (9)重篤な合併症又は治療を必要とする感染症を有する患者。治療を要さない感染症を有する患者であっても化学療法により骨髄抑制の合併症のリスクが高い患者。 (10)無作為割付け前 5 年以内に，治療を必要とする悪性腫瘍（ただし，悪性軟部腫瘍，非メラノーマ性皮膚癌又は完全切除により組織学的に確認された上皮内癌を除く）又はその再発が認められた患者

項　　目	内　　容
	(11)妊娠中又は授乳中の女性（女性被験者は，スクリーニング来院及びベースライン来院に実施する β-ヒト絨毛性ゴナドトロピン［hCG］妊娠検査［β-hCG 25 IU/L と同等以上の感度］が陰性でなければならない） (12)エリブリンあるいはダカルバジン又はその添加剤（ダカルバジン添付文書参照）に対する過敏症を有する患者 (13)治験責任医師又はその指名された者により，臨床試験に参加すべきでないと判断される医学的，その他の条件を有する患者
投与量 投与方法 投与期間	エリブリン：3 週間を 1 サイクルとし，各サイクル第 1 及び 8 日目に本薬 1.4 mg/m^2 を 2～5 分かけて静脈内投与した。 ダカルバジン：3 週間を 1 サイクルとし，第 1 日目に静脈内投与した。用量は 850～1200 mg/m^2 の範囲で，被験者の臨床症状に応じて，治験責任医師又はその指名された者が無作為割付け前に 850，1000 又は 1200 mg/m^2 のいずれかを選択した。 治験薬の投与は，病勢の進行又は許容できない毒性の発現，被験者の同意撤回，或いは治験依頼者による治験中止が決定された場合に中止することとした。
併用療法	併用禁止薬剤及び療法： (1)抗がん療法（化学療法，ホルモン療法，放射線療法，標的療法，免疫療法） 併用制限薬剤及び療法： (1)造血成長因子（顆粒球コロニー刺激因子［G-CSF］，エリスロポエチン）による対症療法は，別途ガイドラインに従って併用可能とした。 (2)合併症及び有害事象の治療及び症状緩和に使用する薬剤（血液製剤，輸血，輸液，抗生物質，止瀉剤等）は，治験の評価に影響を及ぼさない場合に限り，治験責任医師又は治験分担医師の判断で併用可能とした。
観察・検査項目及び実施スケジュール	表 2.7.6.1-2 参照
評価項目	有効性： 主要評価項目：OS 副次評価項目：PFS，PFR$_{12wks}$，CBR（CR+PR+durable SD［11 週以上の SD］の割合） 探索的評価項目：ORR（CR+PR の割合），DCR（CR+PR+SD の割合），dSDR（durable SD の割合），QOL スコア（QLQ C30，EQ-5D 質問票） なお，腫瘍評価は RECIST 1.1 を用いて 12 週までは 6 週間ごと，その後は 9 週間ごとに主治医判定により行った。生存調査は 12 週ごとに行った。 安全性： 有害事象（CTCAE v4.0），血液学的検査，血液生化学検査，尿検査，バイタルサイン，12 誘導心電図，身体所見 薬物動態： 本薬群の被験者を対象に血漿中エリブリン濃度を測定した。
解析方法	有効性： 主要評価項目は OS とした。 本治験では最終解析に必要な死亡イベント数（353 イベント）の 70%（247 イベント）が認められた後に中間解析を実施することを事前に計画した。中間解析に

項　　目	内　　容
	おいて優れた有効性が認められた場合には治験を中止する可能性があるとした。 最終解析は 353 イベントの死亡が認められた時点で行った。 中間解析時に本薬群の OS がダカルバジン群より統計学的に有意に延長（P<0.0148）又は最終解析時に本薬群の OS がダカルバジン群より有意に延長（P<0.0455）した場合は，本治験で優越性が検証されたと判断することとした（P 値は log-rank 検定に基づく）。 有効性解析では，最大の解析対象集団（FAS）を対象とした解析を主とした。 OS 及び PFS は，Kaplan-Meier 法により推定し，Kaplan-Meier プロットを経時的に示した。P 値は組織型（脂肪肉腫，平滑筋肉腫），地理学的地域（「米国及びカナダ」，「西欧，オーストラリア及びイスラエル」，「東欧，ラテンアメリカ及びアジア」），進行悪性軟部腫瘍に対する前化学療法のレジメン数（2 レジメン，3 レジメン以上）を層とした両側 log-rank 検定を用いて算出した。有意水準はα=0.0455 とした。ハザード比は組織型，地理学的地域，進行悪性軟部腫瘍に対する前化学療法のレジメン数を層とし，投与群を共変量とした Cox 比例ハザードモデルに基づき算出した。3，6，12，18，24 ヵ月生存率及び 3，6，12 ヵ月 PFS 率の推定値と両側 95%信頼区間を示し，OS 及び PFS の中央値と両側 95%信頼区間を求めた。 PFR_{12wks} は，Clopper-Pearson の正確な両側 95%信頼区間とともに示した。ORR，DCR，CBR，dSDR は，RECIST 1.1 版に基づく腫瘍縮小効果の判定に基づき推定し，Clopper-Pearson の正確な両側 95%信頼区間とともに示した。 安全性： 全ての安全性解析は投与群ごとに行った。治験薬投与後に認められた有害事象及び重篤な有害事象の発現率を集計した。臨床検査値，バイタルサイン及びそれらのベースラインからの変化量，12 誘導心電図の結果を，記述統計量を用いて要約した。 薬物動態： 母集団薬物動態解析法により母集団薬物動態パラメータを推定した。
症例数の設定根拠	ダカルバジン群の OS の中央値の見積りを約 6 ヵ月とし，2.5 ヵ月の改善は臨床的に意義があると考えられることから，それに相当する本薬群の OS の中央値を 8.5 ヵ月，ハザード比として 0.706 と仮定した。両側検定で，検出力を 90%，全体としての第 1 種の過誤確率を 5%としたとき，必要なイベント（死亡）数は 353 件と推定された。また，被験者の組入れを 1 ヵ月あたり 20 例と仮定すると，約 450 例が無作為割付けされる必要があると推測され，1:1 の割付比から，各群の例数は少なくとも 225 例ずつと推定された。また，OS の最終解析のための目標イベント数が観察される時期は約 29.2 ヵ月（22.5 ヵ月の組み入れ及び 6.7 ヵ月の追跡）と推定された。
目標症例数	各群 225 例，約 450 例
実施施設	23 ヵ国（米国，カナダ，オーストリア，ベルギー，デンマーク，フランス，ドイツ，イスラエル，イタリア，オランダ，スペイン，英国，チェコ，ポーランド，ルーマニア，ロシア，ブラジル，アルゼンチン，韓国，タイ，シンガポール，オーストラリア，ニュージーランド），139 施設
実施期間	2011 年 3 月～20[redacted]年[redacted]月（データカットオフ日）

表 2.7.6.1-2　観察・検査項目及び実施スケジュール（外国 309 試験）

	無作為化前		無作為化期										
期間	スクリーニング	ベースライン	治療期間										追跡調査
			第 1 サイクル			第 2 サイクル			第 3～最終サイクル				
期間（日）	–21 ～ –2	–1	1	8	15	1	8	15	1	8	15	中止時	
調査項目													
文書同意取得	X												
選択／除外基準の確認	X	X											
無作為化		X											
人口統計学的特性	X												
NYHA 心機能分類	X	X											
ECOG-PS	X	X				X			X			X	
腫瘍の悪性度（pTNM 分類）	X												
既往歴／手術歴	X												
バイタルサイン，体重，身長	X	X	X	X	X	X	X	X	X	X		X	
身体所見	X	X	X	X	X	X	X	X	X	X		X	
12 誘導心電図	X	X	X	X		X	X		X	X		X	
血液学的検査	X	X		X	X	X	X	X	X	X		X	
血液生化学検査	X	X		X	X	X	X	X	X	X		X	
尿検査	X	X				X			X			X	
妊娠検査	X	X										X	
腫瘍評価	X		胸部 CT，腹部／骨盤及びスクリーニング時に病変が確認されたその他の部位，更に新たな病変が疑われる部位の CT／MRI を PD が認められるまで最初の 12 週は 6 週ごと，それ以降は 9 週ごと，臨床的に必要な場合はそれより短い間隔で実施する。										

表 2.7.6.1-2　観察・検査項目及び実施スケジュール（外国 309 試験）（続き）

	無作為化前		無作為化期										
期間	スクリーニング	ベースライン	治療期間										追跡調査
			第 1 サイクル			第 2 サイクル			第 3～最終サイクル				
期間（日）	–21 ～ –2	–1	1	8	15	1	8	15	1	8	15	中止時	
調査項目													
骨スキャン	X		X										
QOL 調査	X		X			X			X			X	
治験薬投与			X	X		X	X		X	X			
薬物動態解析用採血			X	X		X	X						
第三者による組織学的評価のための腫瘍検体又は切片	X												
薬力学的効果（バイオマーカー）評価のための腫瘍検体又は切片	X												
ゲノム DNA を入手するための採血		X											
RNA 解析のための採血		X		X									
薬力学的効果（バイオマーカー）評価のための採血		X		X									
併用薬剤	全期間												
有害事象	全期間												X
生存調査													X

ECOG-PS = Eastern Cooperative Oncology Group- performance status, NYHA = New York Heart Association, pTNM = pathological tumor-nodes-metastasis, QOL = quality of life.

2.7.6.1.2 被験者の内訳

本治験では，594 例から同意を取得し，うち，452 例の被験者が無作為化された。無作為化に至らなかった 142 例の理由は，選択・除外基準逸脱（106 例），同意の撤回（10 例），有害事象の発現（7 例），その他（19 例）であった（添付資料 5.3.5.1.1 の Table 14.1.1.1）。

無作為化された被験者の内訳及び投与中止理由を表 2.7.6.1-3 に示した。

無作為化された 452 例は，各群（本薬群 228 例，ダカルバジン群 224 例）に割り付けられ，うち，450 例（本薬群 227 例，ダカルバジン群 223 例）に治験薬が投与された。なお，データカットオフ時に投与を継続中であった 2 例（本薬群，ダカルバジン群の各 1 例）を除く 448 例を投与中止例として取り扱った。

表 2.7.6.1-3　被験者の内訳及び投与中止理由（無作為化例）（外国 309 試験）

	本薬群 228 例	ダカルバジン群 224 例	合計 452 例
無作為化された例数	228 (100.0)	224 (100.0)	452 (100.0)
未投与例	1 (0.4)	1 (0.4)	2 (0.4)
投与例	227 (99.6)	223 (99.6)	450 (99.6)
データカットオフ時点で投与継続	1 (0.4)	1 (0.4)	2 (0.4)
投与中止例	226 (99.1)	222 (99.1)	448 (99.1)
投与中止例の主な理由			
病勢進行	173 (75.9)	165 (73.7)	338 (74.8)
病状の悪化	24 (10.5)	27 (12.1)	51 (11.3)
有害事象	14 (6.1)	10 (4.5)	24 (5.3)
被験者の都合	5 (2.2)	10 (4.5)	15 (3.3)
管理/その他	10 (4.4)	10 (4.5)	20 (4.4)
同意撤回	2 (0.9)	4 (1.8)	6 (1.3)
その他	8 (3.5)	6 (2.7)	14 (3.1)

数字は例数，（　）内は各投与群の無作為化例数に対する割合（%）

（添付資料 5.3.5.1.1 の Table 10 を引用）

2.7.6.1.3 解析対象集団

解析対象集団の内訳を表 2.7.6.1-4 に示した。

無作為化された 452 例（本薬群 228 例，ダカルバジン群 224 例）全例を FAS とし，このうち，治験薬が投与された 450 例（本薬群 226 例，ダカルバジン群 224 例）を安全性解析対象集団とした。

本治験では FAS の 2 例（本薬群，ダカルバジン群の各 1 例）は投与されなかったため，安全性解析対象集団としなかった。また，1 例の被験者は本薬群に無作為化されたが，ダカルバジンを投与されたため，当該被験者をダカルバジン群の安全性解析対象として取り扱った。

表 2.7.6.1-4　解析対象集団（無作為化例）（外国 309 試験）

	本薬群 228 例	ダカルバジン群 224 例	合計 452 例
無作為化された例数	228	224	452
FAS	228 (100.0)	224 (100.0)	452 (100.0)
PPS	215 (94.3)	199 (88.8)	414 (91.6)
安全性解析対象集団	226 (99.1)	224 (100.0)	450 (99.6)

FAS = Full Analysis Set, PPS = Per Protocol Set
数字は例数，（　）内は各投与群の無作為化例数に対する割合（%）

（添付資料 5.3.5.1.1 の Table 12 を引用）

2.7.6.1.4　被験者背景

FAS（452 例）の被験者背景の要約を表 2.7.6.1-5 に，疾患特性の要約を表 2.7.6.1-6 に示した。

年齢の平均値は 55.7 歳，性別の割合は男性 33.0%（149/452 例），女性が 67.0%（303/452 例）であった。ECOG-PS は，PS 0 が 44.5%（201/452 例），PS 1 が 52.0%（235/452 例）であった。登録された主な組織型は，脂肪肉腫 33.8%（153/452 例），平滑筋肉腫 65.7%（297/452 例），その他の悪性軟部腫瘍は 0.4%（2/452 例）であった。また，進行病変に対する前化学療法のレジメン数は 2 レジメンが 47.6%（215/452 例），3 レジメン以上が 39.8%（180/452 例）であり，前化学療法はドキソルビシンが最も多く使用されていた（77.9%，352/452 例）。

表 2.7.6.1-5　被験者背景の要約（FAS）（外国 309 試験）

	本薬群 228 例	ダカルバジン群 224 例	合計 452 例
年齢（歳）			
平均値（標準偏差）	55.6 (11.01)	55.7 (10.35)	55.7 (10.68)
中央値	56	56	56
最小値，最大値	28, 83	24, 83	24, 83
年齢の分布			
65 歳未満	178 (78.1)	178 (79.5)	356 (78.8)
65 歳以上	50 (21.9)	46 (20.5)	96 (21.2)
体表面積（m^2）			
平均値（標準偏差）	1.82 (0.255)	1.84 (0.244)	1.83 (0.250)
中央値	1.80	1.82	1.81
最小値，最大値	1.34, 3.09	1.40, 2.84	1.34, 3.09
性別			
男性	67 (29.4)	82 (36.6)	149 (33.0)
女性	161 (70.6)	142 (63.4)	303 (67.0)
地理学的地域			
米国及びカナダ	87 (38.2)	86 (38.4)	173 (38.3)
西欧，オーストラリア及びイスラエル	106 (46.5)	105 (46.9)	211 (46.7)
東欧，ラテンアメリカ及びアジア	35 (15.4)	33 (14.7)	68 (15.0)
民族			
Hispanic or Latino	23 (10.1)	27 (12.1)	50 (11.1)
Not Hispanic or Latino	170 (74.6)	167 (74.6)	337 (74.6)
Not applicable	35 (15.4)	30 (13.4)	65 (14.4)
人種			
White	162 (71.1)	168 (75.0)	330 (73.0)
Black or African American	6 (2.6)	6 (2.7)	12 (2.7)
Japanese	1 (0.4)	0	1 (0.2)
Chinese	2 (0.9)	1 (0.4)	3 (0.7)
Other Asian	15 (6.6)	15 (6.7)	30 (6.6)
American Indian or Alaskan Native	0	0	0
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.2)
Other	6 (2.6)	4 (1.8)	10 (2.2)
Not applicable	35 (15.4)	30 (13.4)	65 (14.4)
ECOG-PS			
0	111 (48.7)	90 (40.2)	201 (44.5)
1	114 (50.0)	121 (54.0)	235 (52.0)
2	3 (1.3)	13 (5.8)	16 (3.5)

分類別集計の数字は例数，（　）内は各投与群の FAS に対する割合（%）
ECOG-PS = Eastern Cooperative Oncology Group-performance status

（添付資料 5.3.5.1.1 の Table 14.1.3.1 を引用）

表 2.7.6.1-6　疾患特性の要約（FAS）（外国 309 試験）

	本薬群 228 例	ダカルバジン群 224 例	合計 452 例
組織型			
脂肪肉腫	75 (32.9)	78 (34.8)	153 (33.8)
脱分化型	32 (14.0)	37 (16.5)	69 (15.3)
粘液型	26 (11.4)	25 (11.2)	51 (11.3)
多形型	13 (5.7)	15 (6.7)	28 (6.2)
円形細胞型	4 (1.8)	1 (0.4)	5 (1.1)
平滑筋肉腫	152 (66.7)	145 (64.7)	297 (65.7)
その他の悪性軟部腫瘍 [a]	1 (0.4)	1 (0.4)	2 (0.4)
腫瘍の悪性度			
中悪性度	77 (33.8)	69 (30.8)	146 (32.3)
高悪性度	150 (65.8)	152 (67.9)	302 (66.8)
評価せず	1 (0.4)	3 (1.3)	4 (0.9)
原発巣の部位			
子宮その他	57 (25.0)	56 (25.0)	113 (25.0)
後腹膜	40 (17.5)	53 (23.7)	93 (20.6)
結合と軟部組織	43 (18.9)	40 (17.9)	83 (18.4)
その他	21 (9.2)	12 (5.4)	33 (7.3)
骨と関節	9 (3.9)	11 (4.9)	20 (4.4)
子宮体	6 (2.6)	4 (1.8)	10 (2.2)
腎臓	7 (3.1)	3 (1.3)	10 (2.2)
胃	5 (2.2)	5 (2.2)	10 (2.2)
肝臓	5 (2.2)	4 (1.8)	9 (2.0)
肺／気管支	3 (1.3)	5 (2.2)	8 (1.8)
縦隔	3 (1.3)	5 (2.2)	8 (1.8)
子宮頸	4 (1.8)	2 (0.9)	6 (1.3)
小腸	1 (0.4)	5 (2.2)	6 (1.3)
精巣上体，精索，男性生殖器その他	2 (0.9)	2 (0.9)	4 (0.9)
大腸（盲腸を除く）	3 (1.3)	1 (0.4)	4 (0.9)
膵臓	2 (0.9)	2 (0.9)	4 (0.9)
リンパ節	2 (0.9)	1 (0.4)	3 (0.7)
卵巣	0	3 (1.3)	3 (0.7)
副腎	1 (0.4)	1 (0.4)	2 (0.4)
心臓	2 (0.9)	0	2 (0.4)
その他女性生殖器	2 (0.9)	0	2 (0.4)
直腸	1 (0.4)	1 (0.4)	2 (0.4)
皮膚	1 (0.4)	1 (0.4)	2 (0.4)
睾丸	1 (0.4)	1 (0.4)	2 (0.4)
膣及び陰唇	1 (0.4)	1 (0.4)	2 (0.4)
副，洞，中，内耳	1 (0.4)	0	1 (0.2)

分類別集計の数字は例数，（　）内は各投与群の FAS に対する割合（%）
a: 組織型が特定できない場合，その他に分類した。

（添付資料 5.3.5.1.1 の Table 14.1.3.1，Table 14.1.4.2，Table 14.1.4.4 を引用）

表 2.7.6.1-6　疾患特性の要約（FAS）（外国 309 試験）（続き）

	本薬群 228 例	ダカルバジン群 224 例	合計 452 例
原発巣の部位（続き）			
肛門管と肛門	1 (0.4)	0	1 (0.2)
歯肉，口腔底部，その他口腔	1 (0.4)	0	1 (0.2)
眼窩及び涙腺 （網膜，眼その他を除く）	0	1 (0.4)	1 (0.2)
その他神経系	0	1 (0.4)	1 (0.2)
陰茎と陰嚢	1 (0.4)	0	1 (0.2)
前立腺	0	1 (0.4)	1 (0.2)
腎盂，尿管	0	1 (0.4)	1 (0.2)
不明	1 (0.4)	0	1 (0.2)
詳細不明な消化器官	0	1 (0.4)	1 (0.2)
欠測（Missing）	1 (0.4)	0	1 (0.2)
前化学療法の種類			
術前補助化学療法	15 (6.6)	10 (4.5)	25 (5.5)
術後補助化学療法	44 (19.3)	51 (22.8)	95 (21.0)
進行病変に対する化学療法	224 (98.2)	219 (97.8)	443 (98.0)
維持療法	8 (3.5)	12 (5.4)	20 (4.4)
不明	3 (1.3)	1 (0.4)	4 (0.9)
放射線療法歴			
あり	118 (51.8)	118 (52.7)	236 (52.2)
なし	110 (48.2)	106 (47.3)	216 (47.8)
進行病変に対する前化学療法のレジメン数			
0	4 (1.8)	5 (2.2)	9 (2.0)
1	21 (9.2)	27 (12.1)	48 (10.6)
2	115 (50.4)	100 (44.6)	215 (47.6)
3	48 (21.1)	58 (25.9)	106 (23.5)
4	22 (9.6)	17 (7.6)	39 (8.6)
5	9 (3.9)	12 (5.4)	21 (4.6)
6	1 (0.4)	2 (0.9)	3 (0.7)
7	4 (1.8)	3 (1.3)	7 (1.5)
8	2 (0.9)	0	2 (0.4)
9	2 (0.9)	0	2 (0.4)

分類別集計の数字は例数，（　）内は各投与群の FAS に対する割合（%）

（添付資料 5.3.5.1.1 の Table 14.1.3.1， Table 14.1.4.2， Table 14.1.4.4 を引用）

表 2.7.6.1-6　疾患特性の要約（FAS）（外国 309 試験）（続き）

	本薬群 228 例	ダカルバジン群 224 例	合計 452 例
進行病変に対する前化学療法の薬剤 [a]			
ドキソルビシン	179 (78.5)	173 (77.2)	352 (77.9)
ゲムシタビン	119 (52.2)	122 (54.5)	241 (53.3)
イホスファミド	114 (50.0)	112 (50.0)	226 (50.0)
Trabectedin	107 (46.9)	112 (50.0)	219 (48.5)
ドセタキセル	97 (42.5)	91 (40.6)	188 (41.6)
パゾパニブ	18 (7.9)	17 (7.6)	35 (7.7)
エピルビシン	13 (5.7)	14 (6.3)	27 (6.0)
シスプラチン	12 (5.3)	13 (5.8)	25 (5.5)
シクロホスファミド	12 (5.3)	9 (4.0)	21 (4.6)

分類別集計の数字は例数，（　）内は各投与群の FAS に対する割合（%）
a: いずれかの群で 5%以上の頻度で使用された薬剤を示した。
（添付資料 5.3.5.1.1 の Table 14.1.3.1， Table 14.1.4.2， Table 14.1.4.4 を引用）

2.7.6.1.5 治験薬の暴露状況

治験薬（本薬，ダカルバジン）の投与状況を表 2.7.6.1-7 に示した。

本薬群では，暴露期間（初回投与日から最終サイクル 21 日目までの期間）の中央値（最小値，最大値）は本薬群で 10.0 週（3.0，112.0），ダカルバジン群で 9.0 週（3.0，109.6）であり，投与サイクル数の中央値（最小値，最大値）は本薬群で 3.0（1.0，34.0），ダカルバジン群で 3.0（1.0，30.0）であった。また，用量強度（総投与量［mg/m^2］/暴露期間［週］）の中央値（最小値，最大値）は本薬群で 0.87 mg/m^2/週（0.3，1.0），ダカルバジン群で 315.74 mg/m^2/週（130.4，405.2）であった。

表 2.7.6.1-7　治験薬の投与状況（安全性解析対象集団）（外国 309 試験）

	本薬群 226 例	ダカルバジン群 224 例
暴露期間（週）[a]		
平均値（標準偏差）	17.4 (18.65)	13.7 (13.35)
中央値	10.0	9.0
最小値，最大値	3.0, 112.0	3.0, 109.6
投与サイクル数[b]		
平均値（標準偏差）	5.5 (5.75)	4.2 (3.88)
中央値	3.0	3.0
最小値，最大値	1.0, 34.0	1.0, 30.0
用量強度（mg/m^2/週）[c]		
平均値（標準偏差）	0.80 (0.159)	305.64 (50.791)
中央値	0.87	315.74
最小値，最大値	0.3, 1.0	130.4, 405.2

a: (最終サイクルの第 1 日目 ＋21 － 初回投与日) / 7
b: 少なくとも 1 回の治験薬を投与したサイクル数
c: 治験期間中の総投与量 / (暴露期間［日］/ 7)

（添付資料 5.3.5.1.1 の Table 14.3.1.1，Table 14.3.1.2 を引用）

2.7.6.1.6　有効性の結果

2.7.6.1.6.1　全生存期間（OS）（主要評価項目）

有効性解析では，FAS を対象とした解析を主とした。

OS の結果を表 2.7.6.1-8 に，OS の Kaplan-Meier プロットを図 2.7.6.1-1 に示した。

データカットオフ時の死亡例は本薬群で 176 例（77.2%），ダカルバジン群で 181 例（80.8%）であった。OS の中央値（95%信頼区間）は本薬群（228 例）で 13.5 ヵ月（10.9，15.6），ダカルバジン群（224 例）で 11.5 ヵ月（9.6，13.0）であり，本薬群ではダカルバジン群に対して有意な OS の延長が認められた（P＝0.0169；組織型，地理学的地域及び進行悪性軟部腫瘍に対する前化学療法のレジメン数を層とした層別 log-rank 検定，ハザード比：0.768［95%信頼区間：0.618，0.954］）。また，3～24 ヵ月の生存率は一貫して本薬群で良好な結果であった。

表 2.7.6.1-8　全生存期間（OS）の結果（FAS）（外国 309 試験）

	本薬群 228 例	ダカルバジン群 224 例
イベント（死亡）を発生した被験者数，例数（%）	176 (77.2)	181 (80.8)
打ち切り例，例数（%）	52 (22.8)	43 (19.2)
被験者の同意撤回，例数（%）	8 (3.5)	8 (3.6)
データカットオフ時の生存例，例数（%）	44 (19.3)	35 (15.6)
OS（月）		
中央値（95%信頼区間）[a]	13.5 (10.9 , 15.6)	11.5 (9.6 , 13.0)
第 1 四分位値（95%信頼区間）[a]	5.8 (4.2 , 7.2)	5.2 (4.0 , 6.7)
第 3 四分位値（95%信頼区間）[a]	24.7 (22.1 , 30.9)	20.5 (17.4 , 24.9)
P 値（層別 log-rank 検定）[b]	0.0169	
ハザード比（95%信頼区間）[c]	0.768 (0.618, 0.954)	
生存率		
3 ヵ月生存率（95%信頼区間）[a]	0.888 (0.838, 0.923)	0.876 (0.825, 0.914)
6 ヵ月生存率（95%信頼区間）[a]	0.734 (0.671, 0.787)	0.729 (0.665, 0.783)
12 ヵ月生存率（95%信頼区間）[a]	0.548 (0.480, 0.611)	0.475 (0.407, 0.540)
18 ヵ月生存率（95%信頼区間）[a]	0.402 (0.337, 0.466)	0.299 (0.239, 0.361)
24 ヵ月生存率（95%信頼区間）[a]	0.260 (0.202, 0.322)	0.202 (0.150, 0.259)

OS = overall survival.

a: 各群の OS の中央値，第 1 四分位値，第 3 四分位値，3，6，12，18，24 ヵ月生存率（両側 95%信頼区間）は Kaplan-Meier 推定値及び Greenwood 式に基づき算出した。

b: *P* 値は組織型（脂肪肉腫，平滑筋肉腫），地理学的地域（1. 米国及びカナダ，2. 西欧，オーストラリア及びイスラエル，3. 東欧，ラテンアメリカ及びアジア），進行悪性軟部腫瘍に対する前化学療法のレジメン数（2 レジメン，3 レジメン以上）を層とした両側 log-rank 検定を用いて算出した。有意水準は α= 0.0455 とした。

c: ハザード比は組織型，地理学的地域，進行悪性軟部腫瘍に対する前化学療法のレジメン数を層とし，投与群を共変量とした Cox 回帰モデルに基づき算出した。

（添付資料 5.3.5.1.1 の Table 14.2.2.1 を引用）

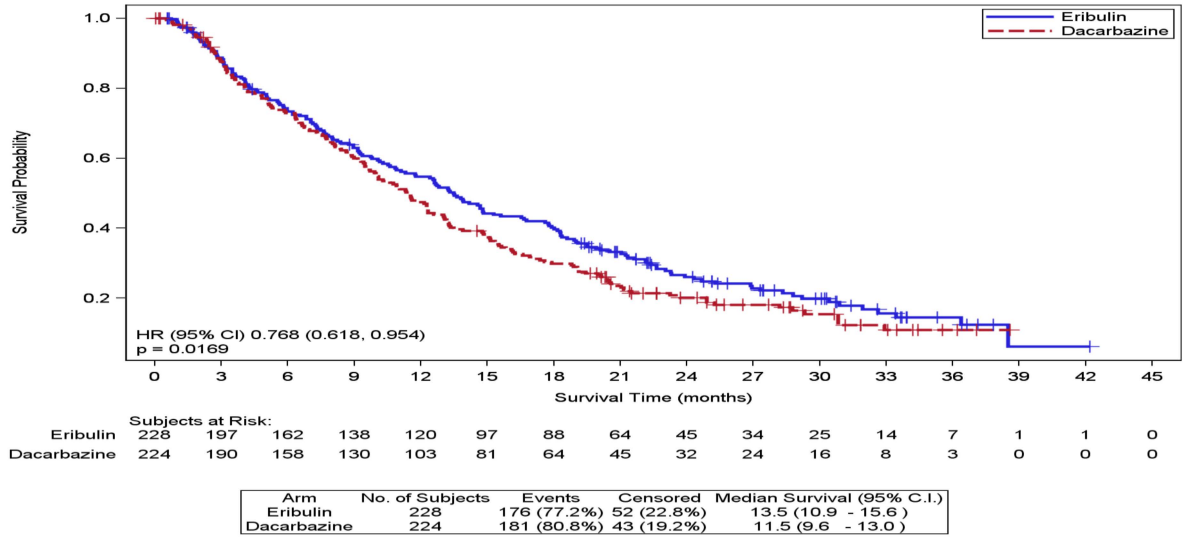


図 2.7.6.1-1　全生存期間（OS）の Kaplan-Meier プロット（FAS）（外国 309 試験）

（添付資料 5.3.5.1.1 の Figure 14.2.1.4 を引用）

OS について，年齢，性別，人種，民族，進行病変に対する前化学療法のレジメン数，地理学的地域，組織型，ECOG-PS，前化学療法の種類，診断時の悪性度別の Forest プロットを図 2.7.6.1-2 に示した。

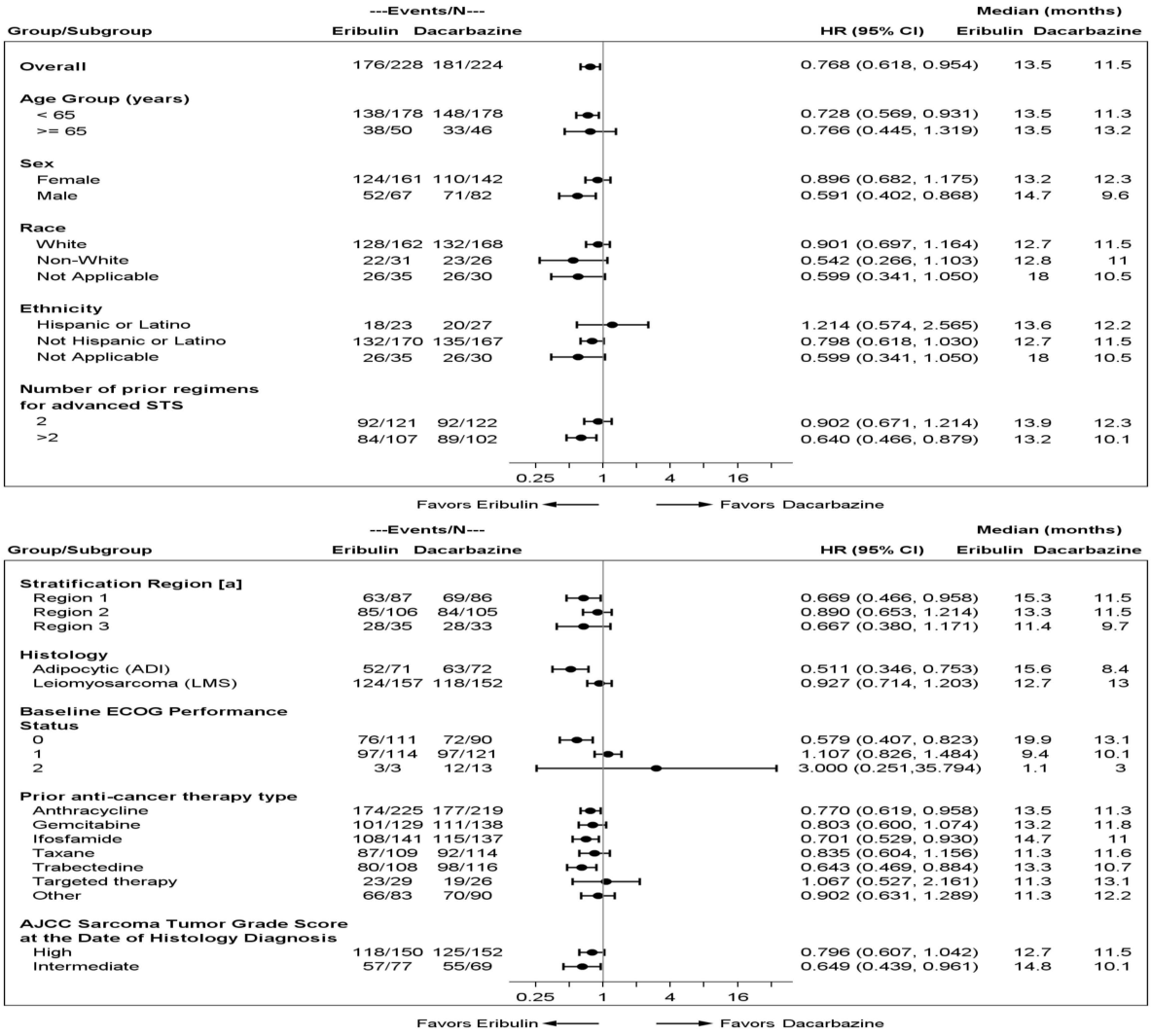


図 2.7.6.1-2　全生存期間（OS）における Forest プロット（FAS）（外国 309 試験）

ハザード比はダカルバジン群に対する本薬群の比で定義した。
Region 1:　米国及びカナダ，Region 2:　西欧，オーストラリア及びイスラエル，Region 3:　東欧，ラテンアメリカ及びアジア

（添付資料 5.3.5.1.1 の Figure 14.2.1.1 を引用）

2.7.6.1.6.2 無増悪生存期間（PFS）（副次評価項目）

PFS の結果を表 2.7.6.1-9 に，PFS の Kaplan-Meier プロットを図 2.7.6.1-3 に示した。

PFS の中央値（95%信頼区間）は本薬群（228 例）で 2.6 ヵ月（1.9，2.8），ダカルバジン群（224 例）で 2.6 ヵ月（1.8，2.7）（P＝0.2287；ハザード比：0.877［95%信頼区間：0.710，1.085］）であり，本薬群が良好な傾向を示したものの，ダカルバジン群に対して有意な PFS の延長は認められなかった。また，3，6 及び 12 ヵ月時点の PFS 率は，本薬群では 0.400，0.216 及び 0.111，ダカルバジン群では 0.343，0.158 及び 0.052 であり，各時点における PFS 率は，本薬群がダカルバジン群と比較して良好な結果であった。

表 2.7.6.1-9　無増悪生存期間（PFS）の結果（FAS）（外国 309 試験）

	本薬群 228 例	ダカルバジン群 224 例
イベントを発生した被験者数，例数（%）	197 (86.4)	188 (83.9)
PD	183 (80.3)	173 (77.2)
死亡	14 (6.1)	15 (6.7)
打ち切り例，例数（%）	31 (13.6)	36 (16.1)
データカットオフ時で進行せずに生存	7 (3.1)	8 (3.6)
新たな抗がん剤治療を開始	18 (7.9)	18 (8.0)
2 回以上の評価欠測後に死亡又は進行	6 (2.6)	10 (4.5)
PFS（月）		
中央値（95%信頼区間）[a]	2.6 (1.9, 2.8)	2.6 (1.8, 2.7)
第 1 四分位値（95%信頼区間）[a]	1.3 (1.2, 1.4)	1.4 (1.2, 1.4)
第 3 四分位値（95%信頼区間）[a]	4.9 (4.7, 6.9)	4.2 (3.3, 4.9)
P 値（層別 log-rank 検定）[b]	0.2287	
ハザード比（95%信頼区間）[c]	0.877 (0.710, 1.085)	
PFS 率		
3 ヵ月時点（95%信頼区間）[a]	0.400 (0.334, 0.466)	0.343 (0.278, 0.409)
6 ヵ月時点（95%信頼区間）[a]	0.216 (0.162, 0.275)	0.158 (0.110, 0.214)
12 ヵ月時点（95%信頼区間）[a]	0.111 (0.070, 0.162)	0.052 (0.024, 0.096)

PD = progressive disease，PFS = progression-free survival.

a: 各群の PFS の中央値，第 1 四分位値，第 3 四分位値，3，6，12 ヵ月生存率（両側 95%信頼区間）は Kaplan-Meier 推定値及び Greenwood 式に基づき算出した。

b: P 値は組織型（脂肪肉腫，平滑筋肉腫），地理学的地域（1. 米国及びカナダ，2. 西欧，オーストラリア及びイスラエル，3. 東欧，ラテンアメリカ及びアジア），進行悪性軟部腫瘍に対する前化学療法のレジメン数（2 レジメン，3 レジメン以上）を層とした両側 log-rank 検定を用いて算出した。

c: ハザード比は組織型，地理学的地域，進行悪性軟部腫瘍に対する前化学療法のレジメン数を層とし，投与群を共変量とした Cox 回帰モデルに基づき算出した。

（添付資料 5.3.5.1.1 の Table 14.2.3.1 を引用）

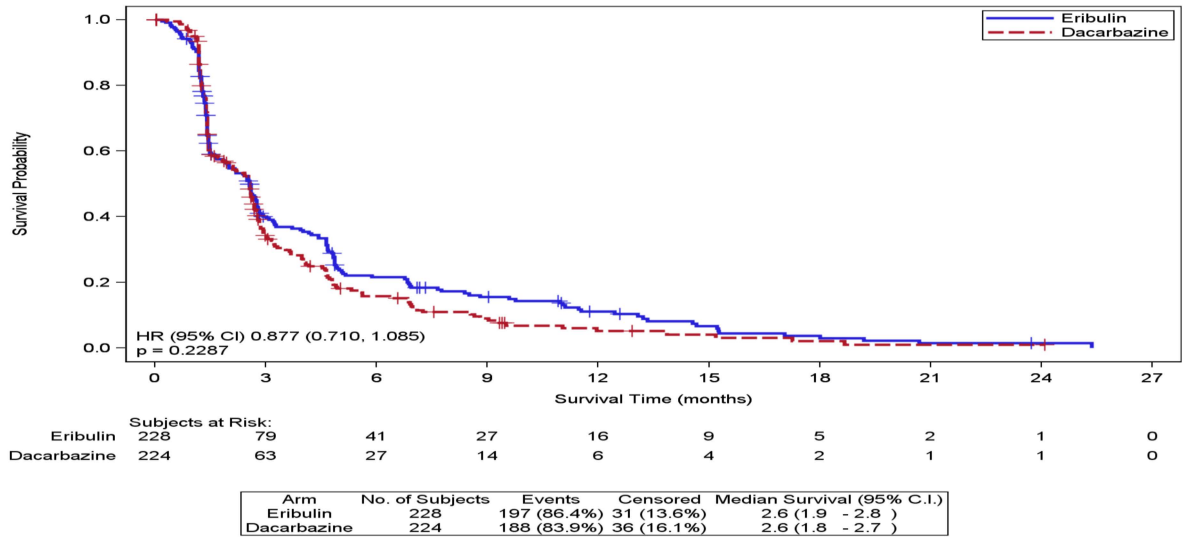


図 2.7.6.1-3　無増悪生存期間（PFS）の Kaplan-Meier プロット（FAS）（外国 309 試験）

（添付資料 5.3.5.1.1 の Figure 14.2.1.5 を引用）

2.7.6.1.6.3　12 週時無増悪生存率（PFR_{12wks}）（副次評価項目）

PFR_{12wks} の結果を表 2.7.6.1-10 に示した。

PFR_{12wks} は本薬群で 33.3%（76/228 例；95%信頼区間：27.2，39.9，以下同様），ダカルバジン群で 28.6%（64/224 例；22.8，35.0）であり，本薬群の PFR_{12wks} はダカルバジン群に対して高かったものの，統計学的な有意差は認められなかった（P＝0.253；オッズ比：1.3［0.8，1.9］）。

表 2.7.6.1-10　12 週時無増悪生存率（PFR_{12wks}）（FAS）（外国 309 試験）

	本薬群 228 例	ダカルバジン群 224 例
PFR_{12wks}，例数（%）	76 (33.3)	64 (28.6)
95%信頼区間 [a]	(27.2, 39.9)	(22.8, 35.0)
P 値（Cochran Mantel-Haenszel 検定） [b]	0.253	
オッズ比（95%信頼区間） [c]	1.3 (0.8, 1.9)	

PFR_{12wks} = propression-free rate at 12 weeks.

a: Clopper-Pearson の正確な両側 95%信頼区間

b: P 値は組織型（脂肪肉腫，平滑筋肉腫），地理学的地域（1. 米国及びカナダ，2. 西欧，オーストラリア及びイスラエル，3. 東欧，ラテンアメリカ及びアジア），進行悪性軟部腫瘍に対する前化学療法のレジメン数（2 レジメン，3 レジメン以上）を層とした Cochran Mantel-Haenszel 検定を用いて算出した。

c: 本薬群とダカルバジン群のオッズ比は上記 b.と同様に組織型，地理学的地域，進行悪性軟部腫瘍に対する前化学療法のレジメン数を層とした Cochran Mantel-Haenszel 法を用いて算出した。オッズ比の 95%信頼区間は漸近正規近似に基づき算出した。

（添付資料 5.3.5.1.1 の Table 14.2.4.1 を引用）

2.7.6.1.6.4 抗腫瘍効果

抗腫瘍効果の結果を表 2.7.6.1-11 に示した。また，標的病変の総計和のベースラインから最小値への変化率を図 2.7.6.1-4 に示した。

2.7.6.1.6.4.1 CBR（副次評価項目）

本治験では完全奏効（CR）の被験者はみられなかったが，CBR は本薬群では 46.1%（105/228 例），ダカルバジン群では 47.8%（107/224 例）であり，両群間で大きな差異は認められなかった（*P*=0.741；Cochran Mantel-Haenszel 検定，オッズ比：0.9［0.7，1.4］）。

2.7.6.1.6.4.2 ORR，DCR，dSDR（探索的評価項目）

ORR は本薬群で 3.9%（9/228 例），ダカルバジン群で 4.9%（11/224 例）であり，両群間で大きな差異は認められなかった（*P*=0.616；Cochran Mantel-Haenszel 検定）。DCR は本薬群では 56.1%（128/228 例），ダカルバジン群では 52.7%（118/224 例），dSDR は本薬群では 42.1%（96/228 例），ダカルバジン群では 42.9%（96/224 例）であった。

また，PR が認められた被験者の奏効期間の中央値は，本薬群で 12.5 ヵ月，ダカルバジン群で 4.2 ヵ月であり，奏効例における本薬群の奏効期間はダカルバジン群と比較して良好な結果であった。

表 2.7.6.1-11　抗腫瘍効果（FAS）（外国 309 試験）

	本薬群 228 例	ダカルバジン群 224 例
最良総合効果，例数（%）		
CR	0	0
部分奏効（PR）	9 (3.9)	11 (4.9)
安定（SD）	119 (52.2)	107 (47.8)
PD	89 (39.0)	88 (39.3)
評価不能（NE）	2 (0.9)	3 (1.3)
不明	9 (3.9)	15 (6.7)
ORR，例数（%）	9 (3.9)	11 (4.9)
95%信頼区間 [a]	(1.8, 7.4)	(2.5, 8.6)
P 値（Cochran Mantel-Haenszel 検定） [b]	0.616	
DCR，例数（%）	128 (56.1)	118 (52.7)
95%信頼区間 [a]	(49.4, 62.7)	(45.9, 59.4)
P 値（Cochran Mantel-Haenszel 検定） [b]	0.438	
CBR，例数（%）	105 (46.1)	107 (47.8)
95%信頼区間 [a]	(39.5, 52.8)	(41.1, 54.5)
P 値（Cochran Mantel-Haenszel 検定） [b]	0.741	
オッズ比（95%信頼区間） [c]	0.9 (0.7, 1.4)	
dSDR，例数（%）	96 (42.1)	96 (42.9)
95%信頼区間 [a]	(35.6, 48.8)	(36.3, 49.6)
P 値（Cochran Mantel-Haenszel 検定） [b]	0.900	
奏効期間の中央値 [d]（月）	12.5	4.2
95%信頼区間	(1.7, NE)	(2.2, 14.7)

CBR = clinical benefit rate，CR = complete response，DCR = disease control rate，dSDR = durable stable disease rate，NE ＝not evaluable，ORR = objective response rate，PD = progressive disease，PR = partial response，SD = stable disease.

a: Clopper-Pearson の 2 項分布を用いた正確な両側 95%信頼区間

b: *P* 値は組織型（脂肪肉腫，平滑筋肉腫），地理学的地域（1. 米国及びカナダ，2. 西欧，オーストラリア及びイスラエル，3. 東欧，ラテンアメリカ及びアジア），進行悪性軟部腫瘍に対する前化学療法のレジメン数（2 レジメン，3 レジメン以上）を層とした Cochran Mantel-Haenszel 検定を用いて算出した。

c: 本薬群とダカルバジン群のオッズ比は上記 b.と同様に組織型，地理学的地域，進行悪性軟部腫瘍に対する前治療のレジメン数を層とした Cochran Mantel-Haenszel 法を用いて算出した。オッズ比の両側 95%信頼区間は漸近正規近似に基づき算出した。

d: 奏効例を対象

（添付資料 5.3.5.1.1 の Table 14.2.5.1，Table 14.2.6.1，Table 14.2.7.1 を引用）

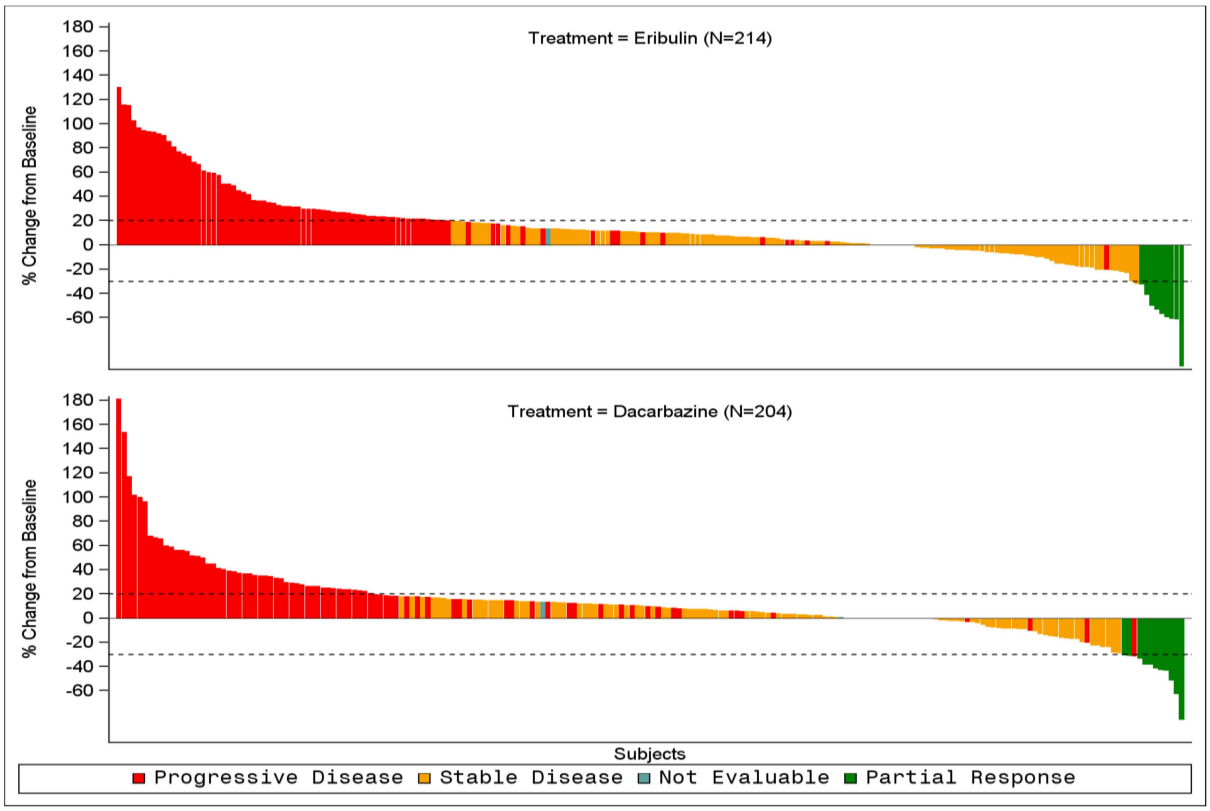


図 2.7.6.1-4　標的病変の総計和のベースラインから最小値への変化率（FAS）（外国 309 試験）

（添付資料 5.3.5.1.1 の Figure 14.2.1.3 を引用）

2.7.6.1.7 安全性の結果

本治験における有害事象の概要を表 2.7.6.1-12 に示した。

有害事象は本薬群で 99.1%（224/226 例），ダカルバジン群で 97.3%（218/224 例）に認められ，治験薬との因果関係が否定できない有害事象（副作用）は本薬群で 92.9%（210/226 例），ダカルバジン群で 90.6%（203/224 例）に認められた。発現率が 10%以上（いずれかの群で全 Grade の発現率が 10%以上）の有害事象を表 2.7.6.1-13 に示した。

投与期間中又は追跡期間中（治験薬最終投与 30 日後まで）の有害事象による死亡は本薬群で 4.4%（10/226 例），ダカルバジン群で 1.3%（3/224 例）に認められ，死亡に至った有害事象は本薬群で呼吸不全（2 例），腸閉塞，大腸穿孔，全身健康状態低下，好中球減少性敗血症，敗血症性ショック，肺転移，急性呼吸不全，誤嚥性肺炎（各 1 例），ダカルバジン群で心停止，全身健康状態低下，呼吸不全（各 1 例）であった。このうち，本薬群の好中球減少性敗血症（1 例）は，治験薬との因果関係が否定されなかった。

重篤な有害事象は，本薬群で 33.6%（76/226 例），ダカルバジン群で 31.7%（71/224 例）に認められ，認められた主な重篤な有害事象（いずれかの群で発現率が 3%以上）は，本薬群で好中球減少症（11 例［4.9%］），発熱（10 例［4.4%］），ダカルバジン群で血小板減少症（13 例［5.8%］），好中球減少症（10 例［4.5%］），貧血（9 例［4.0%］）であった。このうち，本薬群の好中球減少症（11 例［4.9%］），発熱（4 例［1.8%］），ダカルバジン群の血小板減少症（13 例［5.8%］），好中球減少症（10 例［4.5%］），貧血（7 例［3.1%］）は治験薬との因果関係が否定されなかった。

治験薬の投与中止に至った有害事象は，本薬群で 7.5%（17/226 例），ダカルバジン群で 4.9%（11/224 例）に認められ，当該事象（いずれかの群で発現例が 2 例以上）は，本薬群で血小板減少症，疲労（各 2 例［0.9%］），ダカルバジン群で血小板減少症（3 例［1.3%］），疲労（2 例［0.9%］）であった。このうち，本薬群及びダカルバジン群で認められた血小板減少症，疲労は，いずれも治験薬との因果関係が否定されなかった。

表 2.7.6.1-12　有害事象の概要（安全性解析対象集団）（外国 309 試験）

	本薬群 226 例	ダカルバジン群 224 例
有害事象	224 (99.1)	218 (97.3)
副作用	210 (92.9)	203 (90.6)
CTCAE Grade 3 以上の有害事象	152 (67.3)	126 (56.3)
CTCAE Grade 3 以上の副作用	123 (54.4)	90 (40.2)
重篤な有害事象	76 (33.6)	71 (31.7)
死亡	10 (4.4)	3 (1.3)
重篤な副作用	31 (13.7)	31 (13.8)
死亡	1 (0.4)	0
治験薬の用量調整に至った有害事象		
治験薬の投与中止に至った有害事象	17 (7.5)	11 (4.9)
治験薬の投与減量に至った有害事象	58 (25.7)	32 (14.3)
治験薬の投与休薬に至った有害事象	74 (32.7)	72 (32.1)
治験薬の用量調整に至った副作用		
治験薬の投与中止に至った副作用	9 (4.0)	8 (3.6)
治験薬の投与減量に至った副作用	53 (23.5)	30 (13.4)
治験薬の投与休薬に至った副作用	53 (23.5)	64 (28.6)

数字は発現例数，（ ）内は発現率（%）
副作用：治験薬との因果関係が否定できない有害事象

（添付資料 5.3.5.1.1 の Table 14.3.2.1，Table 14.3.2.2 を引用）

2.7.6.1.7.1　主な有害事象及び副作用

主な有害事象（いずれかの群で全 Grade の発現率が 10%以上）の発現例数（発現率）を表 2.7.6.1-13 に示した。また，主な治験薬との因果関係が否定できない有害事象（以下，副作用）（いずれかの群で全 Grade の発現率が 10%以上）の発現例数（発現率）を表 2.7.6.1-14 に示した。全ての有害事象及び副作用（全 Grade，Grade 3 以上）を付録 2.7.6-1 及び付録 2.7.6-2 に示した。

本薬群で発現率が 30%以上の有害事象は，好中球減少症，疲労（各 43.8%，99/226 例），悪心（40.3%，91/226 例），脱毛症（35.0%，79/226 例），便秘（31.4%，71/226 例）であった。また，本薬群で発現率が 30%以上の副作用は，好中球減少症（42.5%，96/226 例），疲労（36.7%，83/226 例），脱毛症（34.5%，78/226 例），悪心（33.2%，75/226 例）であった。

ダカルバジン群で発現率が 30%以上の有害事象は，悪心（47.3%，106/224 例），疲労（38.4%，86/224 例），貧血（30.8%，69/224 例）であった。また，ダカルバジン群で発現率が 30%以上の副作用は，悪心（45.1%，101/224 例），疲労（33.9%，76/224 例）であった。

本薬群で Grade 3 以上の有害事象は 67.3%（152/226 例）に発現し，主な Grade 3 以上の有害事象（発現率が 5%以上）は，好中球減少症（35.4%，80/226 例），白血球減少症（10.2%，23/226 例），貧血，好中球減少（各 7.1%，16/226 例）であった。

ダカルバジン群で Grade 3 以上の有害事象は 56.3%（126/224 例）に発現し，主な Grade 3 以上の有害事象（発現率が 5%以上）は，好中球減少症（15.6%，35/224 例），血小板減少症（15.2%，34/224 例），貧血（12.1%，27/224 例）であった。