

# **Dossier zur Nutzenbewertung gemäß § 35a SGB V**

*Nivolumab (Opdivo®)*

Bristol-Myers Squibb GmbH & Co. KGaA

## **Modul 4 G**

*Plattenepithelkarzinom des Kopf-Hals-Bereichs mit  
einer Progression während oder nach einer Platin-  
basierten Therapie bei Erwachsenen*

Zusatzdokument zur Nachforderung  
fehlender Unterlagen/Angaben  
(gemäß 5. Kapitel, § 17 Abs. 1 VerfO)

Stand: 27.06.2017

# Inhaltsverzeichnis

	Seite
<b>Abbildungsverzeichnis .....</b>	<b>3</b>
<b>Allgemeine Informationen zur Nachforderung fehlender Unterlagen/Angaben (gemäß 5. Kapitel, § 17 Abs. 1 Verfo) .....</b>	<b>6</b>
4.3.1.3.1 Endpunkte – CA209-141 .....	6
4.3.1.3.1.1 Endpunkt Mortalität .....	6
4.3.1.3.1.2 Endpunkte Morbidität – Krankheitsbedingte Symptome gemäß EORTC QLQ-H&N35 .....	7
4.3.1.3.1.3 Endpunkte Morbidität – Krankheitsbedingte Symptome gemäß EORTC QLQ-C30 .....	44
4.3.1.3.1.4 Endpunkte Morbidität – Gesundheitszustand gemäß EQ-5D- VAS .....	63
4.3.1.3.1.5 Endpunkte gesundheitsbezogener Lebensqualität gemäß EORTC QLQ-C30 .....	67
4.3.1.3.1.6 Endpunkte generischer Lebensqualität gemäß EQ-5D .....	80
4.3.1.3.1.7 Endpunkte Verträglichkeit .....	83
4.3.1.3.2 Subgruppenanalysen – CA209-141 .....	99
4.3.1.3.2.1 Subgruppenanalysen für Endpunkt Mortalität – Gesamtüberleben (OS) .....	99
4.3.1.3.2.2 Subgruppenanalysen für Endpunkte Verträglichkeit .....	102

**Abbildungsverzeichnis**

	<b>Seite</b>
Abbildung 1: Kaplan-Meier-Kurven der Endpunkte Morbidität (Krankheitsbedingte Symptome gemäß EORTC QLQ-H&N35) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	25
Abbildung 2: Kaplan-Meier-Kurven der Endpunkte Morbidität (Krankheitsbedingte Symptome gemäß EORTC QLQ-H&N35) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	43
Abbildung 3: Kaplan-Meier-Kurven der Endpunkte Morbidität (Krankheitsbedingte Symptome gemäß EORTC QLQ-C30) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	53
Abbildung 4: Kaplan-Meier-Kurven der Endpunkte Morbidität (Krankheitsbedingte Symptome gemäß EORTC QLQ-C30) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	62
Abbildung 5: Kaplan-Meier-Kurven des Endpunkts Gesundheitszustand gemäß EQ-5D-VAS aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	64
Abbildung 6: Kaplan-Meier-Kurven des Endpunkts Gesundheitszustand gemäß EQ-5D-VAS aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016).....	66
Abbildung 7: Kaplan-Meier-Kurven der Endpunkte gesundheitsbezogener Lebensqualität gemäß EORTC QLQ-C30 aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016).....	73
Abbildung 8: Kaplan-Meier-Kurven der Endpunkte gesundheitsbezogener Lebensqualität gemäß EORTC QLQ-C30 aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016).....	79
Abbildung 9: Kaplan-Meier-Kurve des Endpunkts generischer Lebensqualität gemäß EQ-5D-Index-Wert aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016).....	81
Abbildung 10: Kaplan-Meier-Kurve des Endpunkts generischer Lebensqualität gemäß EQ-5D-Index-Wert aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016).....	82
Abbildung 11: Kaplan-Meier-Kurve des Endpunkts jegliches UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	83
Abbildung 12: Kaplan-Meier-Kurve des Endpunkts UE Grad 3-4 ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	84
Abbildung 13: Kaplan-Meier-Kurve des Endpunkts schwerwiegende UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	85
Abbildung 14: Kaplan-Meier-Kurve des Endpunkts Therapieabbruch wegen UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	86

Abbildung 15: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts jegliches UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	87
Abbildung 16: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts UE Grad 3-4 (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	88
Abbildung 17: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts schwerwiegende UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	89
Abbildung 18: Sensitivitätsanalyse:Kaplan-Meier-Kurve des Endpunkts Therapieabbruch wegen UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016) .....	90
Abbildung 19: Kaplan-Meier-Kurve des Endpunkts jegliches UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	91
Abbildung 20: Kaplan-Meier-Kurve des Endpunkts UE Grad 3-4 ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	92
Abbildung 21: Kaplan-Meier-Kurve des Endpunkts schwerwiegende UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	93
Abbildung 22: Kaplan-Meier-Kurve des Endpunkts Therapieabbruch wegen UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	94
Abbildung 23: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts jegliches UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	95
Abbildung 24: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts UE Grad 3-4 (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	96
Abbildung 25: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts schwerwiegende UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	97
Abbildung 26: Sensitivitätsanalyse:Kaplan-Meier-Kurve des Endpunkts Therapieabbruch wegen UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016).....	98
Abbildung 27: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt Gesamtüberleben (OS) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016).....	100
Abbildung 28: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt Gesamtüberleben (OS) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016).....	102

Abbildung 29: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt jegliches UE aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	109
Abbildung 30: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt UE Grad 3-4 aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016).....	111
Abbildung 31: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt UE Grad 3-4 aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	114
Abbildung 32: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt SUE aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016).....	116
Abbildung 33: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt SUE aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016) .....	118

**Allgemeine Informationen zur Nachforderung fehlender Unterlagen/Angaben (gemäß 5. Kapitel, § 17 Abs. 1 VerfO)**

Bei der Überprüfung der formalen Vollständigkeit der von Bristol-Myers Squibb am 26. Mai 2017 eingereichten Dossierunterlagen für den Wirkstoff Nivolumab (Opdivo®) wurde vom Gemeinsamen Bundesausschuss (G-BA) festgestellt, dass nicht alle nach 5. Kapitel, § 9 der Verfahrensordnung (VerfO) des G-BA vorzulegenden Unterlagen für den Wirkstoff Nivolumab (Dossier-Nr. 2017-06-01-D-291) eingereicht wurden.

Fehlende Angaben in den Modulen 1 bis 4 müssen separat in Form entsprechender Texte, Abbildungen oder Tabellen, bei mehreren Angaben zusammengefasst in einem Dokument, nachgereicht werden. Dieses Dokument wird als Ergänzung zu den eingereichten Dossierunterlagen in das Verfahren einbezogen und im Internet als Bestandteil des Dossiers veröffentlicht. Für eine eindeutige Zuordnung soll für jede Angabe das betroffene Modul benannt, sowie die Benennung der jeweiligen Abschnitte, Abbildungen oder Tabellen aus der Dossievorlage verwendet werden.

Nachfolgend wird für Modul 4 G für den 2. Datenschnitt vom 20.09.2016 jeweils für die Gesamt- und die MTX-Teilpopulation Folgendes ergänzt:

- Fehlende Kaplan-Meier-Kurven für alle Endpunkte mit Überlebenszeitanalysen
- Kaplan-Meier-Kurven für die dargestellten Subgruppenanalysen, für die sich ein Beleg für eine Interaktion zeigte

**4.3.1.3.1 Endpunkte – CA209-141****4.3.1.3.1.1 Endpunkt Mortalität**

Siehe Abschnitt 4.3.1.3.1.1 des Moduls 4 G

#### **4.3.1.3.1.2 Endpunkte Morbidität – Krankheitsbedingte Symptome gemäß EORTC QLQ-H&N35**

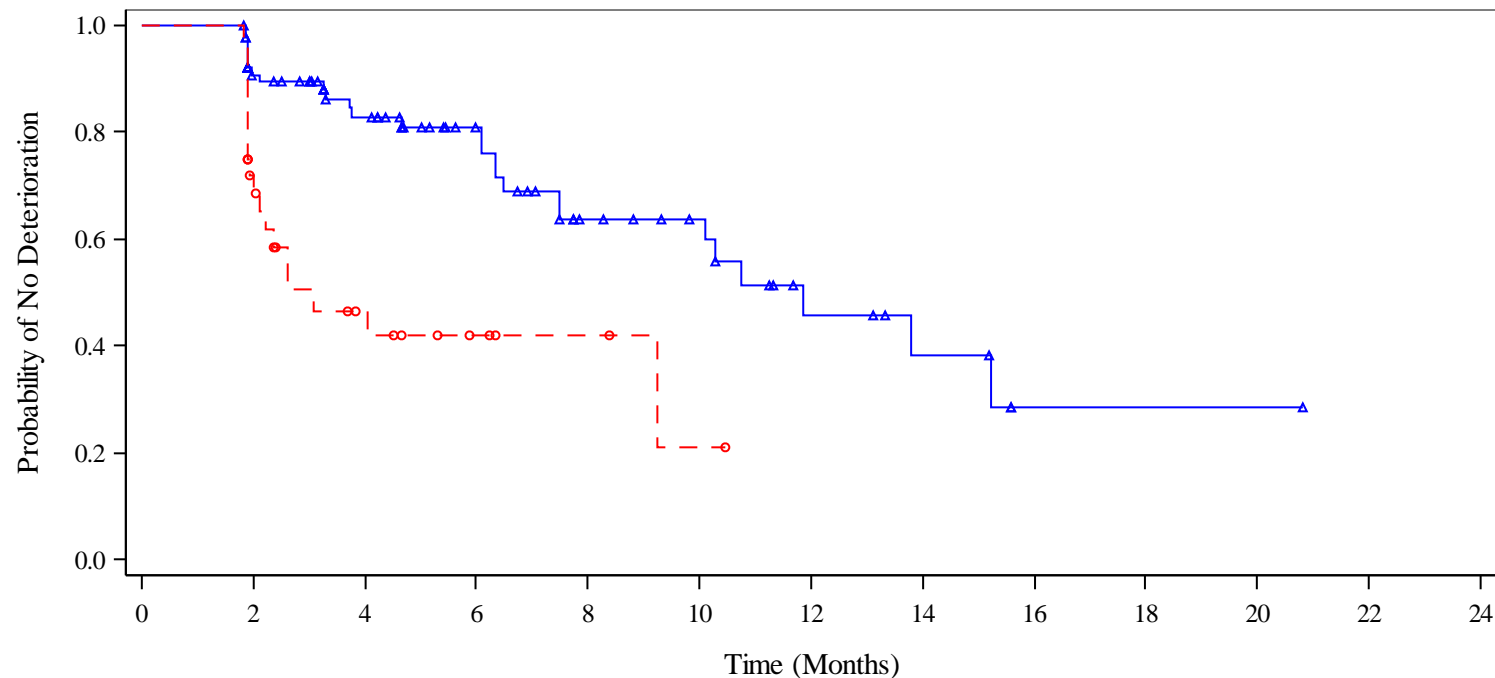
##### Ergänzung der Kaplan-Meier-Kurven

Nachfolgend werden die Kaplan-Meier-Kurven für die Skalen des EORTC QLQ-H&N35 jeweils für die Gesamtpopulation und die MTX-Teilpopulation dargestellt:

Schmerzen, Schluckbeschwerden, Geruchs-/Geschmacksstörungen, Sprachstörungen, Essen in Gesellschaft, Sozialkontakte, Sexualverhalten, Zahnprobleme, Probleme beim Mundöffnen, Mundtrockenheit, klebriger Speichel, Husten, Krankheitsgefühl, Schmerzmitteleinnahme, Nahrungsergänzungs-mitteleinnahme, Ernährungssondeneinsatz, Gewichtsverlust, Gewichtszunahme

**Gesamtpopulation**

Figure 4.2.1: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Pain



—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

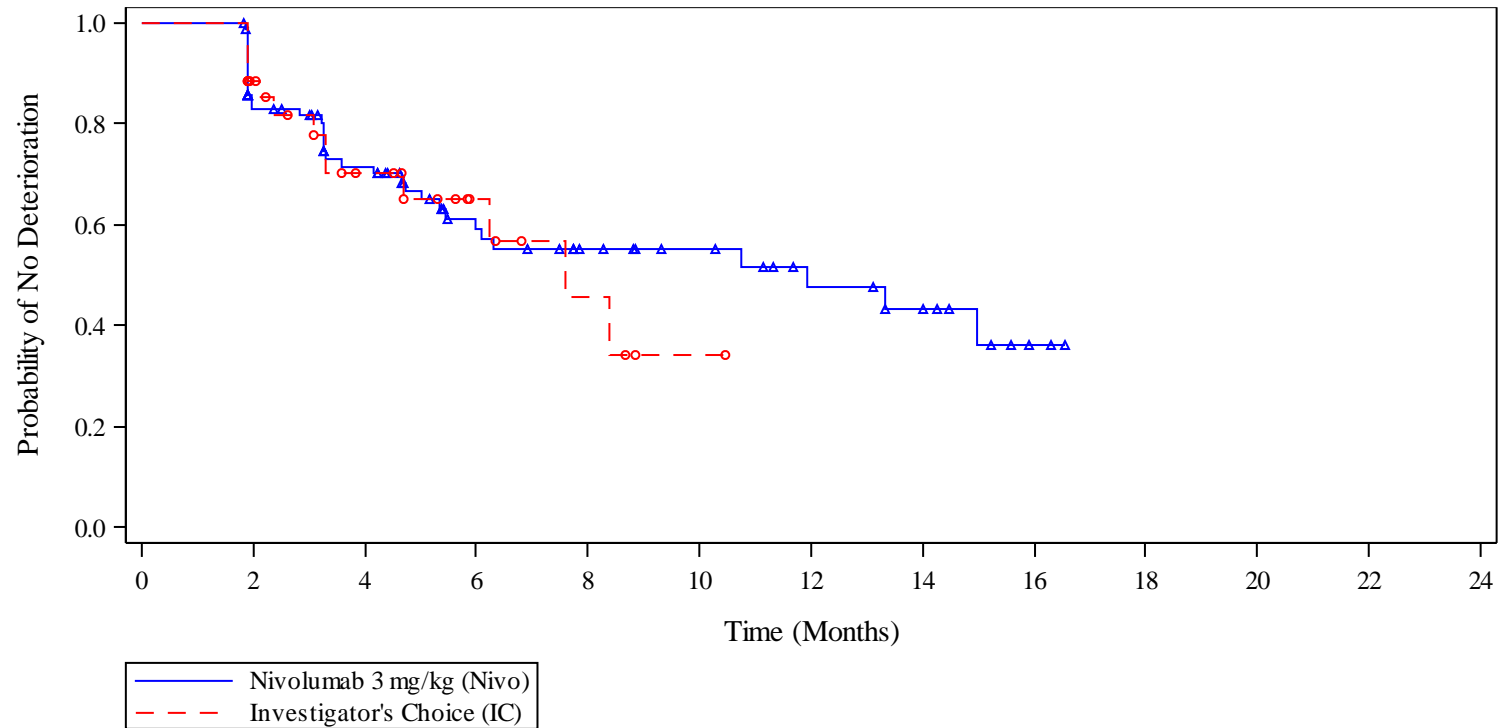
Number of Subjects at Risk

Nivo	92	66	49	35	20	16	8	5	1	1	1	0
IC	36	22	10	5	3	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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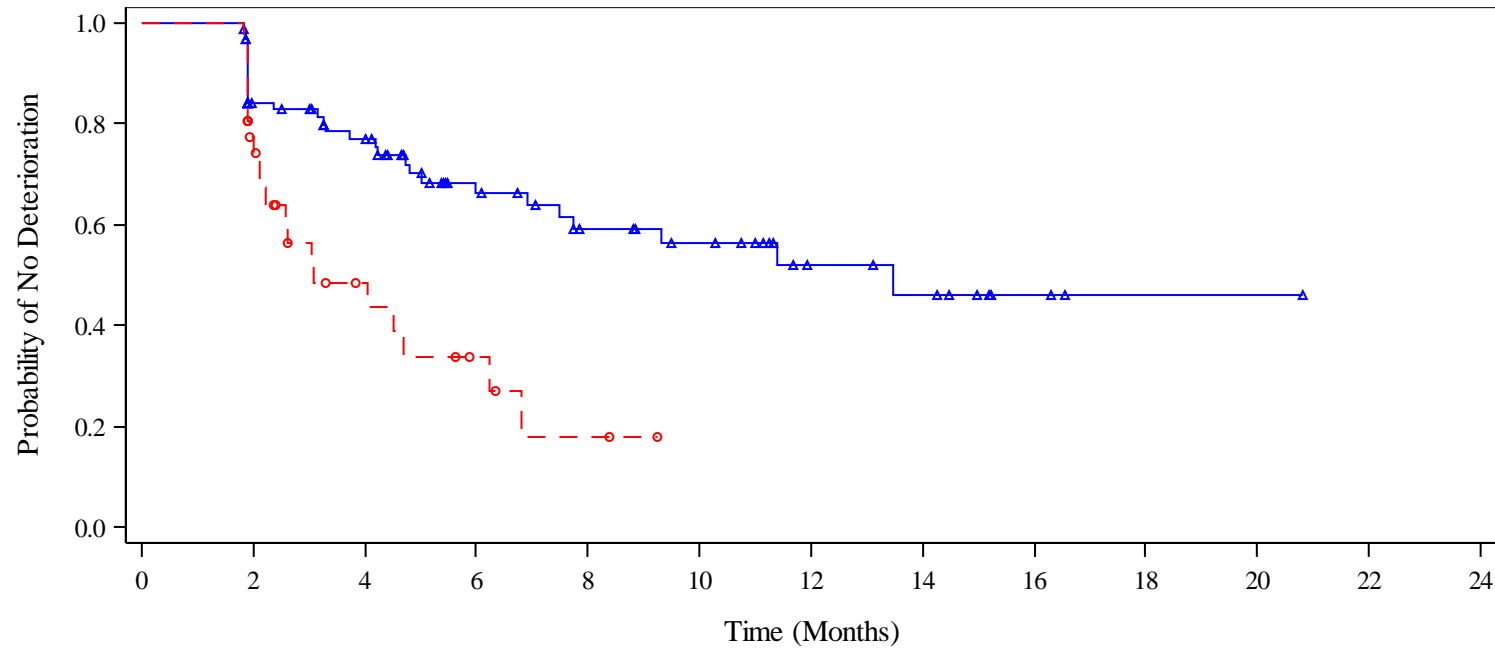
**Figure 4.2.2: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Swallowing**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo	92	64	48	30	22	18	12	9	2	0	
IC	35	27	16	8	4	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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**Figure 4.2.3: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Sense Problems**



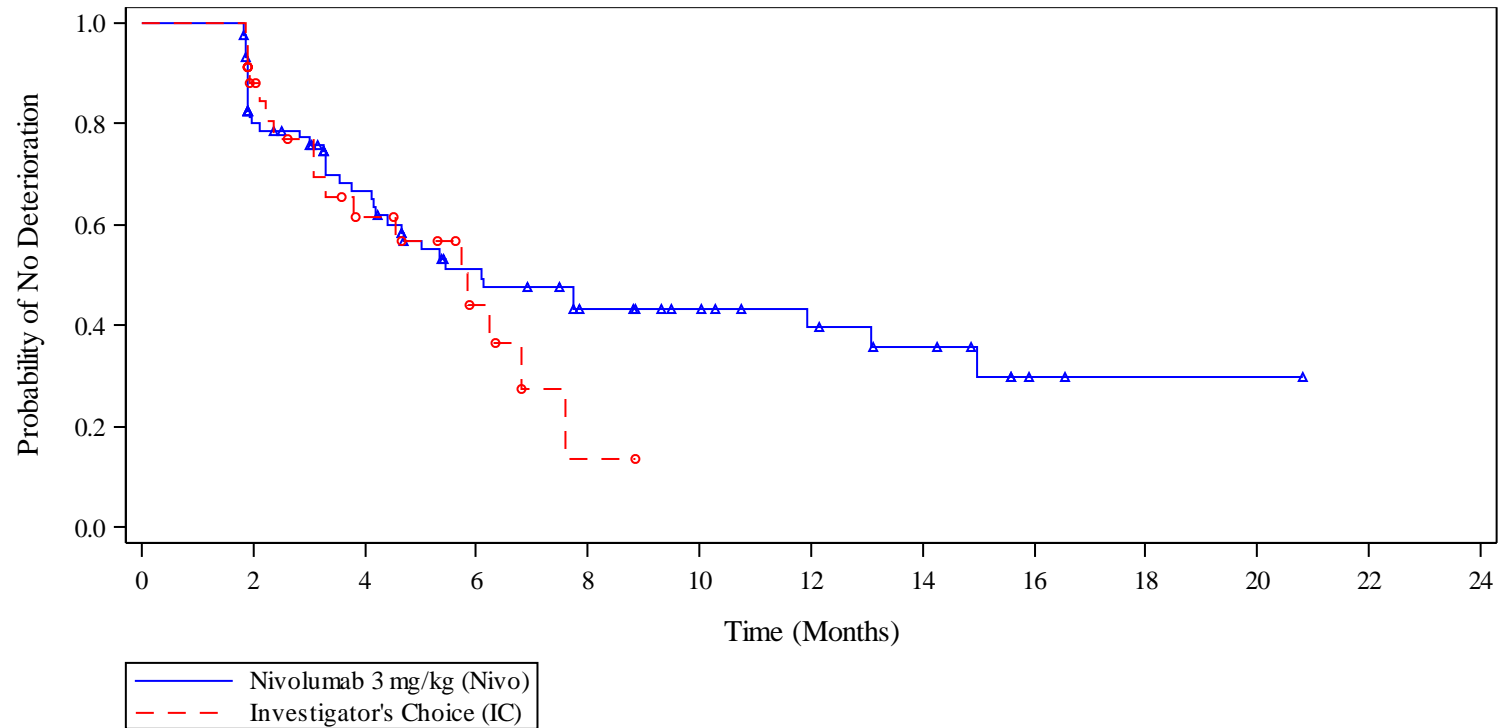
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	91	62	51	32	23	19	10	8	3	1	1	0
IC	36	24	10	5	2	0						

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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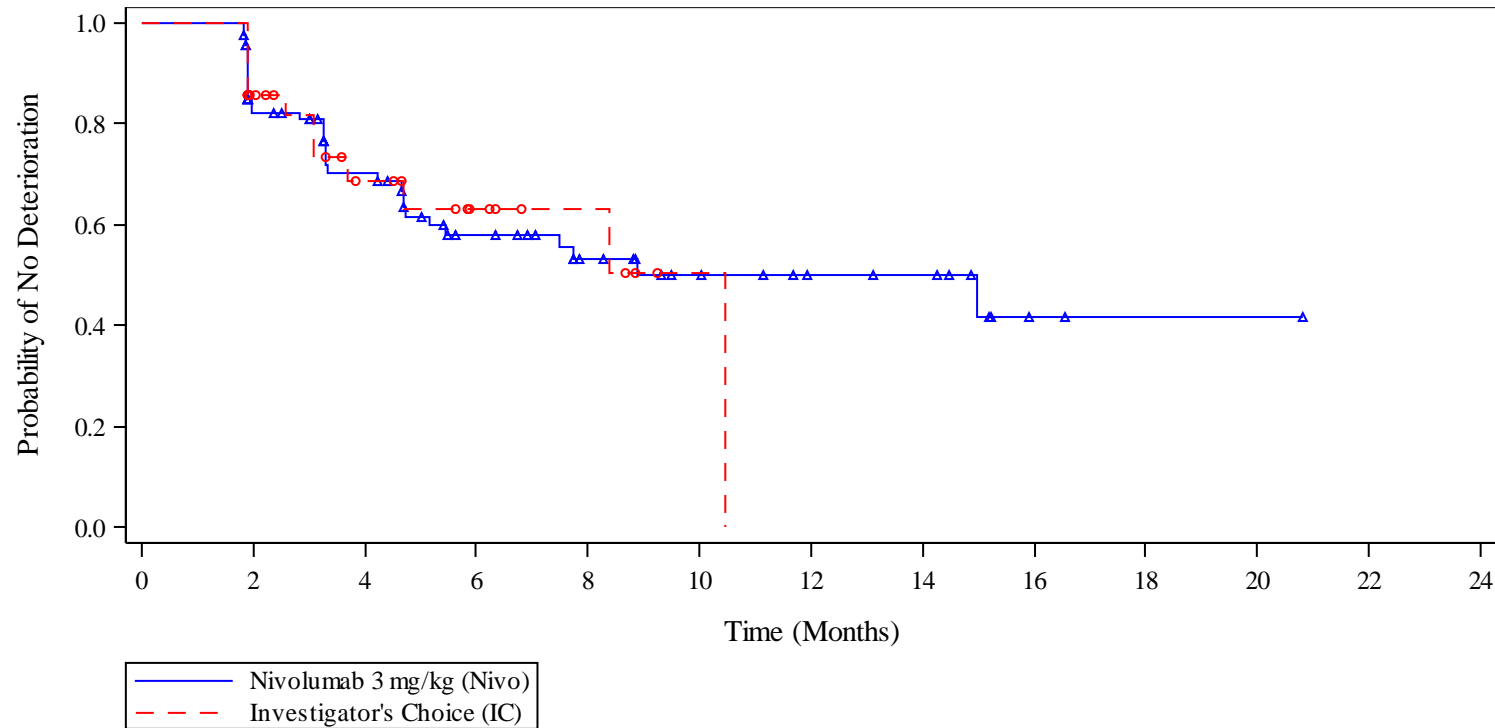
**Figure 4.2.4: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Speech Problems**



		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	88	60	42	27	19	15	11	8	2	1	1	1	0	
IC	35	25	14	6	1	0								

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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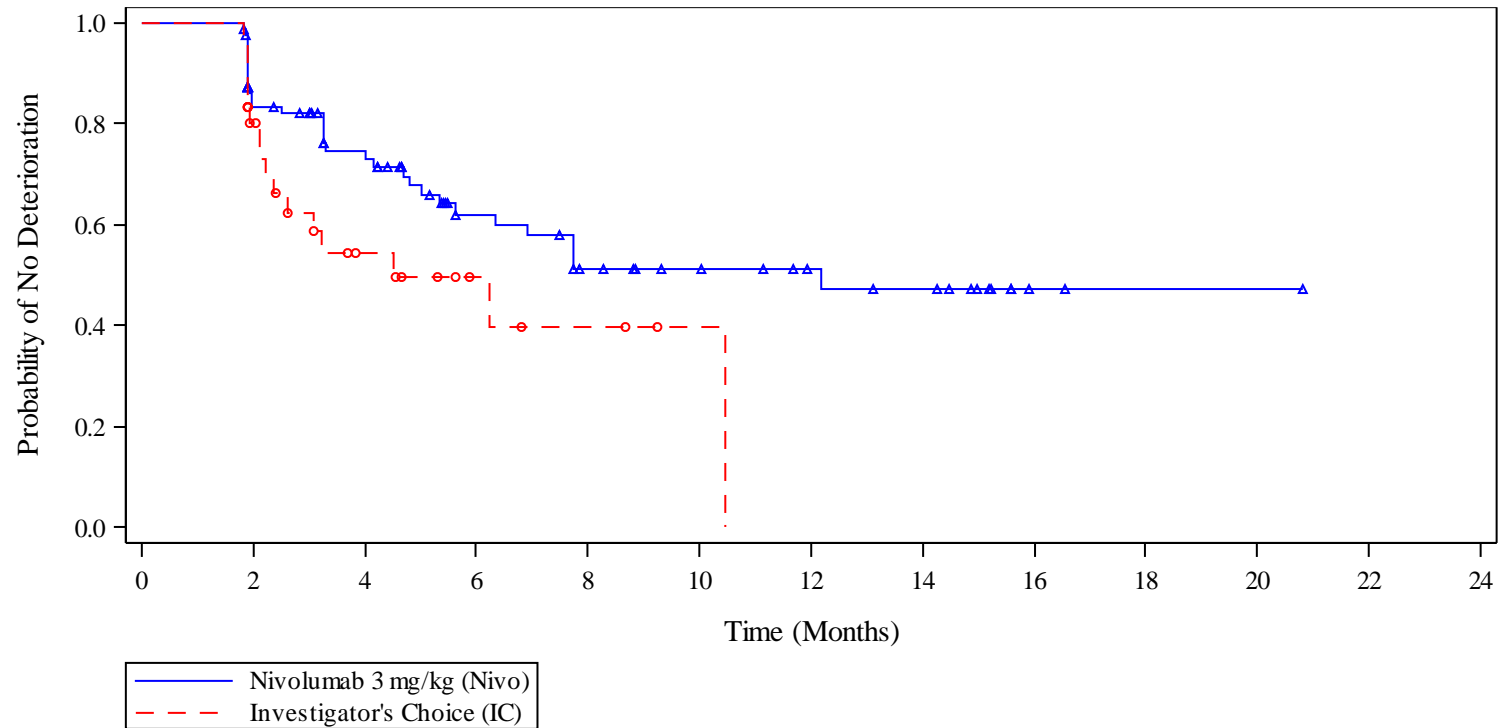
**Figure 4.2.5: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Trouble with Social Eating**



	Number of Subjects at Risk											
	0	2	4	6	8	10	12	14	16	18	20	21
Nivo	89	61	44	29	20	14	10	9	2	1	1	0
IC	35	24	14	8	5	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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**Figure 4.2.6: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Trouble with Social Contact**

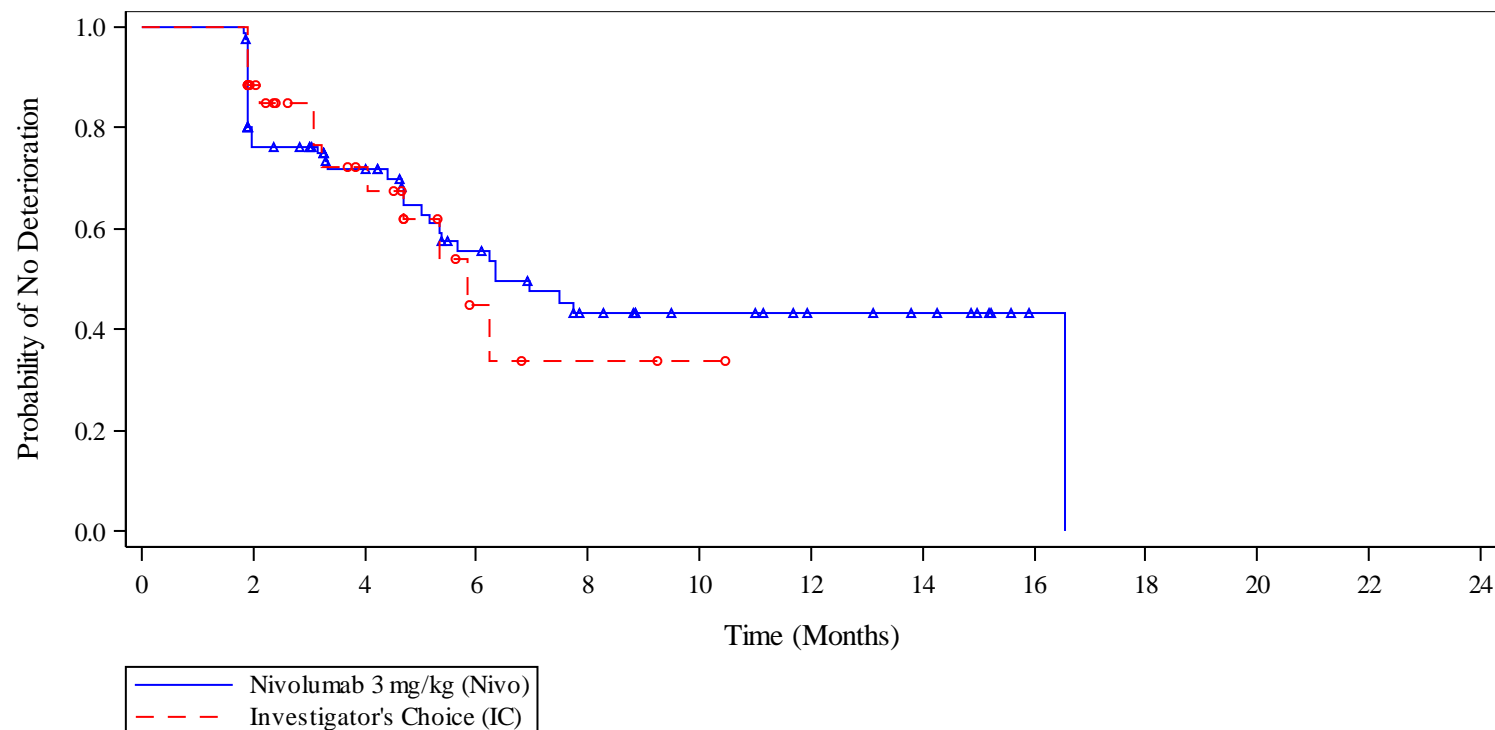


Number of Subjects at Risk

Nivo	89	62	48	29	21	17	13	11	2	1	1	0
IC	36	24	11	5	3	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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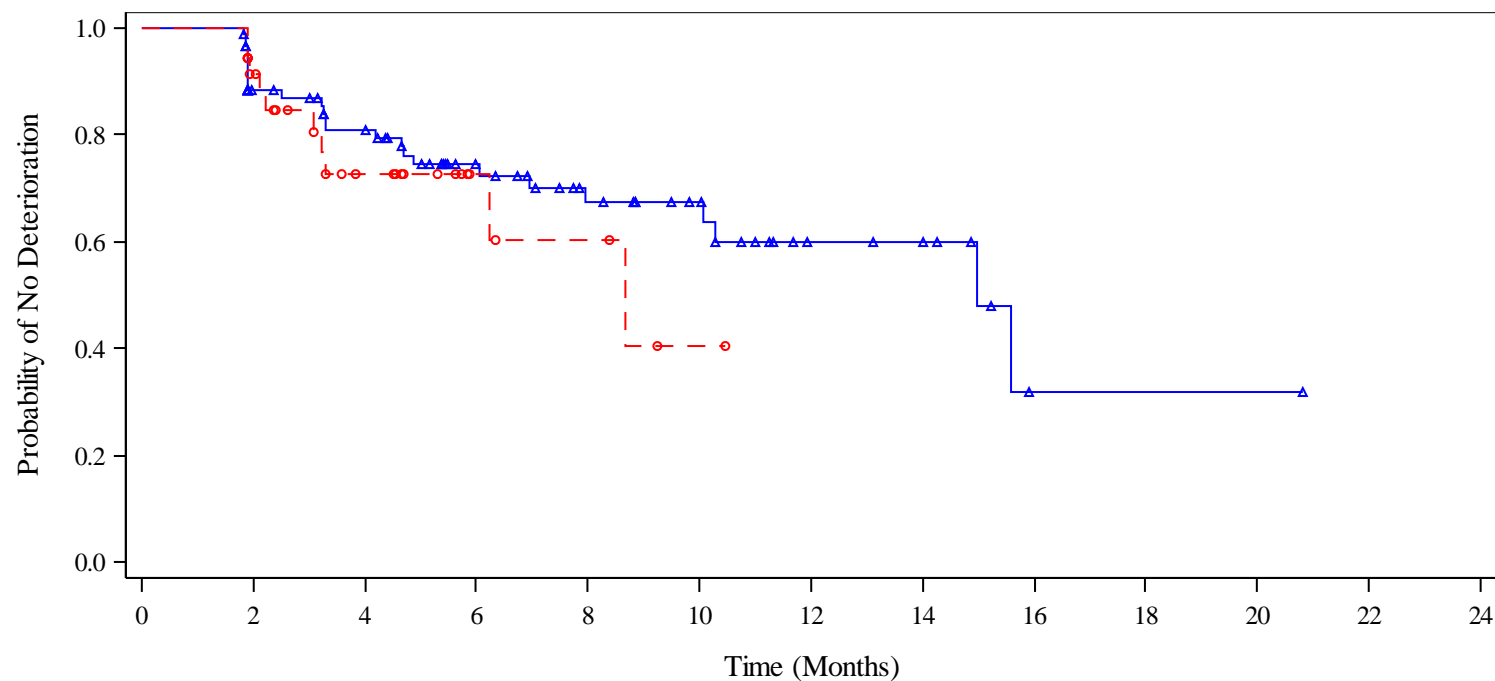
**Figure 4.2.7: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Less Sexuality**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		87	58	45	29	19	14	10	8	1	0
IC		35	26	15	4	2	1	0			

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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Figure 4.2.8: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Teeth



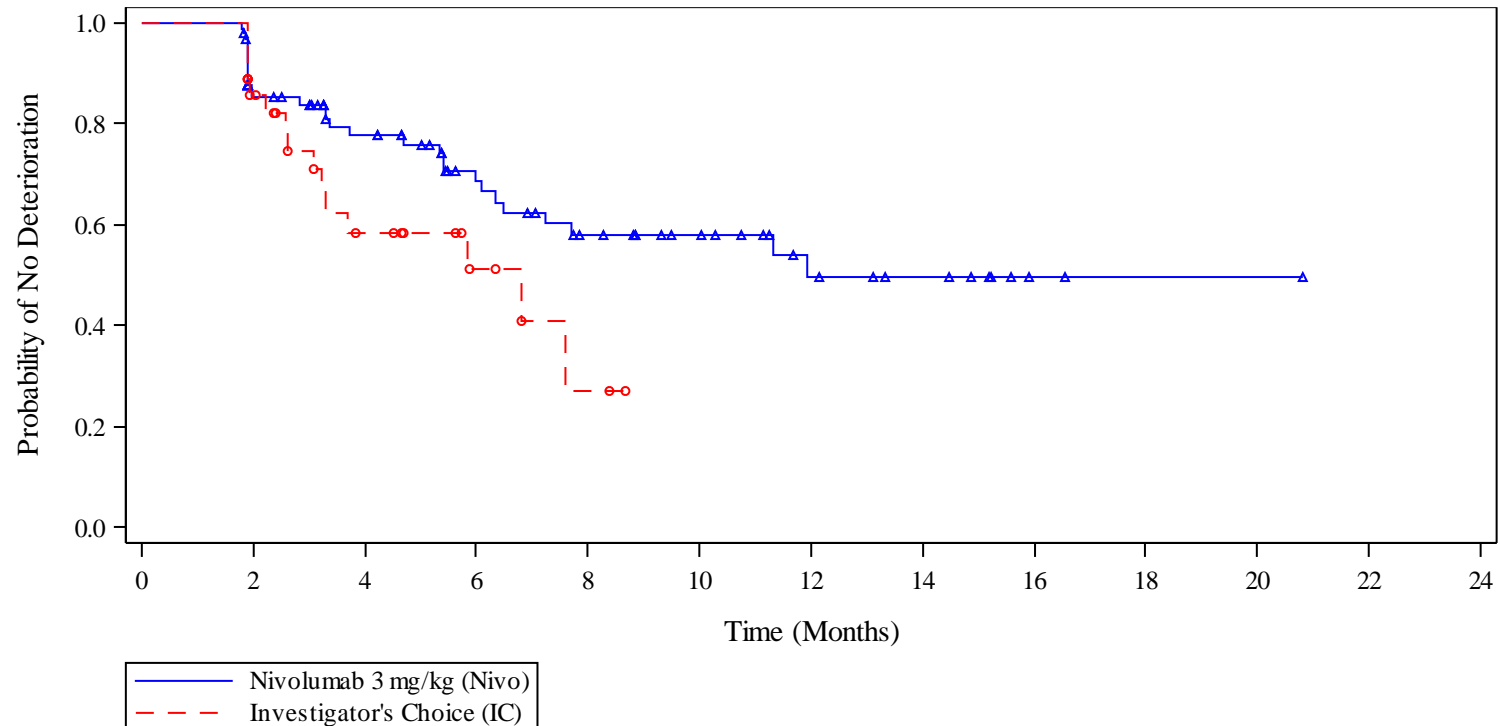
— Nivolumab 3 mg/kg (Nivo)  
 - - - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	89	63	53	36	25	19	9	8	1	1	1	0
IC	36	28	15	6	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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Figure 4.2.9: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Opening Mouth

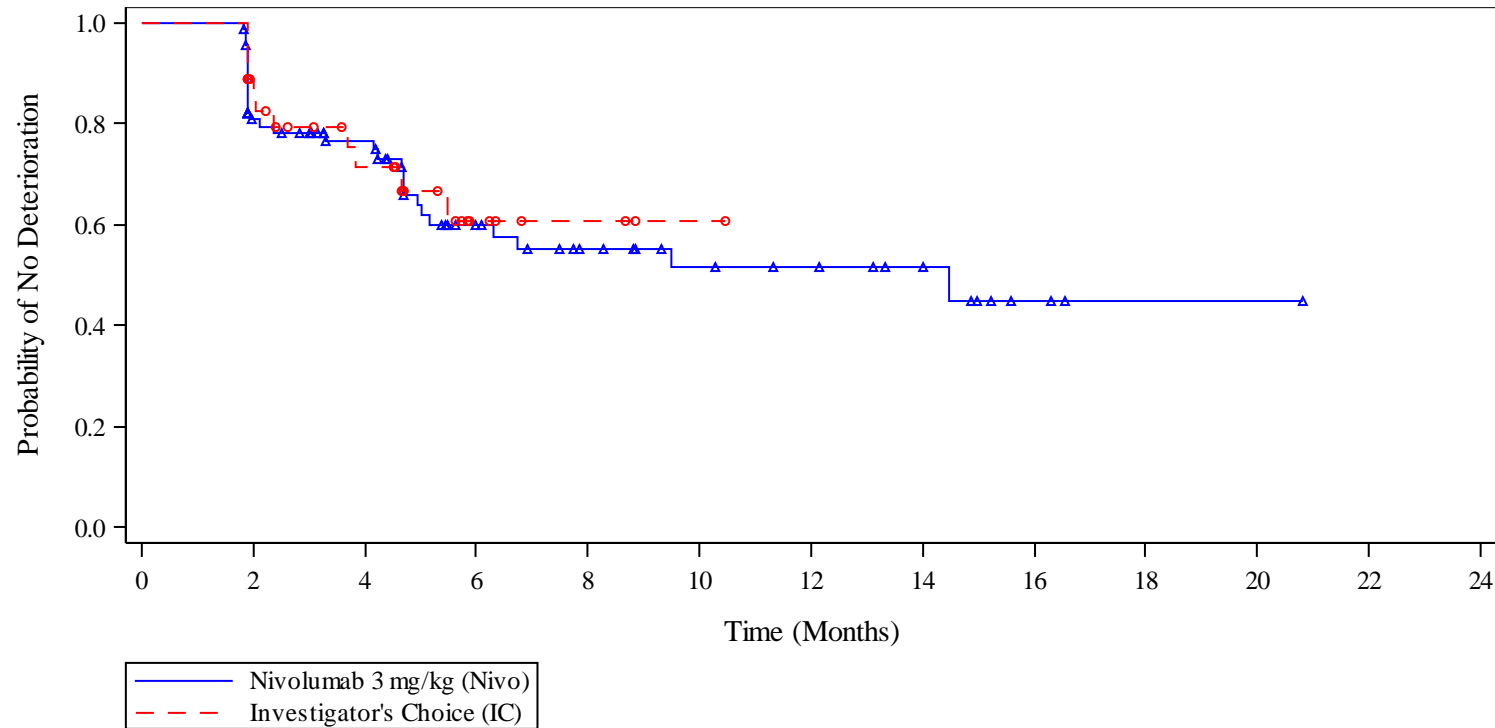


		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	92	65	50	35	25	19	11	8	2	1	1	0		
IC	36	26	13	6	2	0								

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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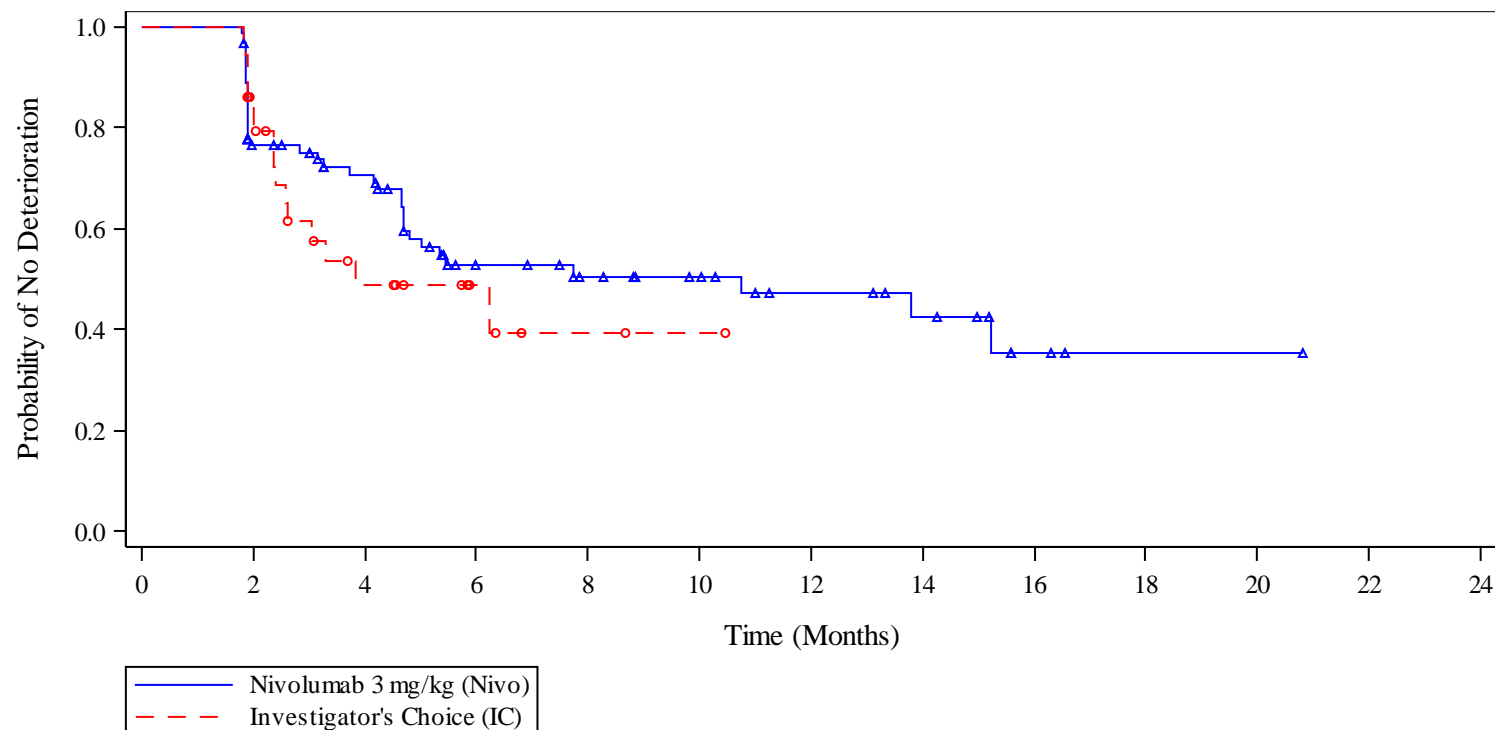
Figure 4.2.10: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Dry Mouth



		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo		92	59	46	27	19	14	12	9	3	1	1	0	
IC		36	28	18	6	3	1	0						

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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**Figure 4.2.11: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Sticky Saliva**

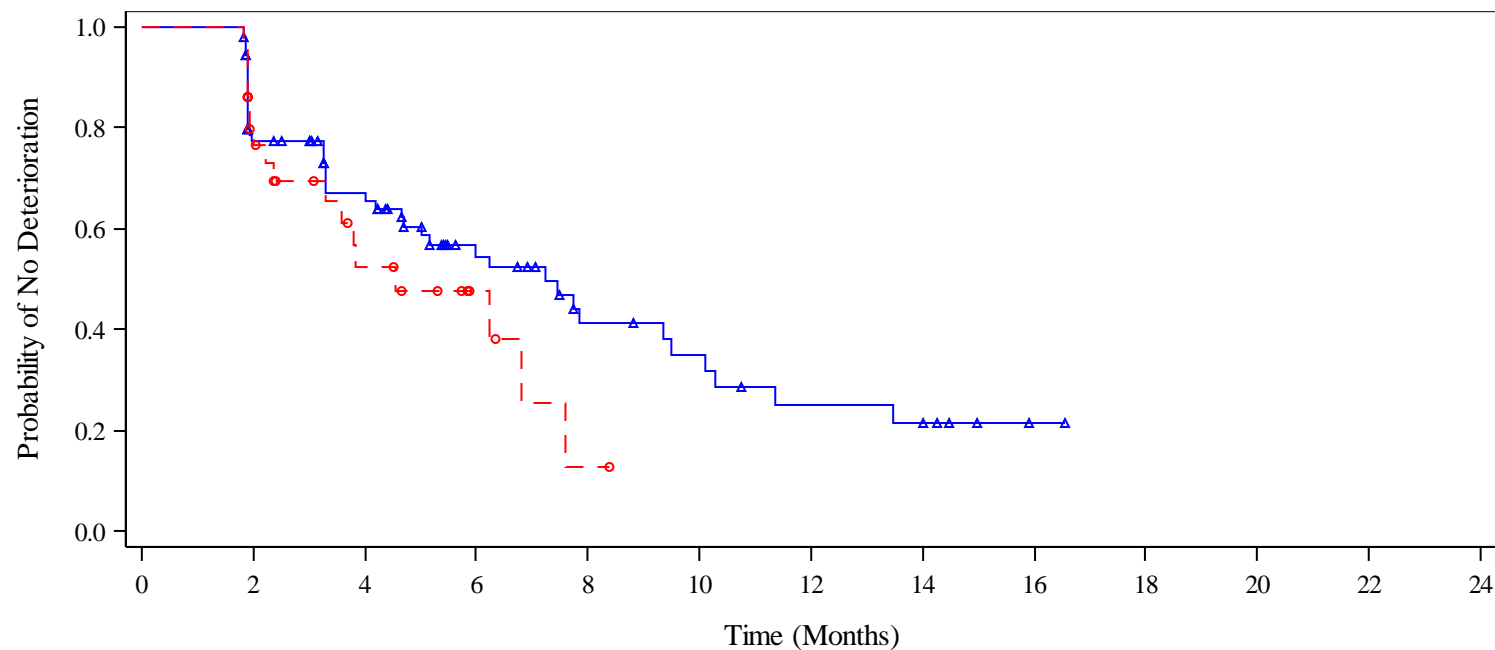


Number of Subjects at Risk

Nivo	91	58	47	27	21	17	12	9	3	1	1	0
IC	36	26	11	5	2	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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Figure 4.2.12: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Coughing



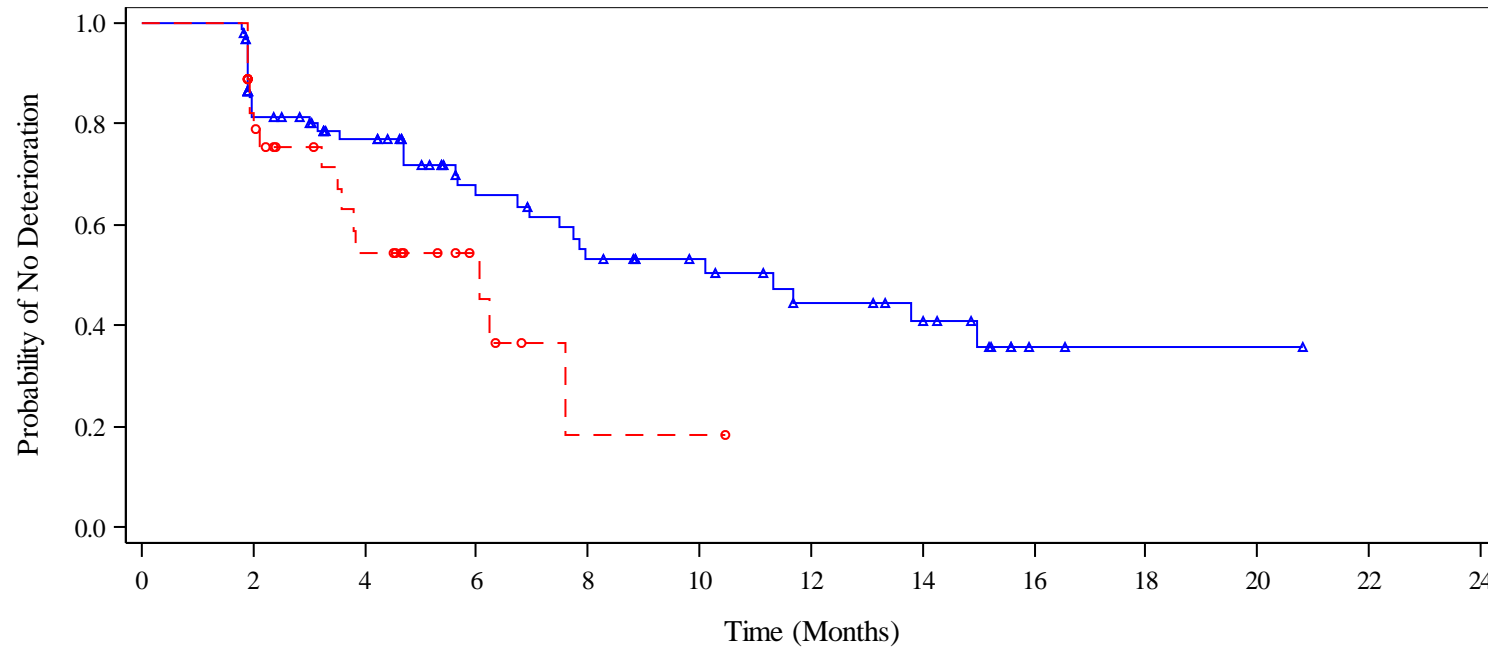
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	92	60	44	25	14	11	7	6	1	0
IC	36	24	12	5	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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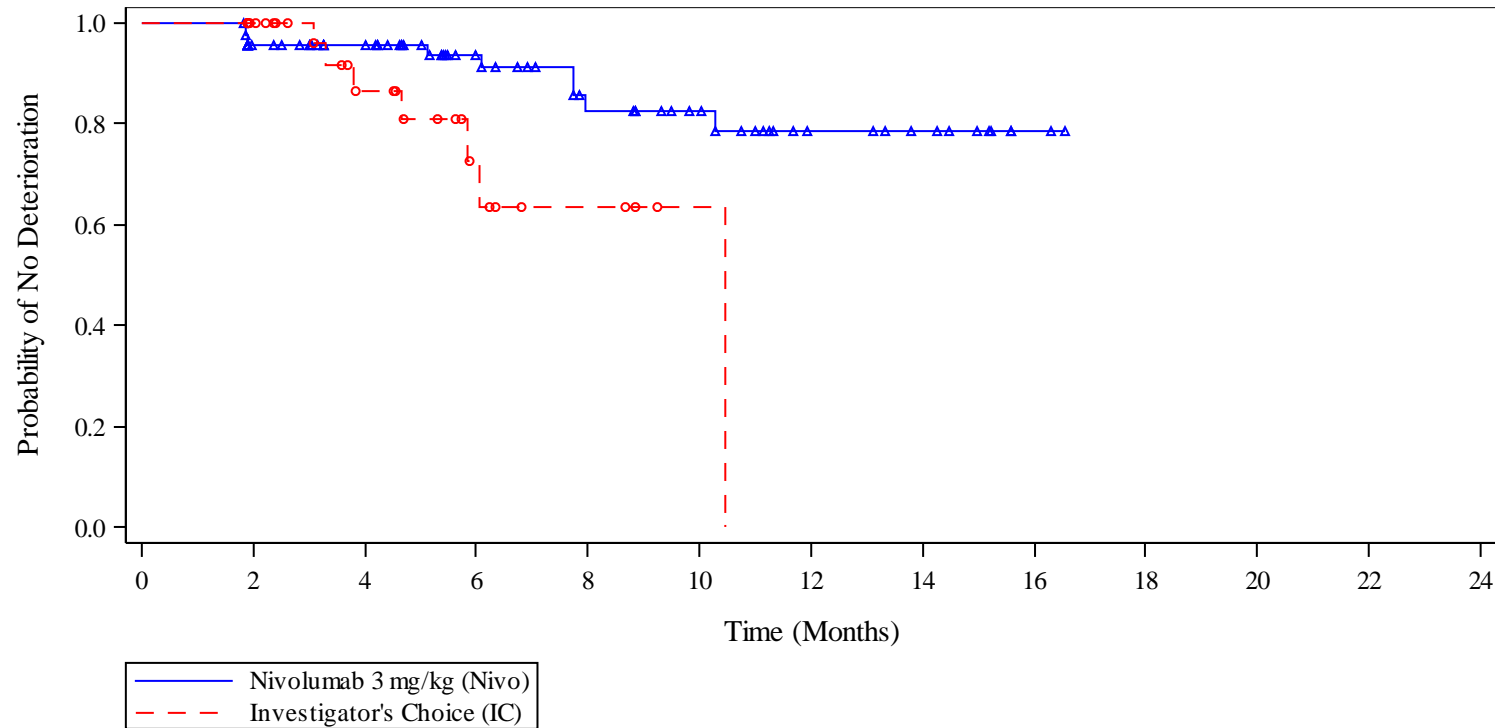
Figure 4.2.13: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Felt  
 111



	0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	92	63	50	33	25	20	14	11	2	1	1	0	
IC	36	25	13	6	1	1	0						

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
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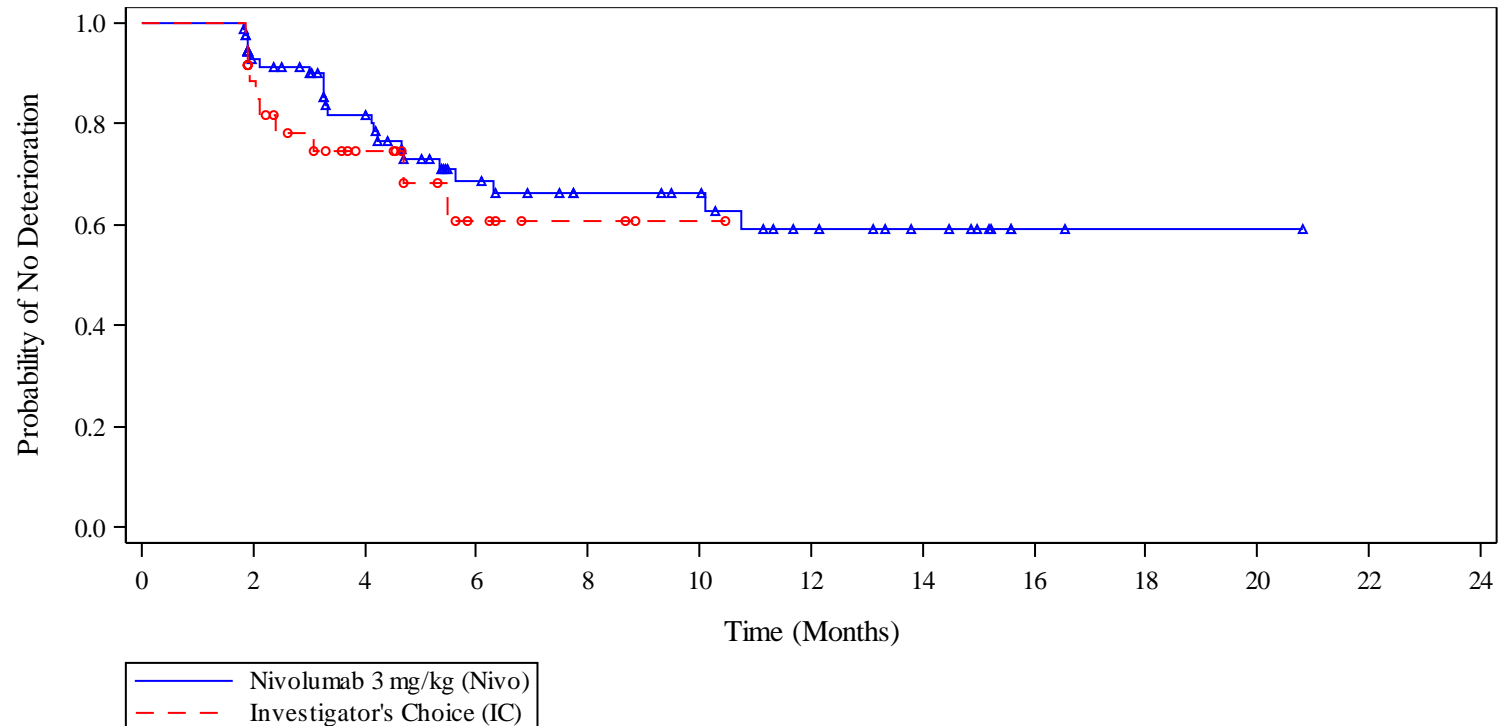
Figure 4.2.14: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Pain Killers



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		90	69	58	40	28	22	12	9	2	0
IC		36	29	17	8	4	1	0			

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

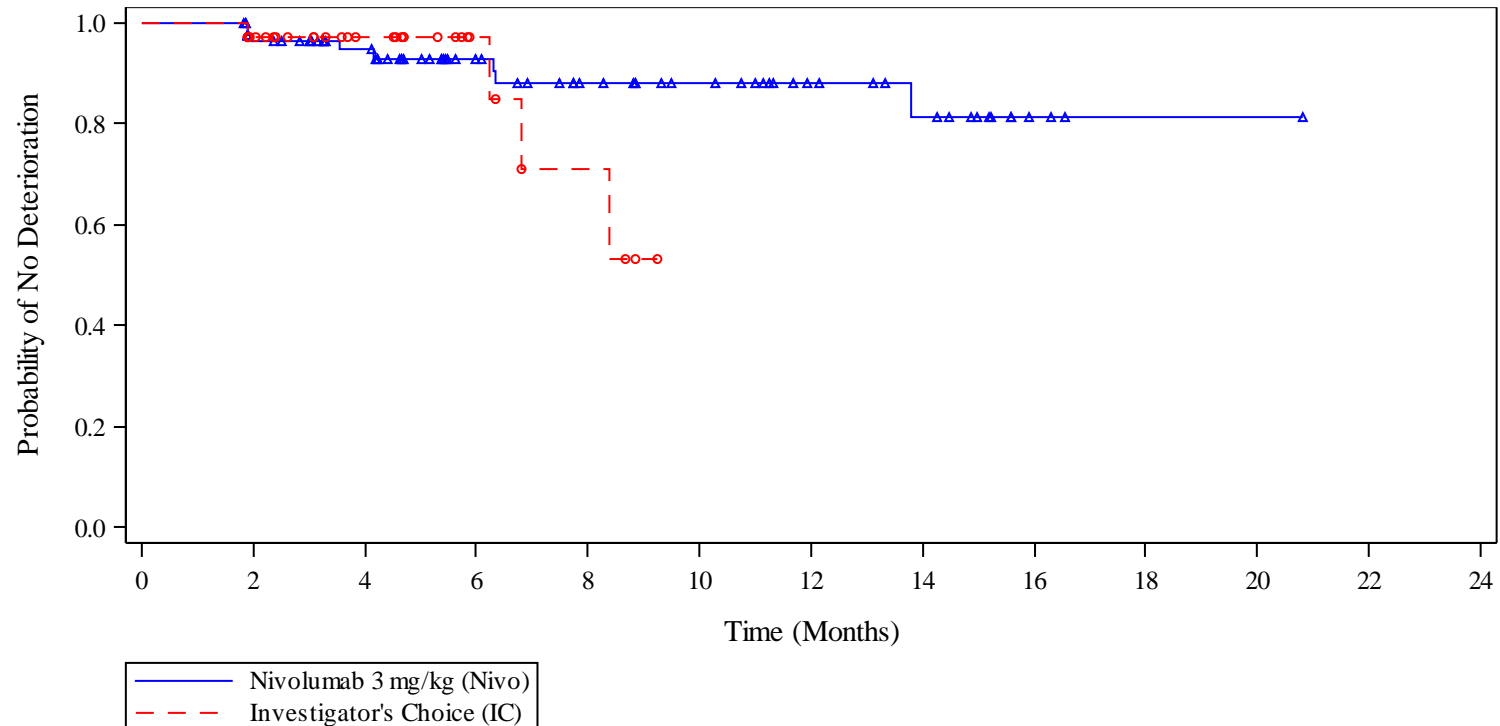
**Figure 4.2.15: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Nutritional Supplements**



		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	89	65	49	29	22	20	13	9	2	1	1	0		
IC	36	27	15	6	3	1	0							

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

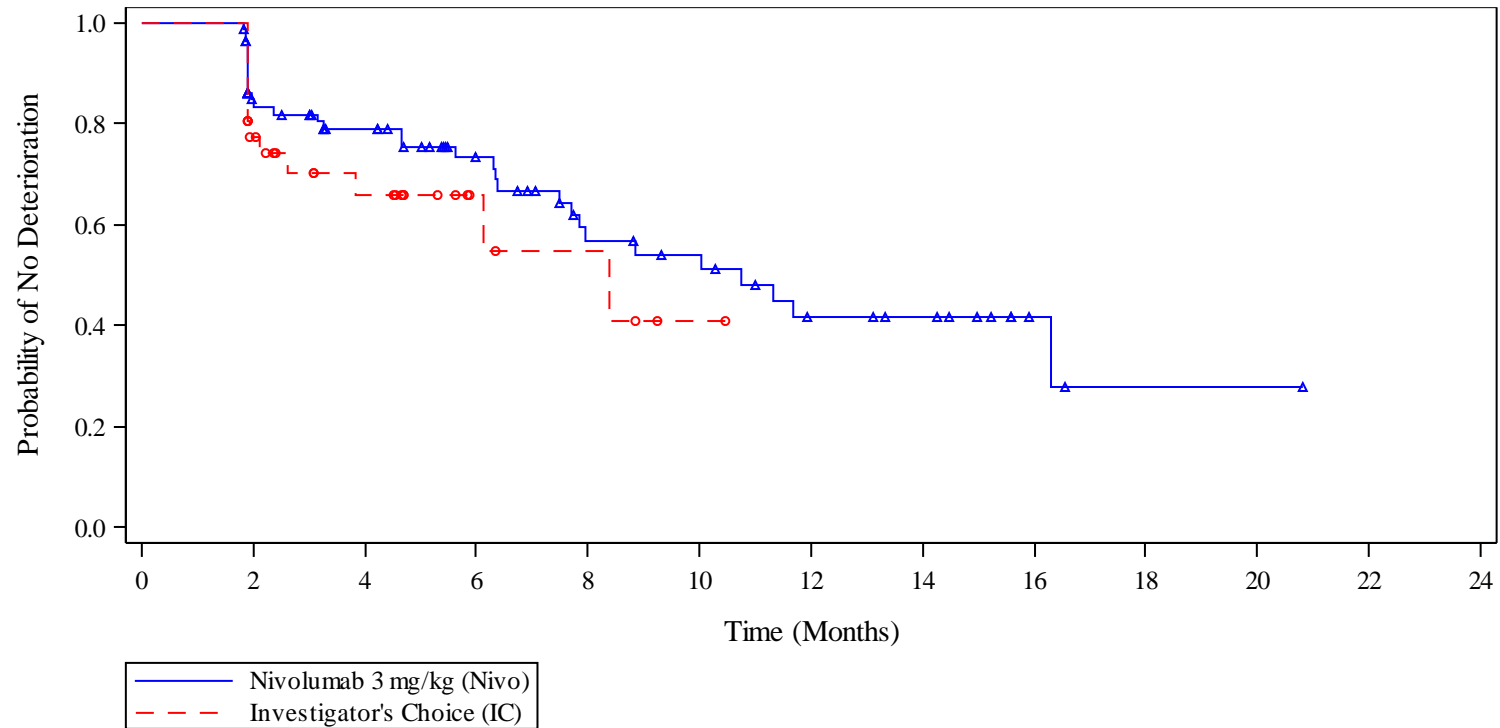
**Figure 4.2.16: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Feeding Tube**



		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	90	71	58	40	30	24	16	12	3	1	1	0		
IC	36	29	18	8	4	0								

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

**Figure 4.2.17: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Weight Loss**

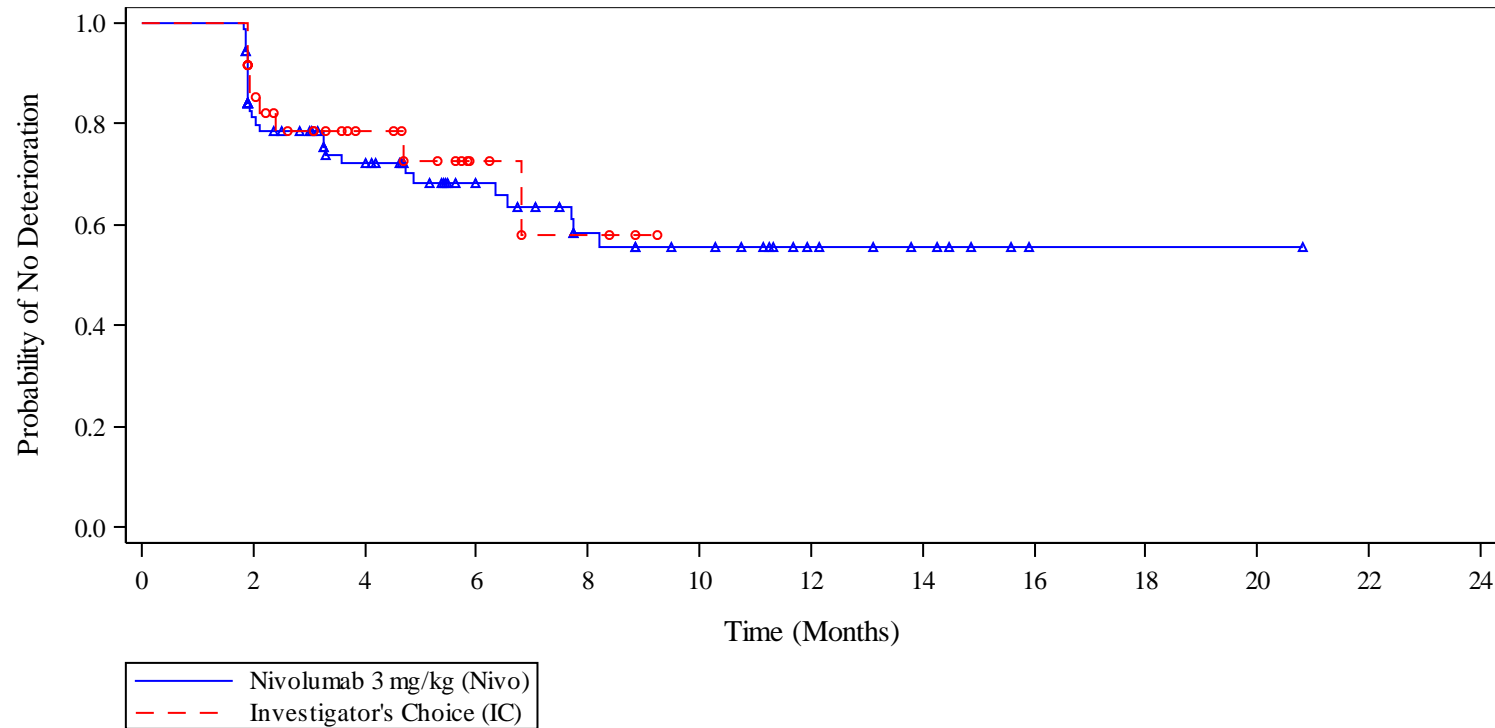


		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	89	60	48	35	22	19	12	10	3	1	1	0		
IC	36	24	15	6	4	1	0							

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe



**Figure 4.2.18: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Weight Gain**



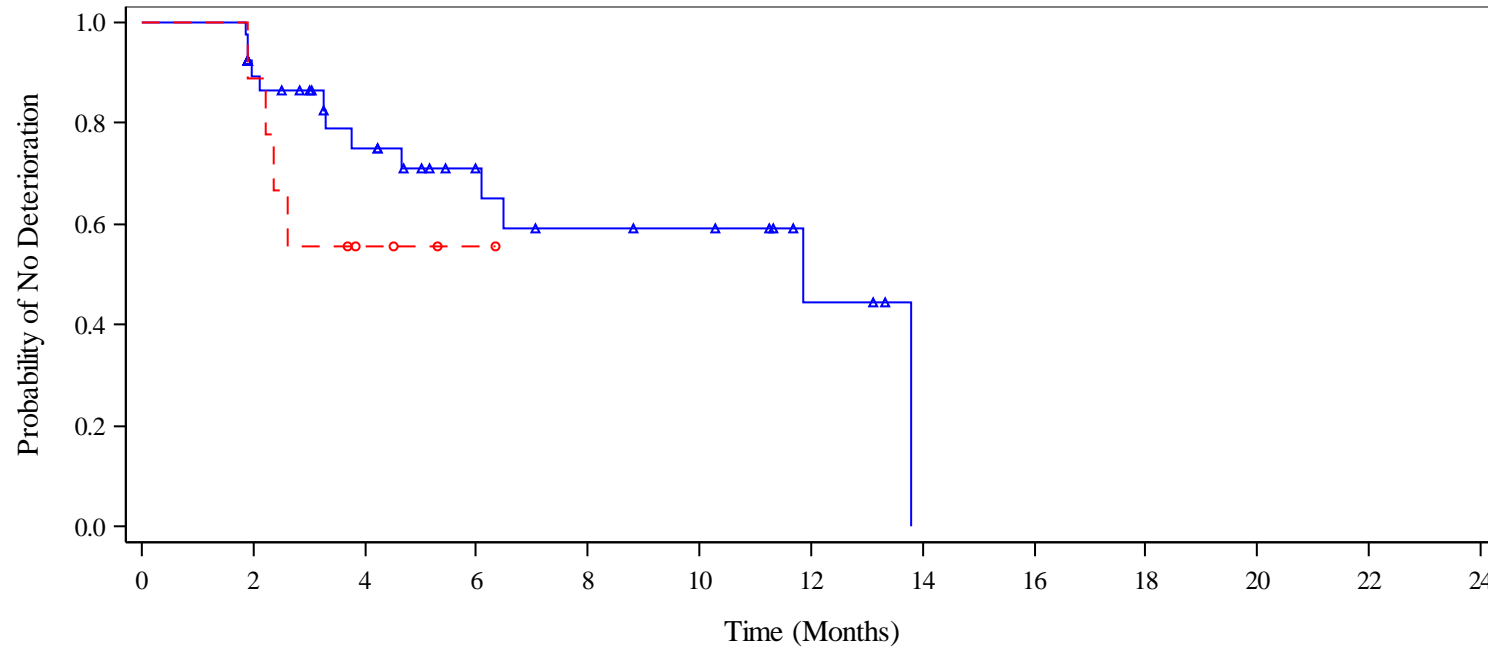
		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	89	59	44	30	20	16	9	6	1	1	1	0		
IC	36	27	15	6	3	0								

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Abbildung 1: Kaplan-Meier-Kurven der Endpunkte Morbidität (Krankheitsbedingte Symptome gemäß EORTC QLQ-H&N35) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

**MTX-Teilpopulation**

**Figure 4.2.1: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Pain (MTX)**



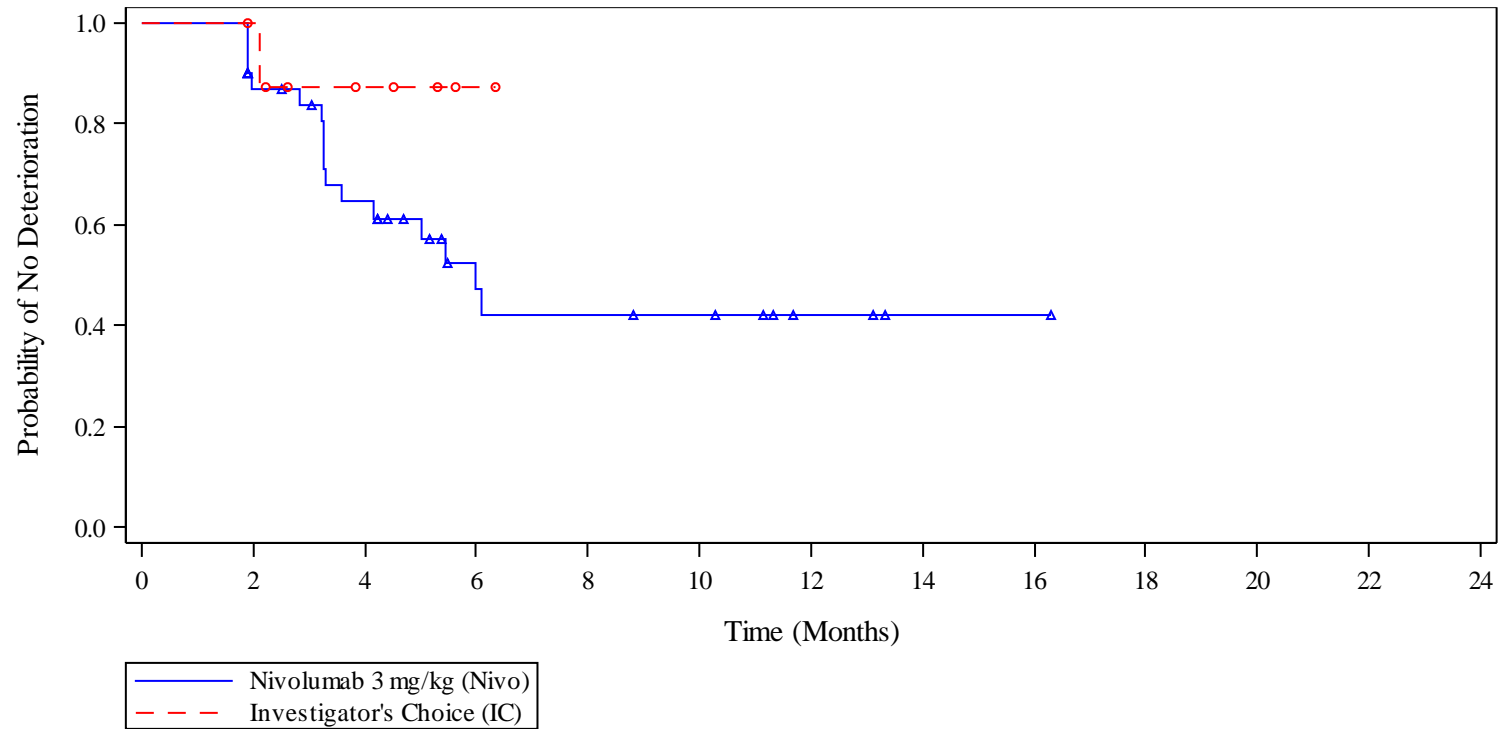
— Nivolumab 3 mg/kg (Nivo)  
 - - - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	40	29	20	13	9	8	3	0
IC	9	8	3	1	0			

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

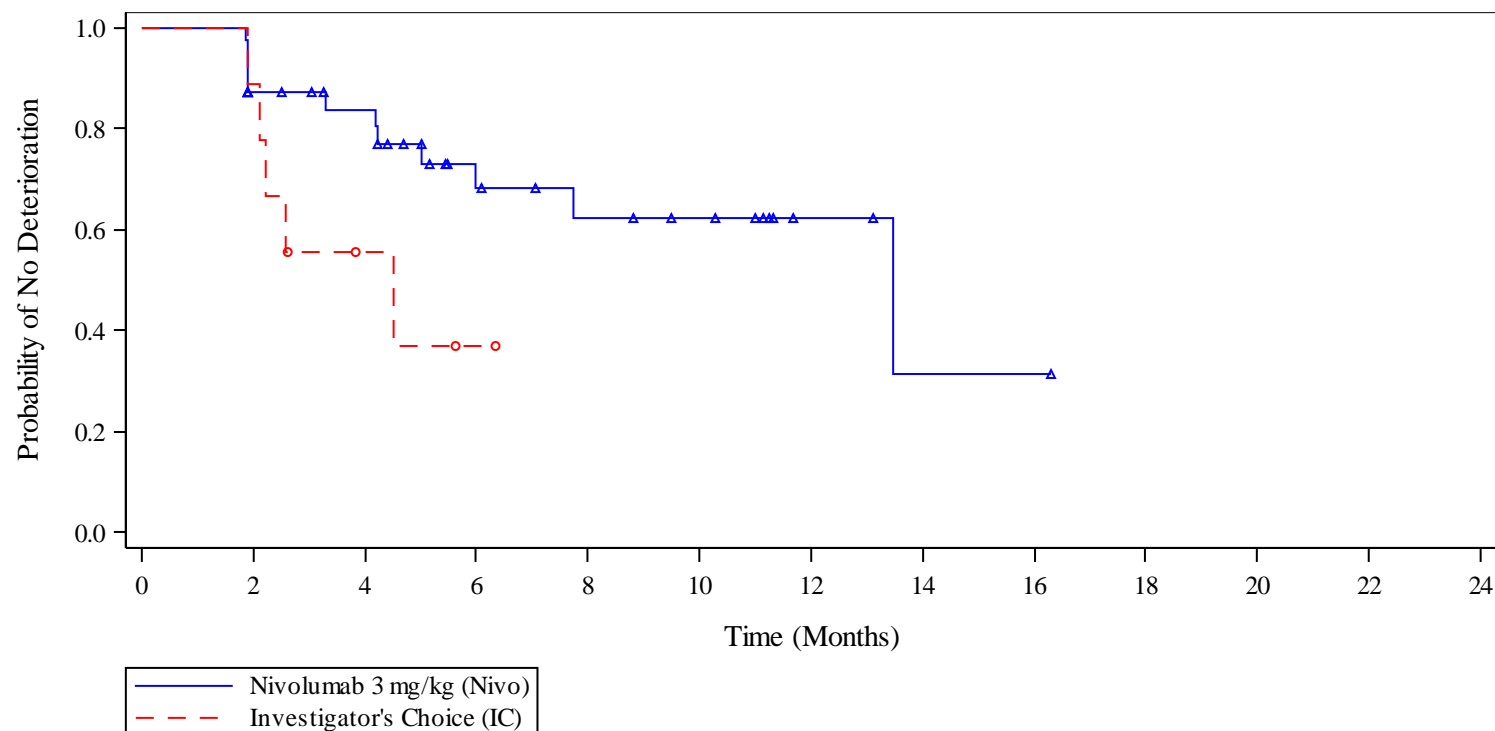
**Figure 4.2.2: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Swallowing (MTX)**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		40	29	20	10	8	7	3	1	1	0
IC		9	8	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

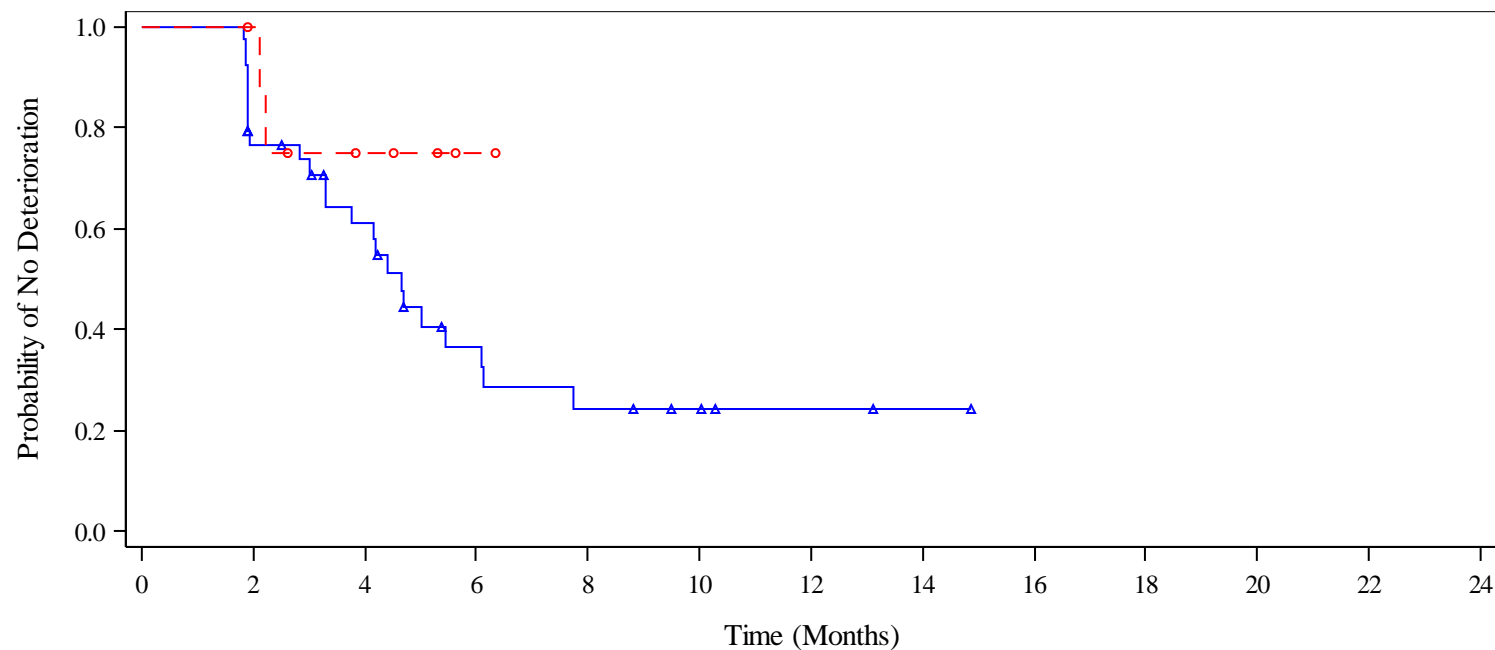
**Figure 4.2.3: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Sense Problems (MTX)**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		39	29	25	15	11	9	3	1	1	0
IC		9	8	3	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

**Figure 4.2.4: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Speech Problems (MTX)**



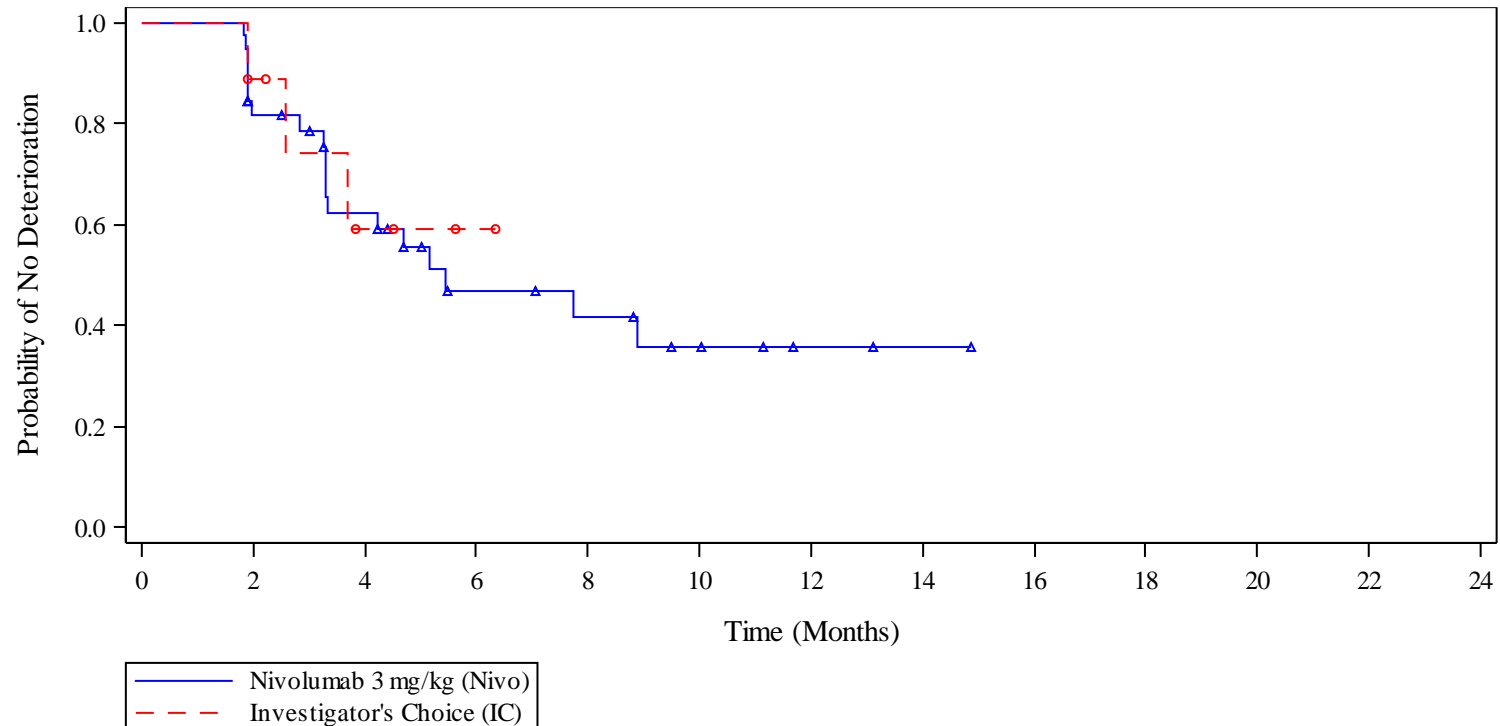
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	39	27	19	9	6	4	2	1	0
IC	9	8	4	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

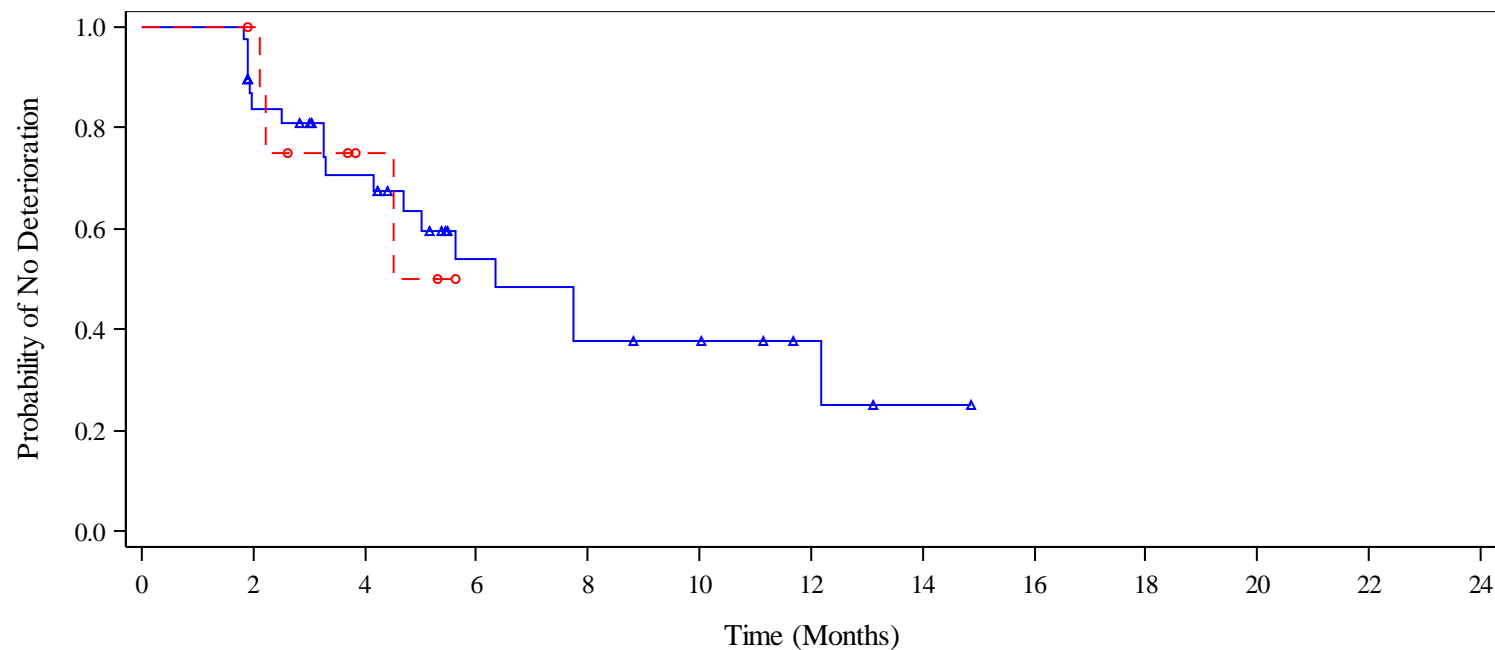
**Figure 4.2.5: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Trouble with Social Eating (MTX)**



		Number of Subjects at Risk								
		0	2	4	6	8	10	12	14	16
Nivo		39	28	19	10	8	5	2	1	0
IC		9	7	3	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

**Figure 4.2.6: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Trouble with Social Contact (MTX)**



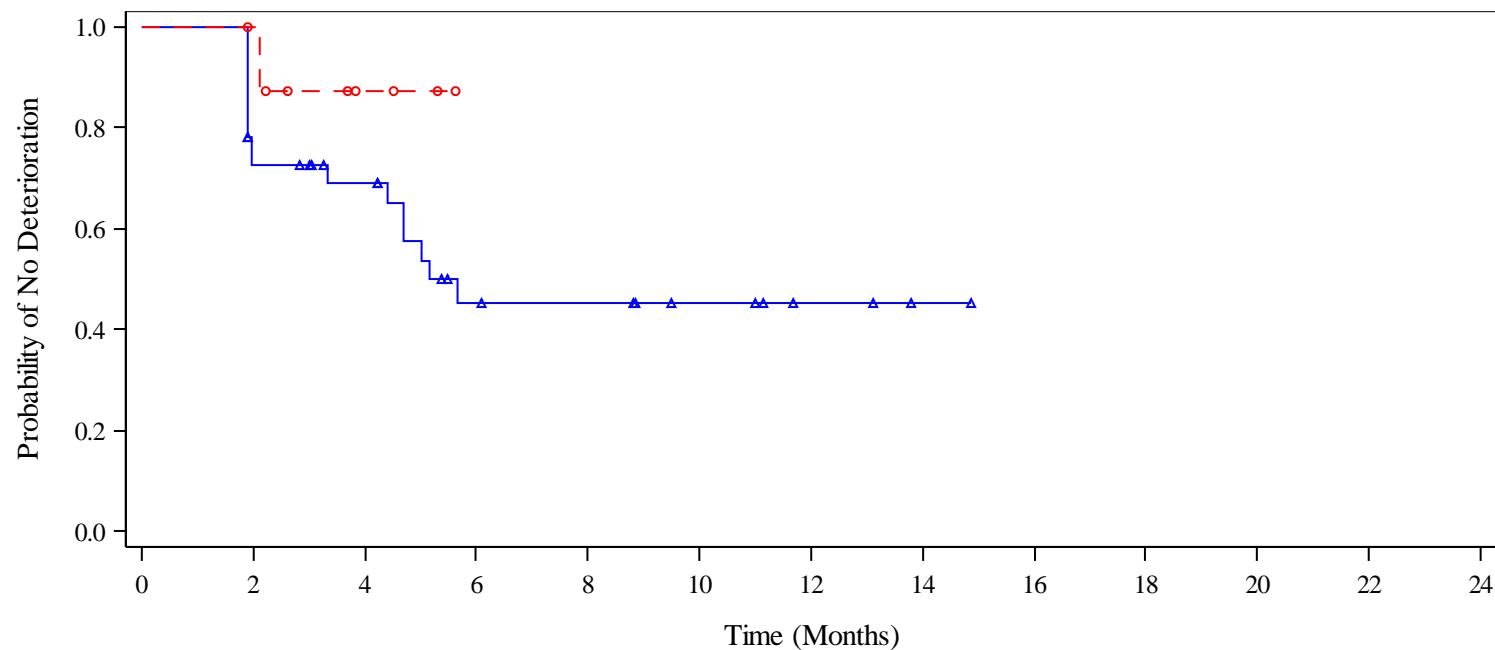
— Nivolumab 3 mg/kg (Nivo)  
- - - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	39	28	21	10	7	6	3	1	0
IC	9	8	3	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

**Figure 4.2.7: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Less Sexuality (MTX)**



—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

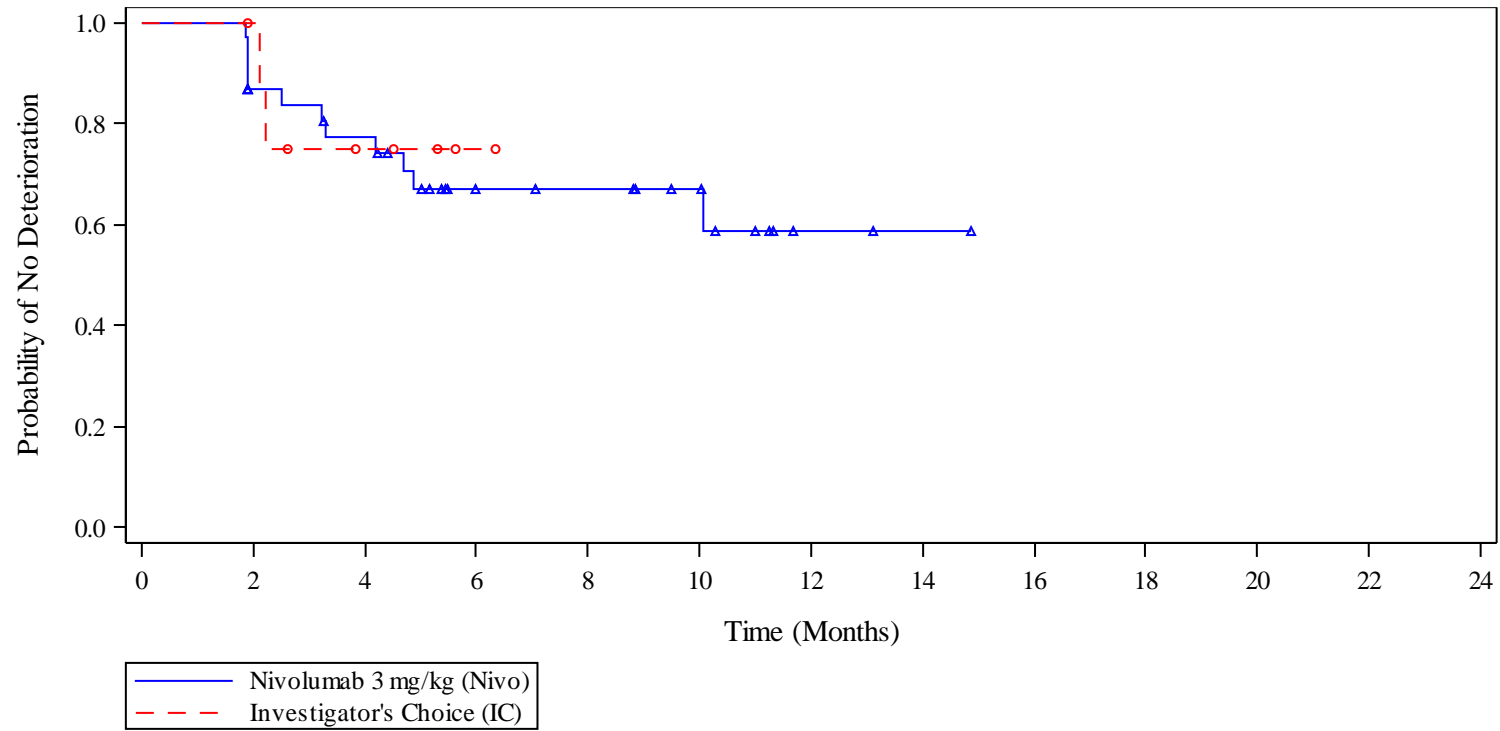
Number of Subjects at Risk

Nivo	37	25	20	10	9	6	3	1	0
IC	9	8	3	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe



Figure 4.2.8: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Teeth (MTX)

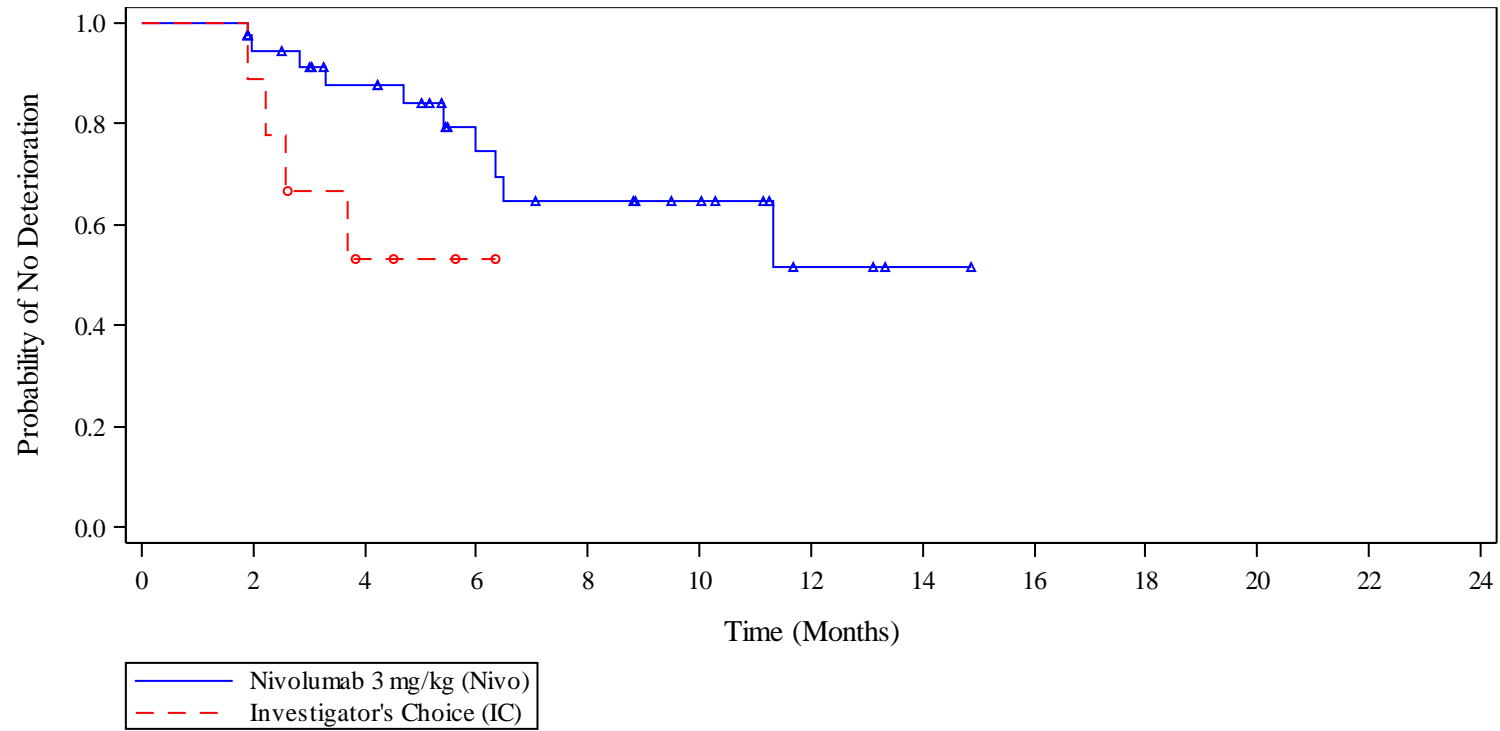


Number of Subjects at Risk

Nivo	38	28	24	14	12	9	2	1	0
IC	9	8	4	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

**Figure 4.2.9: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Opening Mouth (MTX)**

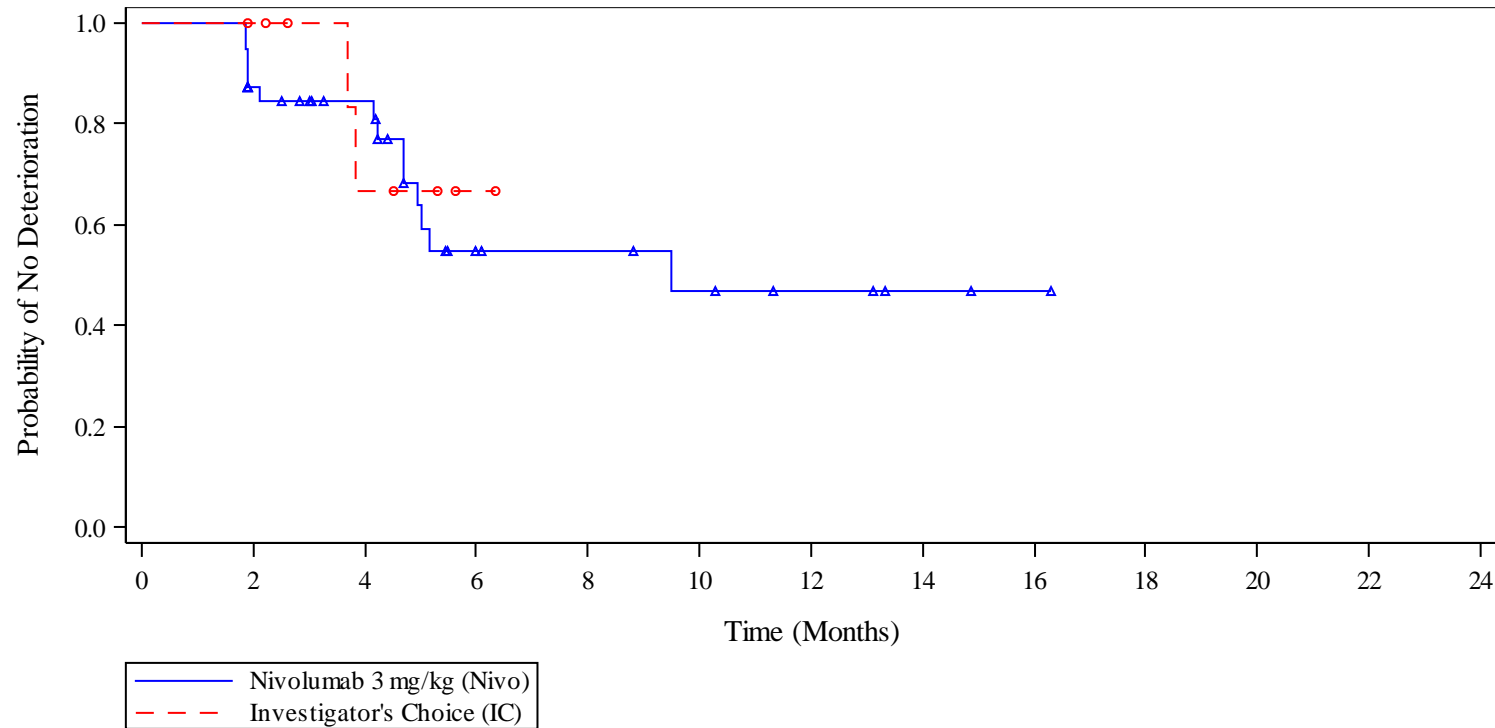


Number of Subjects at Risk

Nivo	40	31	25	16	12	9	3	1	0
IC	9	8	3	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

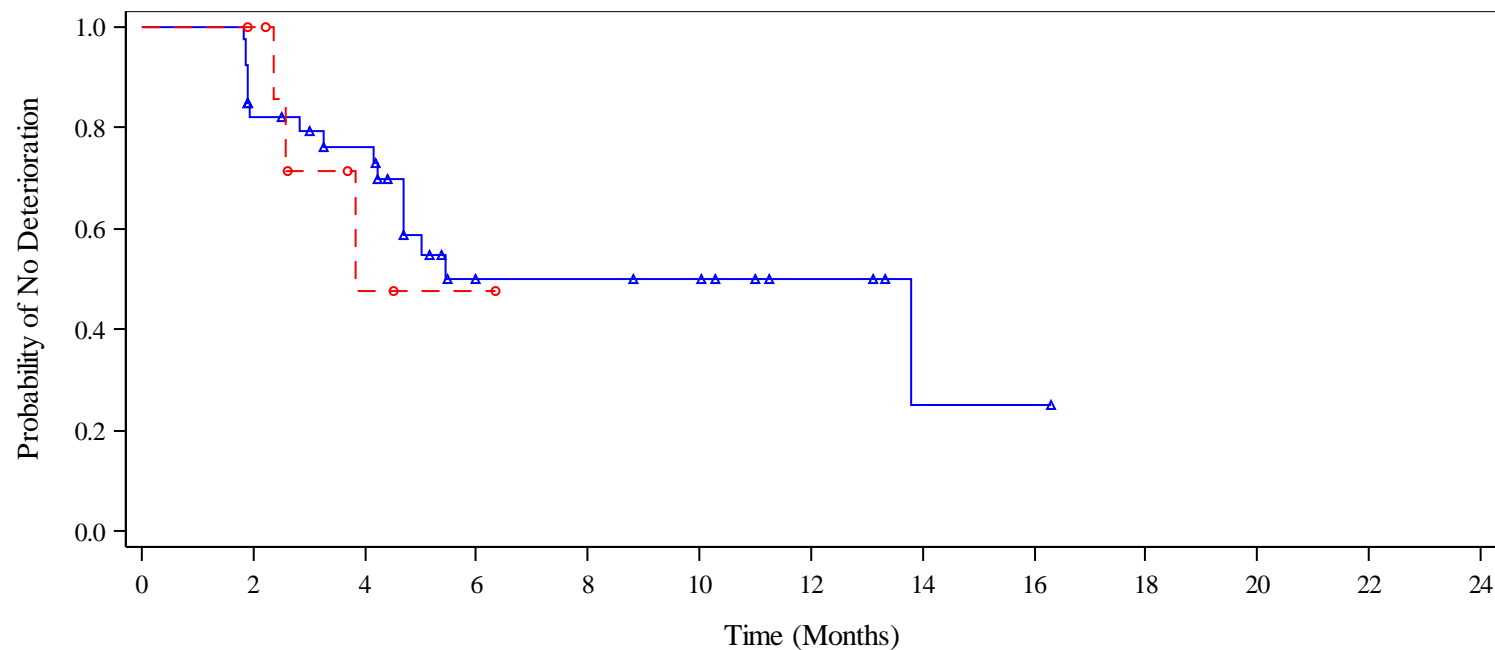
**Figure 4.2.10: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Dry Mouth (MTX)**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		40	29	23	10	8	6	4	2	1	0
IC		9	8	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

Figure 4.2.11: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Sticky Saliva (MTX)



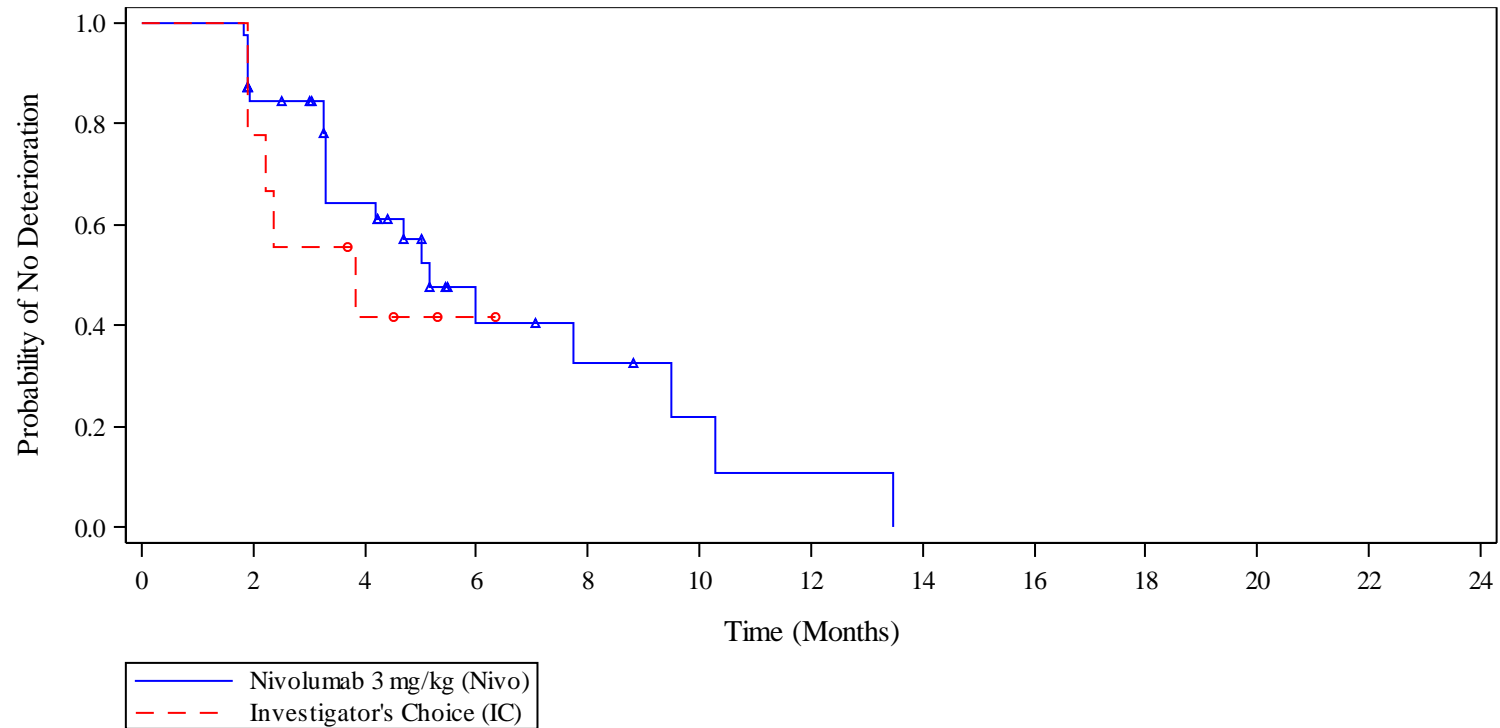
—▲— Nivolumab 3 mg/kg (Nivo)  
- -○- - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	40	29	24	10	9	8	4	1	1	0
IC	9	8	2	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

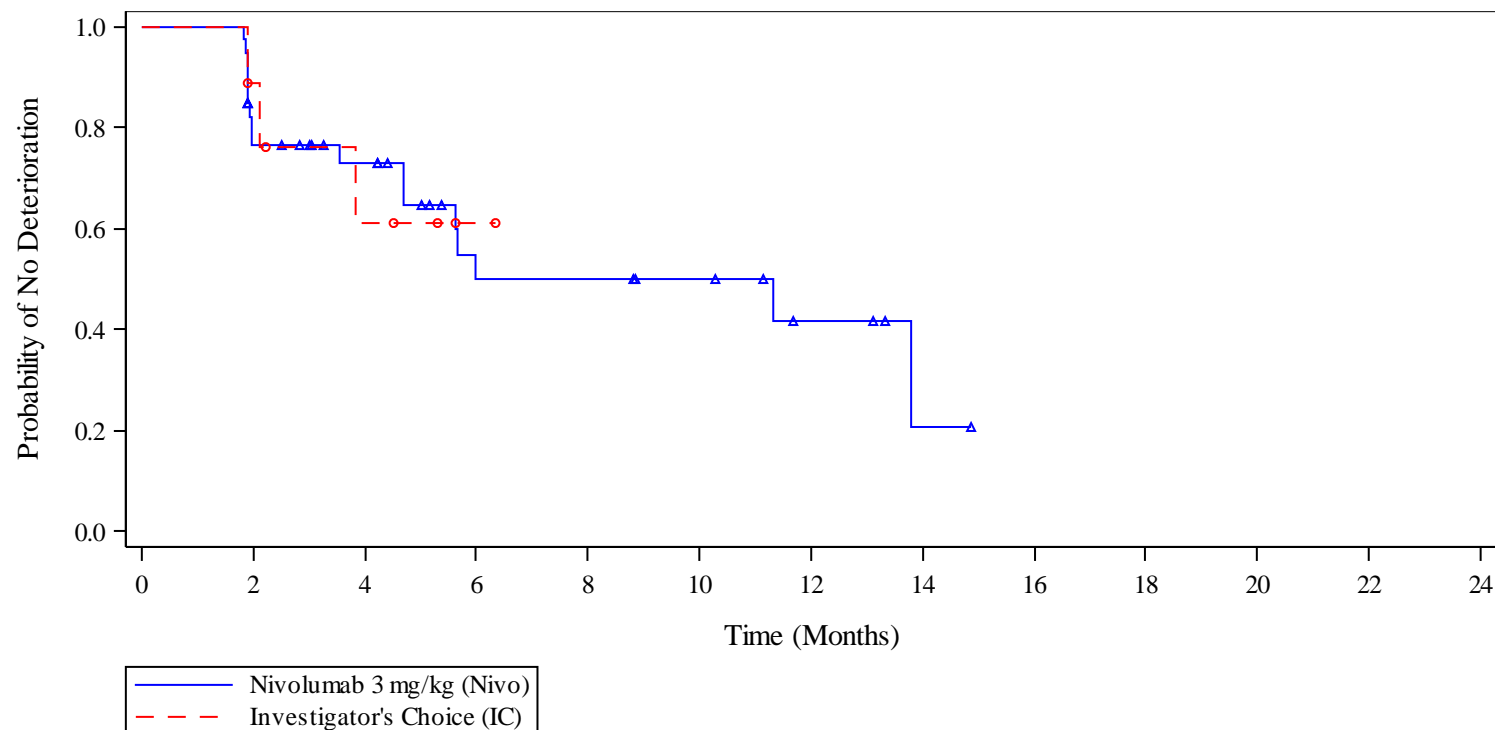
**Figure 4.2.12: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Coughing (MTX)**



		Number of Subjects at Risk							
		0	2	4	6	8	10	12	14
Nivo	40	29	19	7	4	2	1	0	
IC	9	7	3	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

Figure 4.2.13: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Felt ill (MTX)

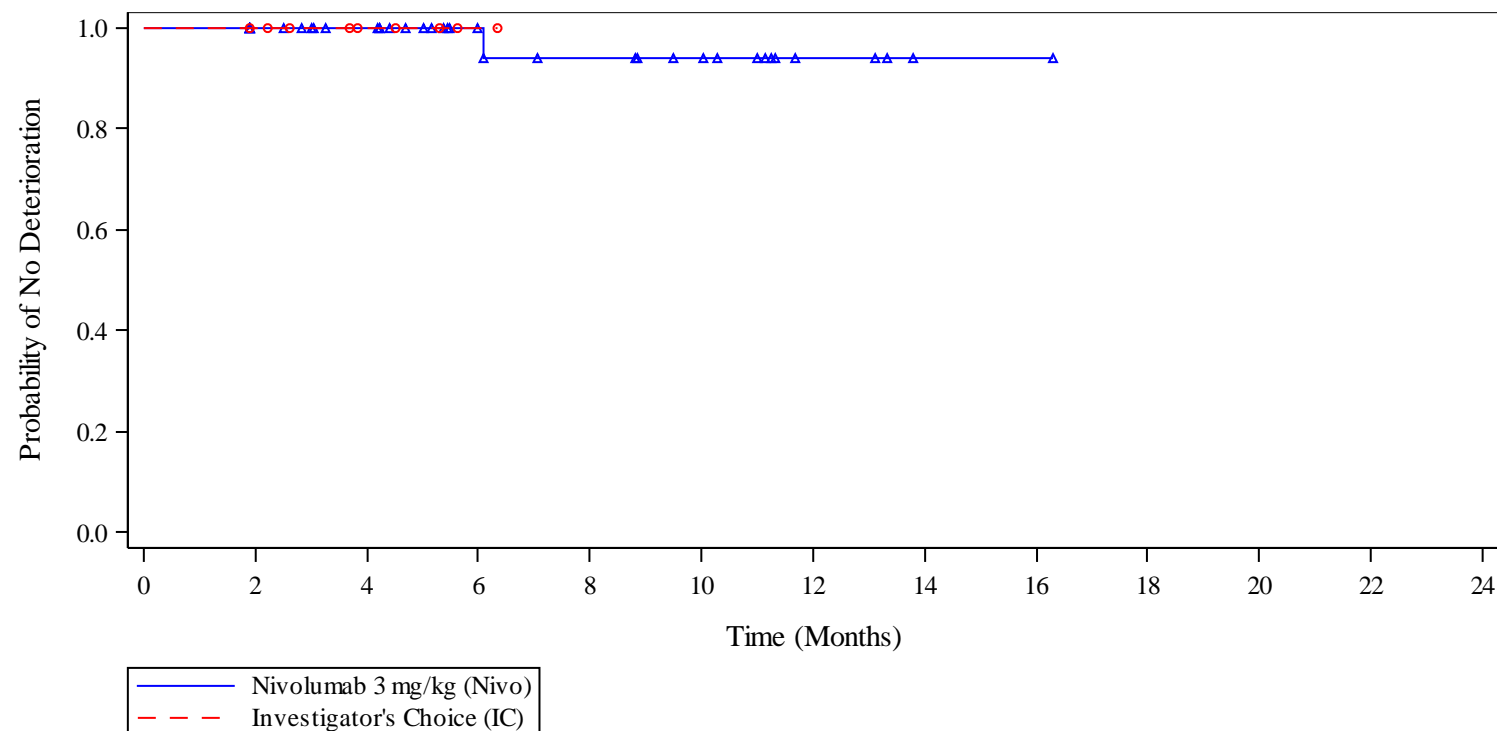


Number of Subjects at Risk

Nivo	40	27	21	11	10	8	4	1	0
IC	9	7	4	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

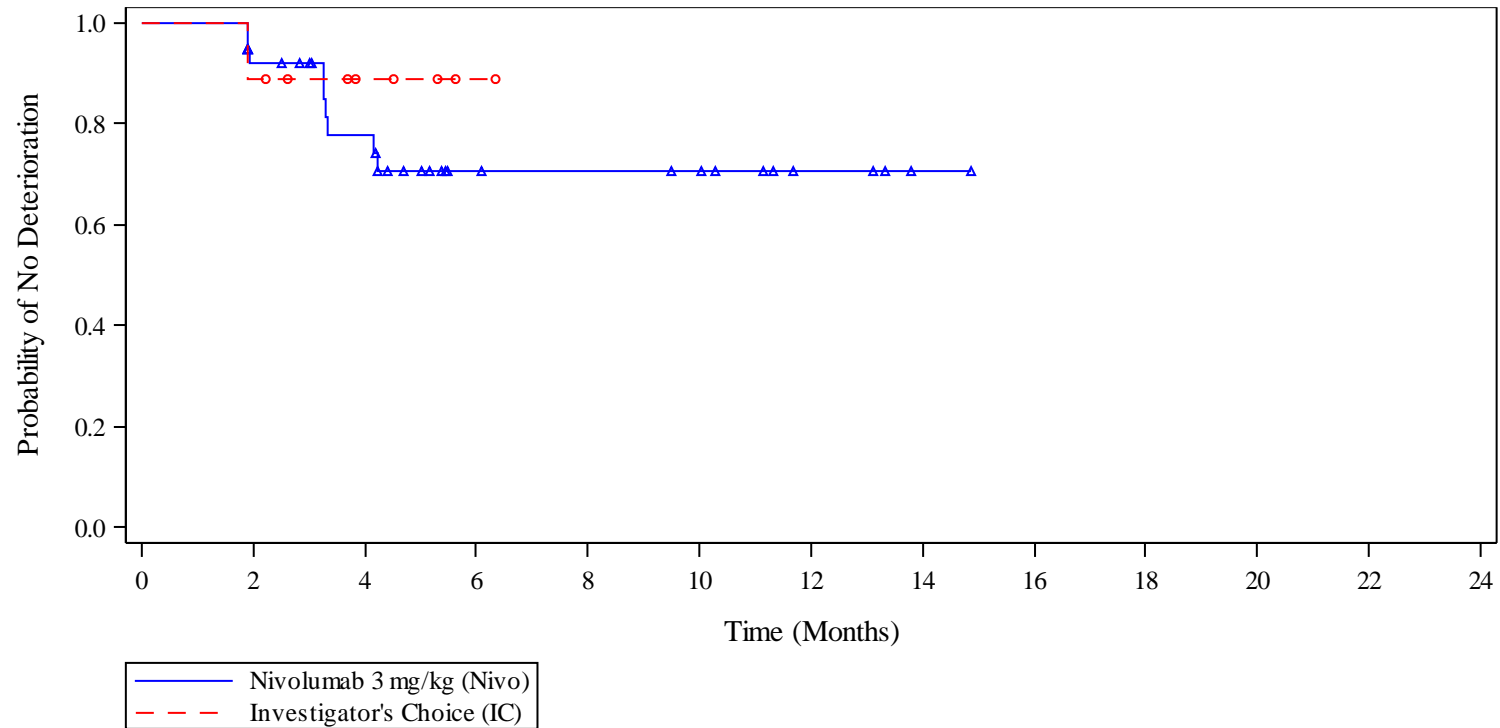
**Figure 4.2.14: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Pain Killers (MTX)**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		40	33	28	18	14	11	4	1	1	0
IC		9	8	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

**Figure 4.2.15: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Nutritional Supplements (MTX)**

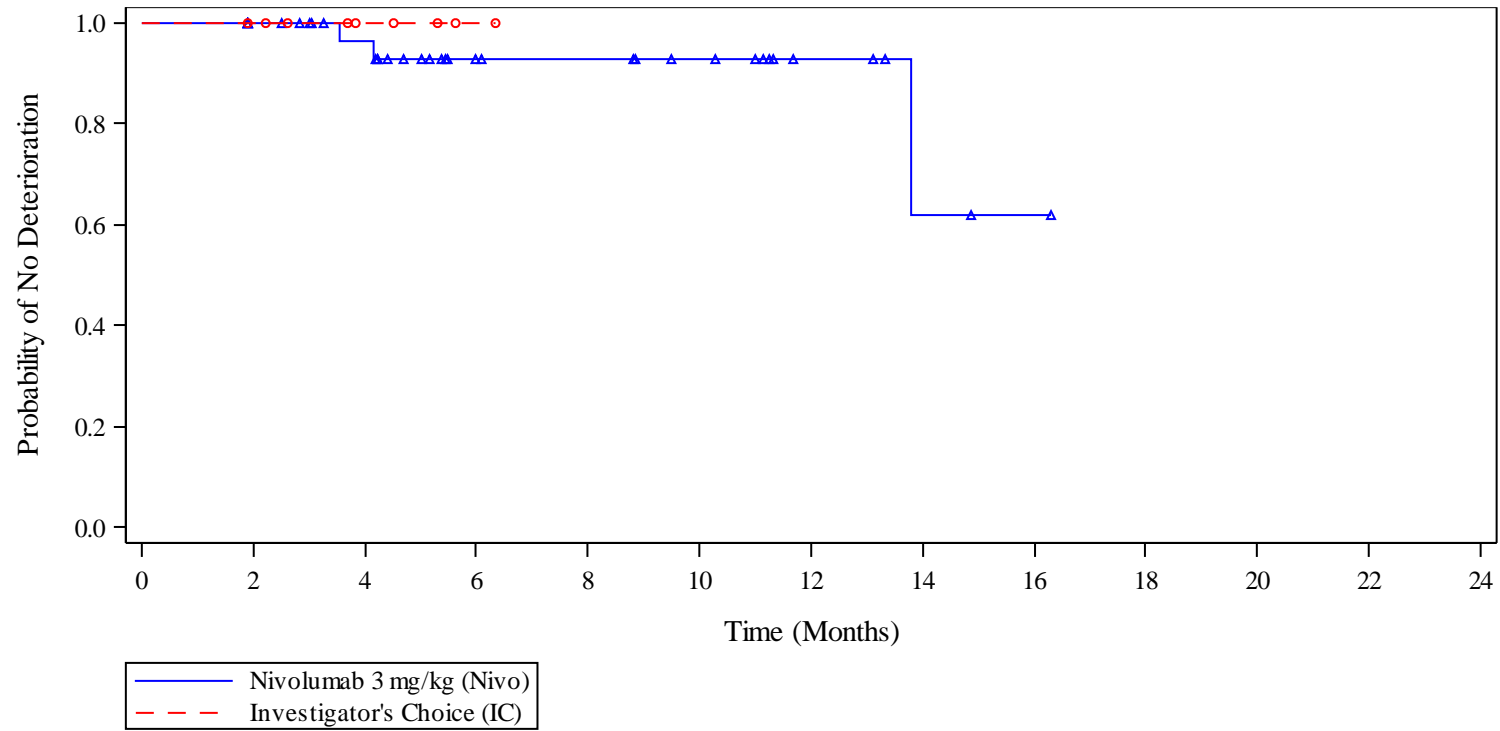


		Number of Subjects at Risk								
		0	2	4	6	8	10	12	14	16
Nivo		40	30	22	11	10	9	4	1	0
IC		9	8	4	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe



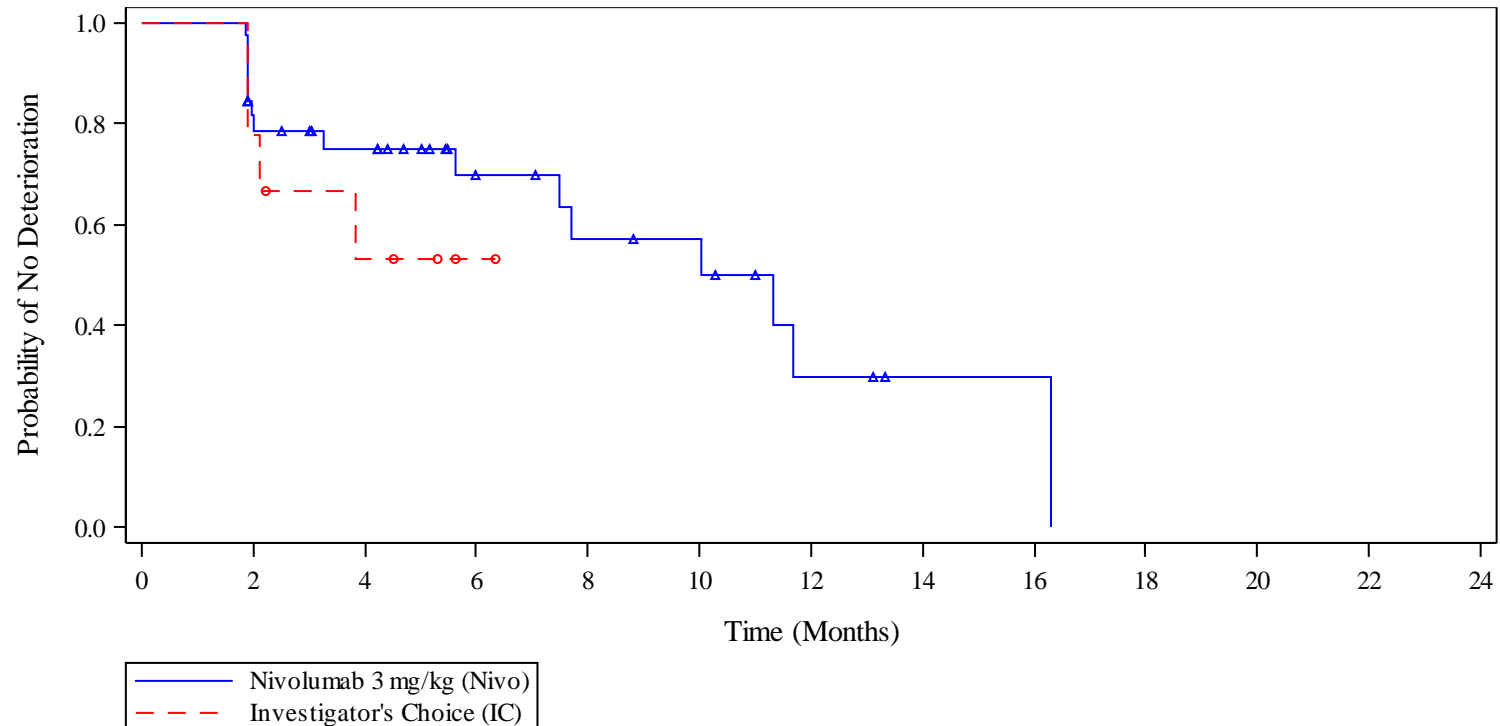
**Figure 4.2.16: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Feeding Tube (MTX)**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		40	33	27	16	14	11	5	2	1	0
IC		9	8	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

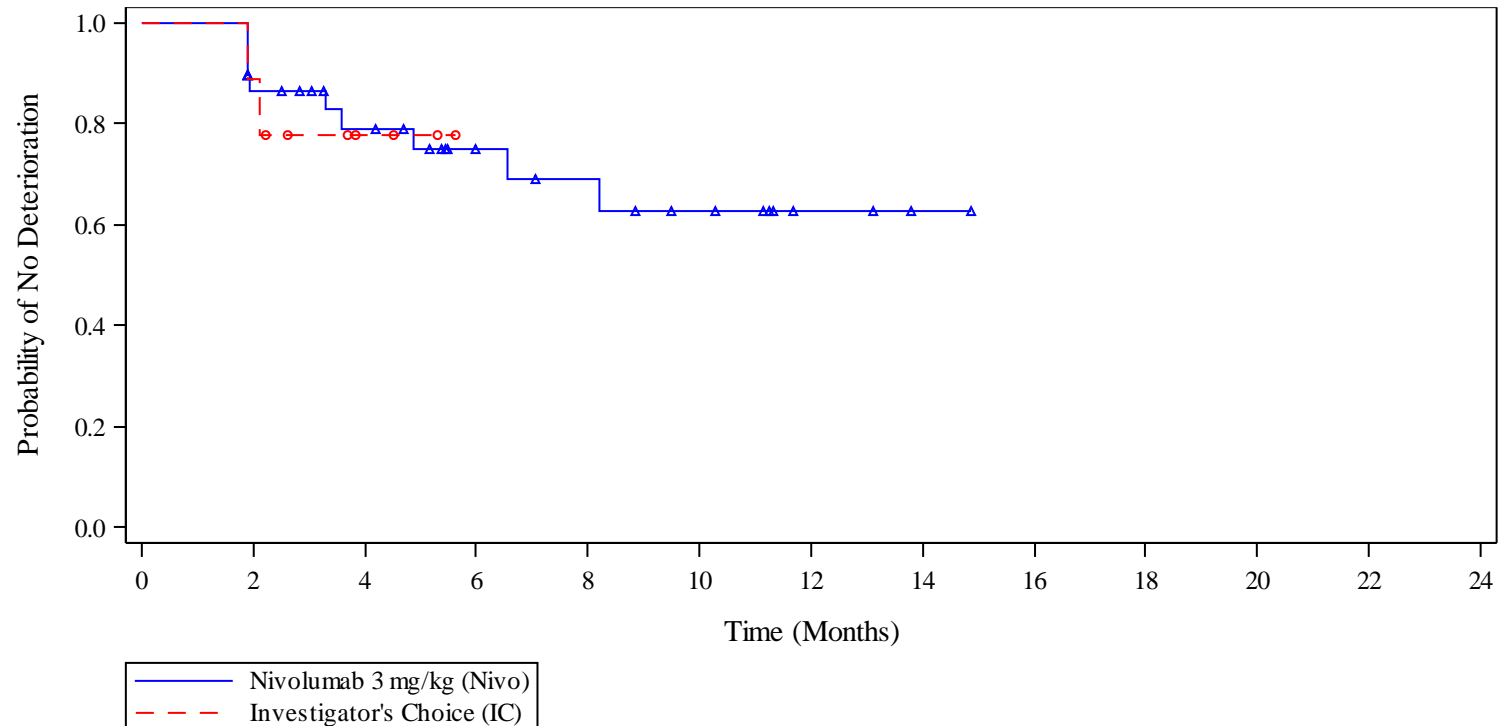
**Figure 4.2.17: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Weight Loss (MTX)**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		39	27	22	13	9	8	3	1	1	0
IC		9	7	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

**Figure 4.2.18: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ H AND N35 Weight Gain (MTX)**



		Number of Subjects at Risk								
		0	2	4	6	8	10	12	14	16
Nivo		39	27	21	14	11	8	3	1	0
IC		9	8	3	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

Abbildung 2: Kaplan-Meier-Kurven der Endpunkte Morbidität (Krankheitsbedingte Symptome gemäß EORTC QLQ-H&N35) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

#### **4.3.1.3.1.3 Endpunkte Morbidität – Krankheitsbedingte Symptome gemäß EORTC QLQ-C30**

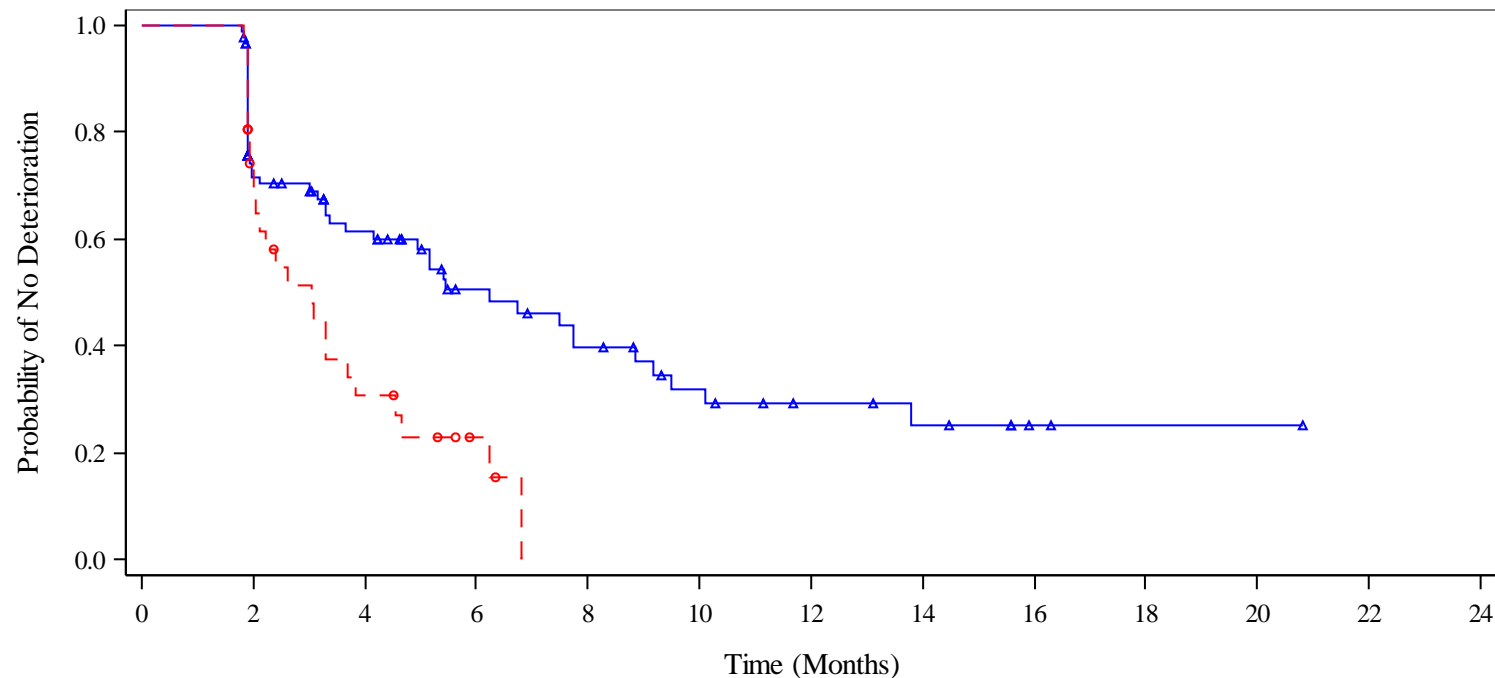
##### Ergänzung der Kaplan-Meier-Kurven

Nachfolgend werden die Kaplan-Meier-Kurven für die Morbiditätsskalen des EORTC QLQ-C30 jeweils für die Gesamtpopulation und die MTX-Teilpopulation dargestellt:

Fatigue, Übelkeit und Erbrechen, Schmerz, Dyspnoe, Schlaflosigkeit, Appetitminderung, Obstipation, Diarrhoe, Finanzielle Schwierigkeiten

**Gesamtpopulation**

Figure 4.1.7: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Fatigue



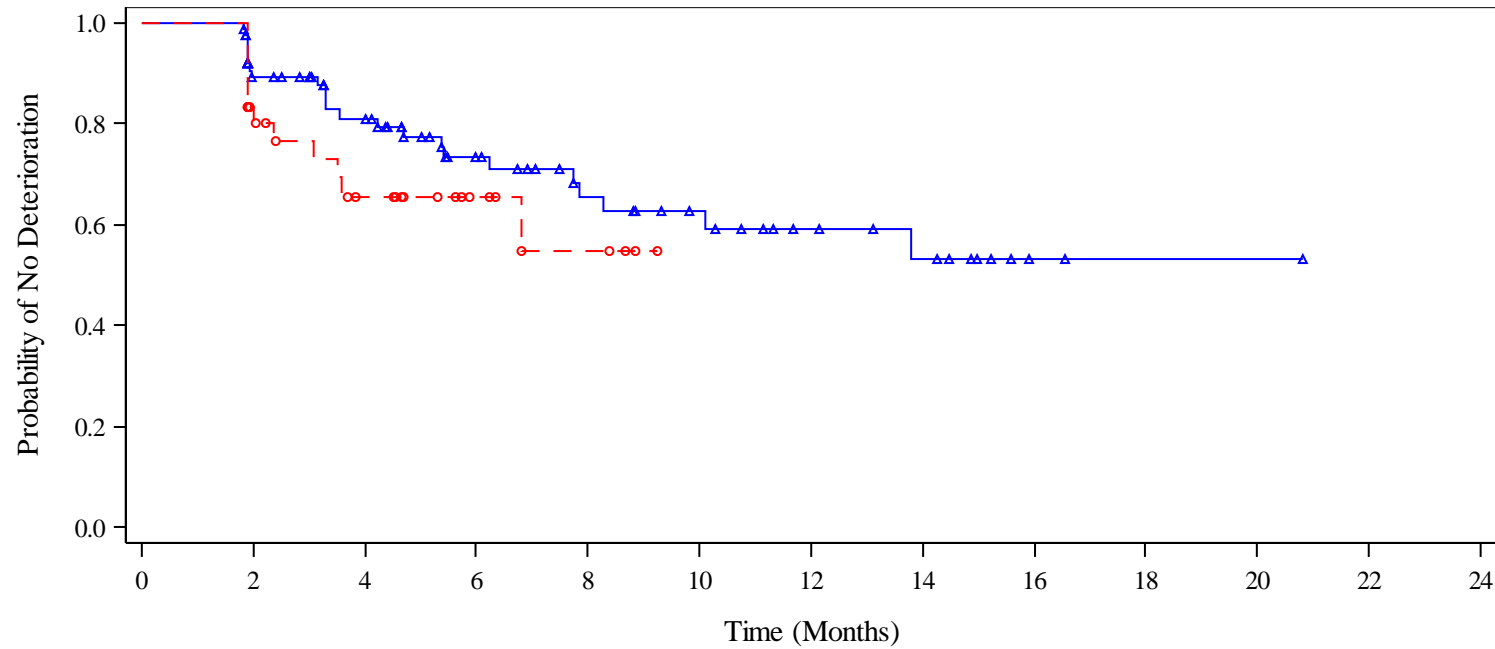
—▲— Nivolumab 3 mg/kg (Nivo)  
- -○- - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	89	54	40	24	18	12	8	6	2	1	1	0
IC	36	23	9	3	0							

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Figure 4.1.8: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Nausea and Vomiting



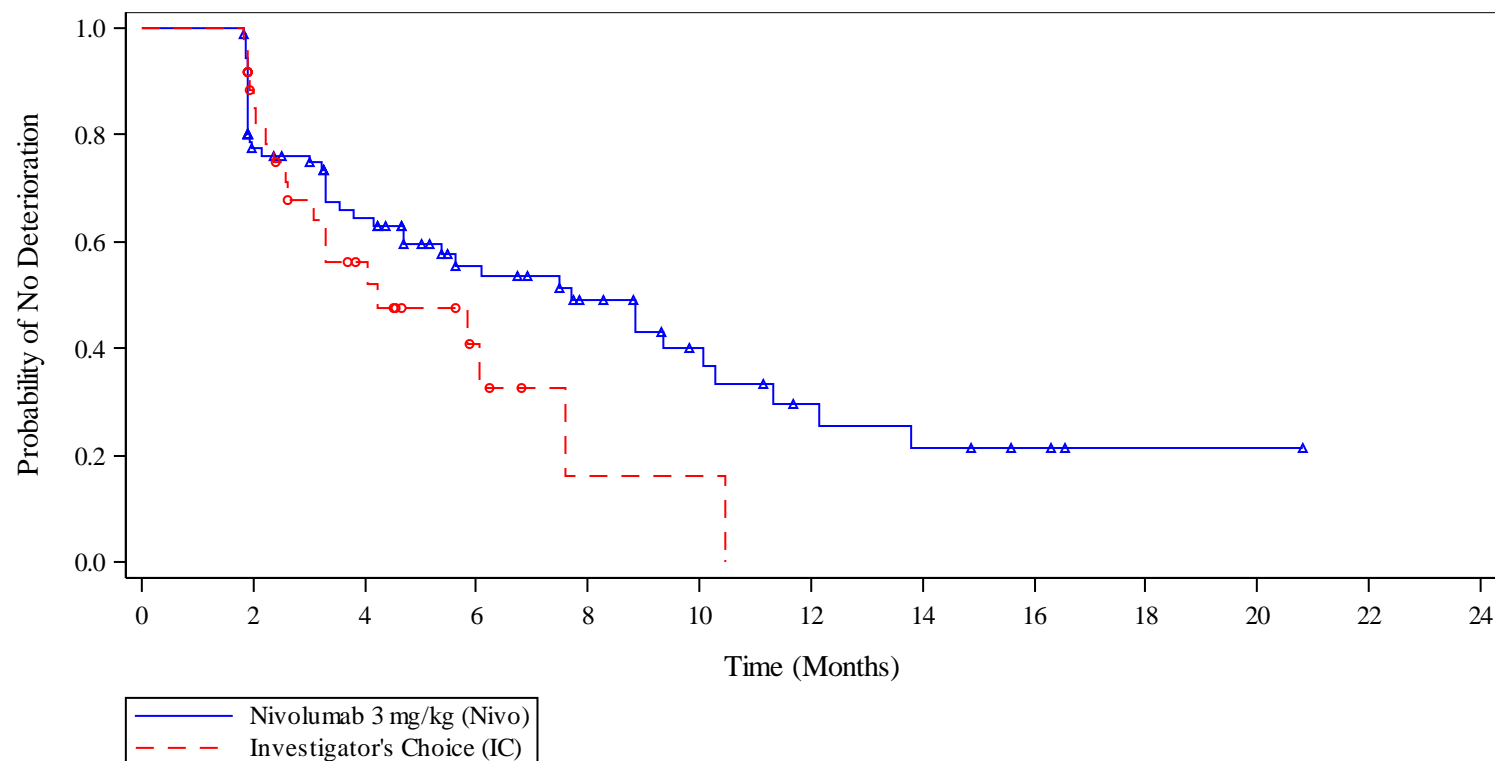
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	89	64	50	33	23	18	12	9	2	1	1	0	
IC	36	26	16	8	4	0							

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

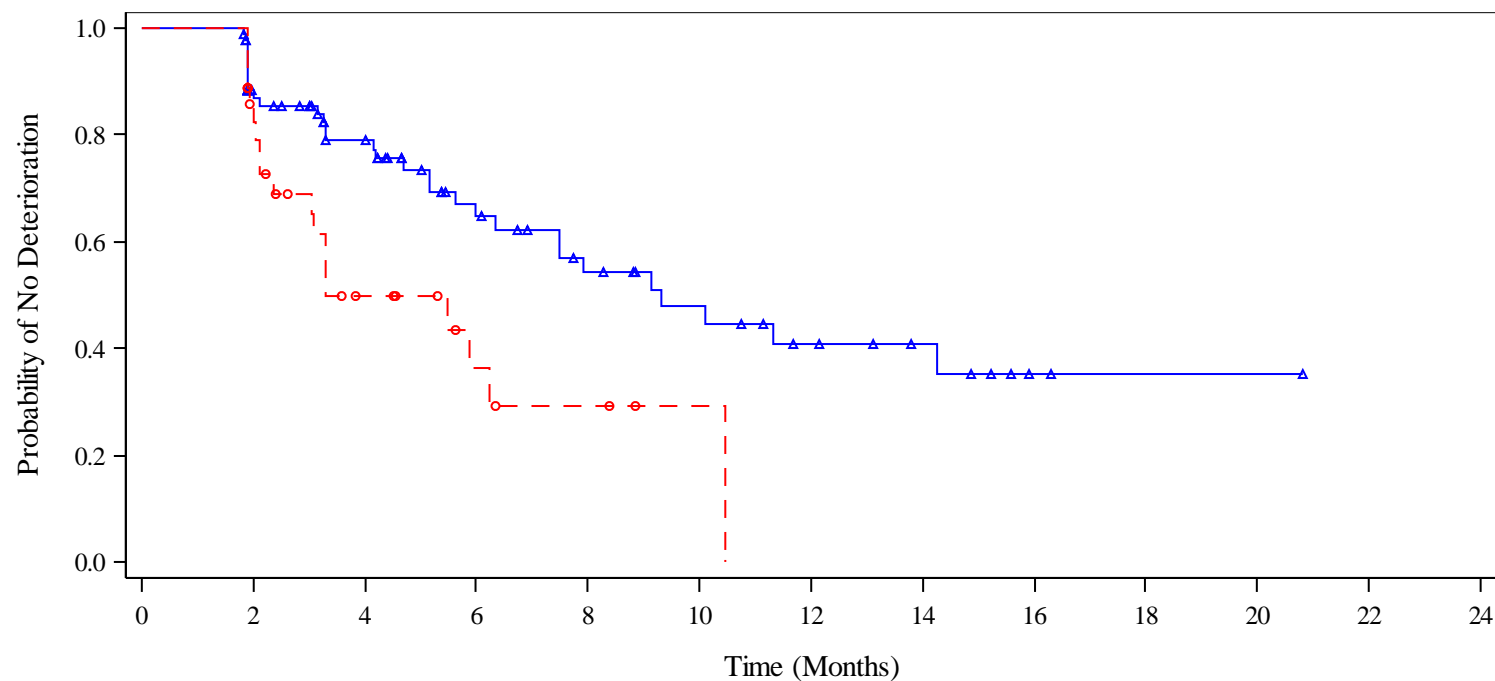
Figure 4.1.9: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Pain



		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	91	59	43	27	19	12	7	5	3	1	1	0		
IC	36	26	13	5	1	1	0							

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Figure 4.1.10: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Dyspnea



—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

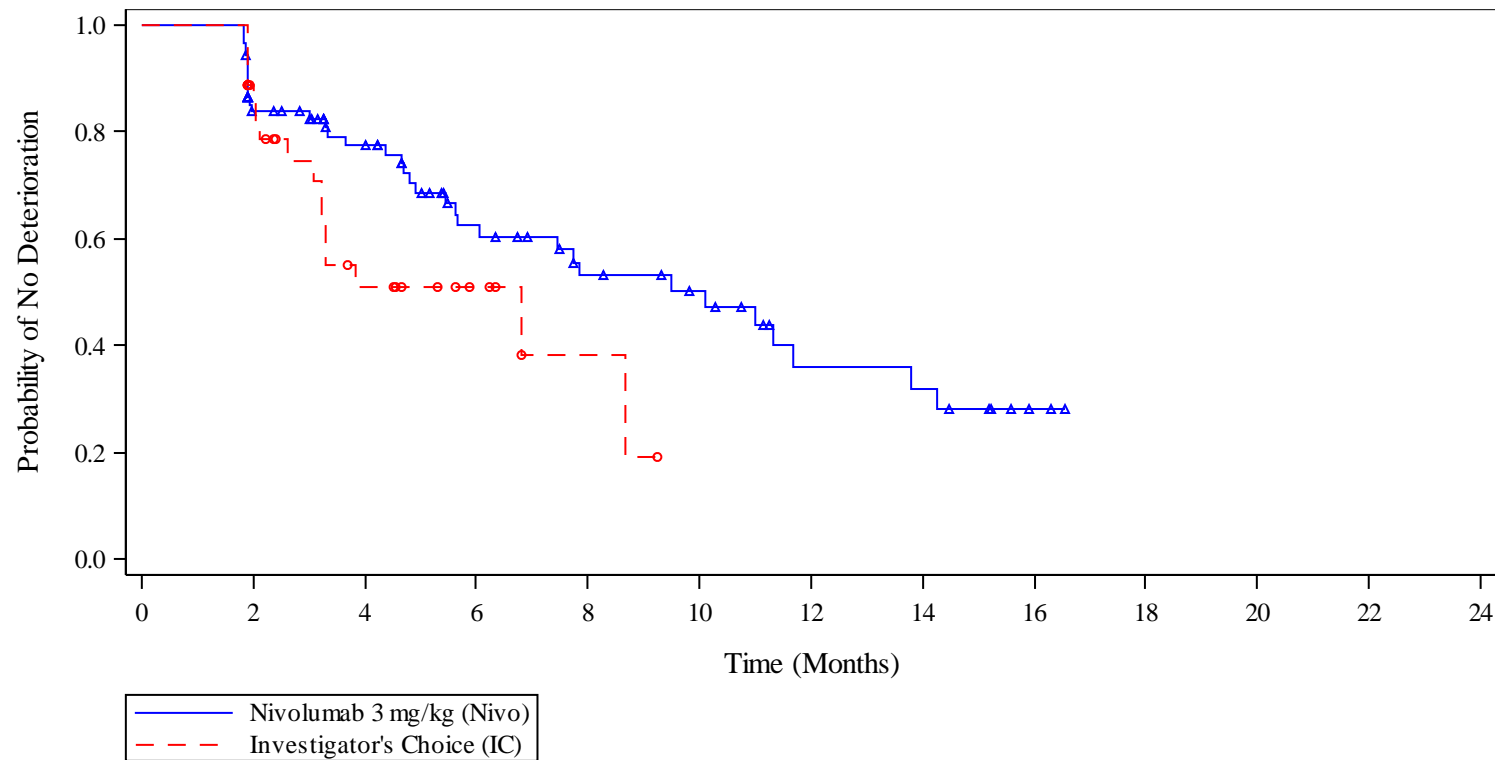
Number of Subjects at Risk

Nivo	89	62	46	29	20	15	10	7	2	1	1	0
IC	36	26	11	5	3	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe



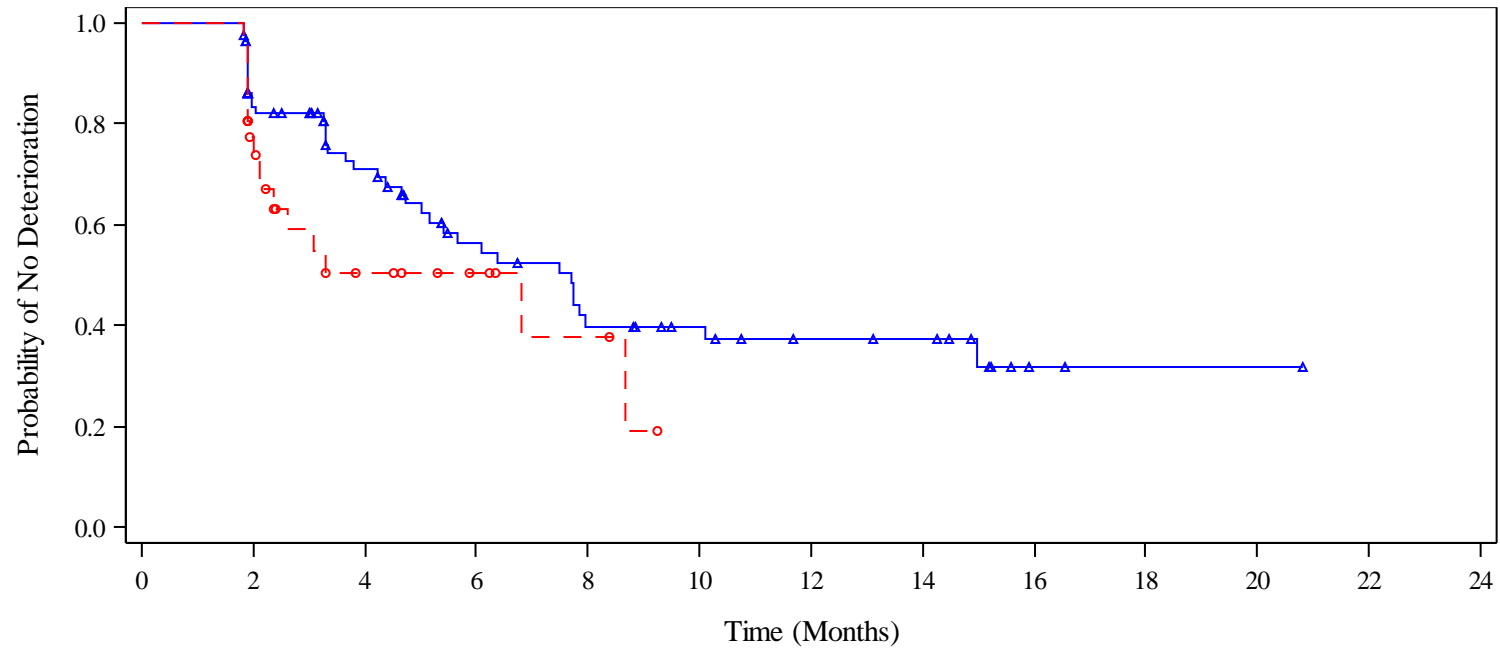
Figure 4.1.11: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Insomnia



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		89	62	48	30	21	17	9	8	2	0
IC		36	26	12	6	2	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Figure 4.1.12: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Appetite Loss



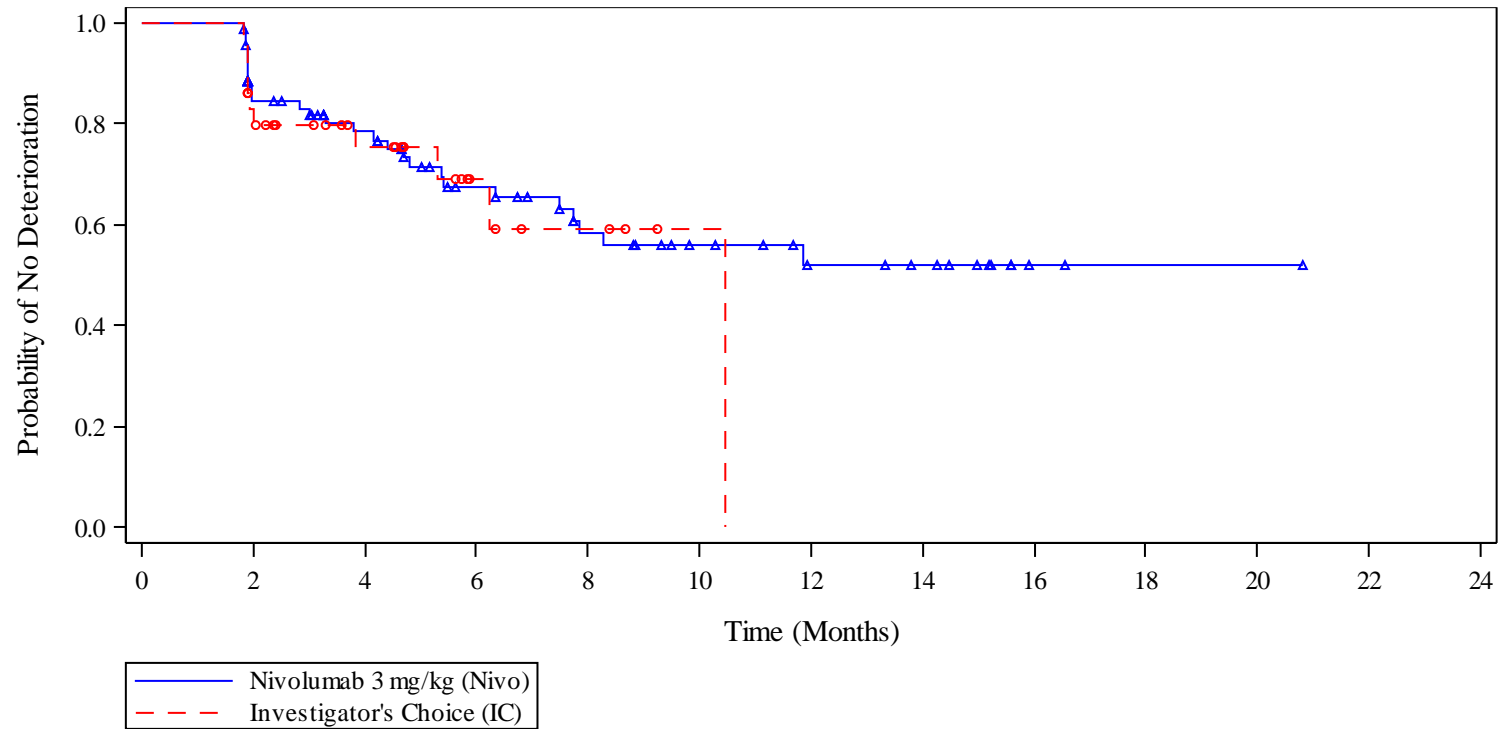
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	89	61	44	28	19	15	11	10	2	1	1	0	
IC	36	23	10	6	3	0							

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Figure 4.1.13: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Constipation

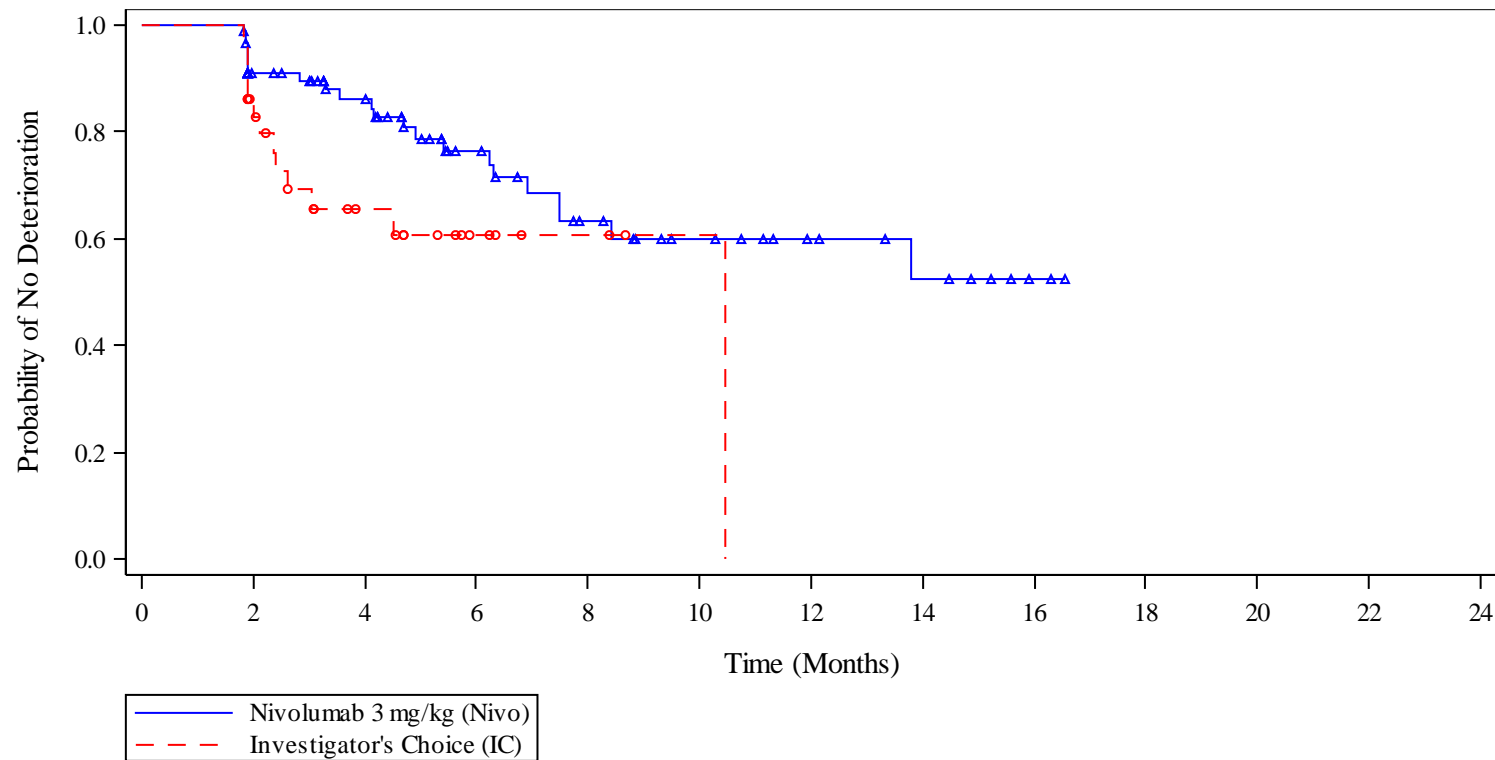


Number of Subjects at Risk

Nivo	90	61	48	33	23	17	12	10	2	1	1	0
IC	36	27	17	7	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

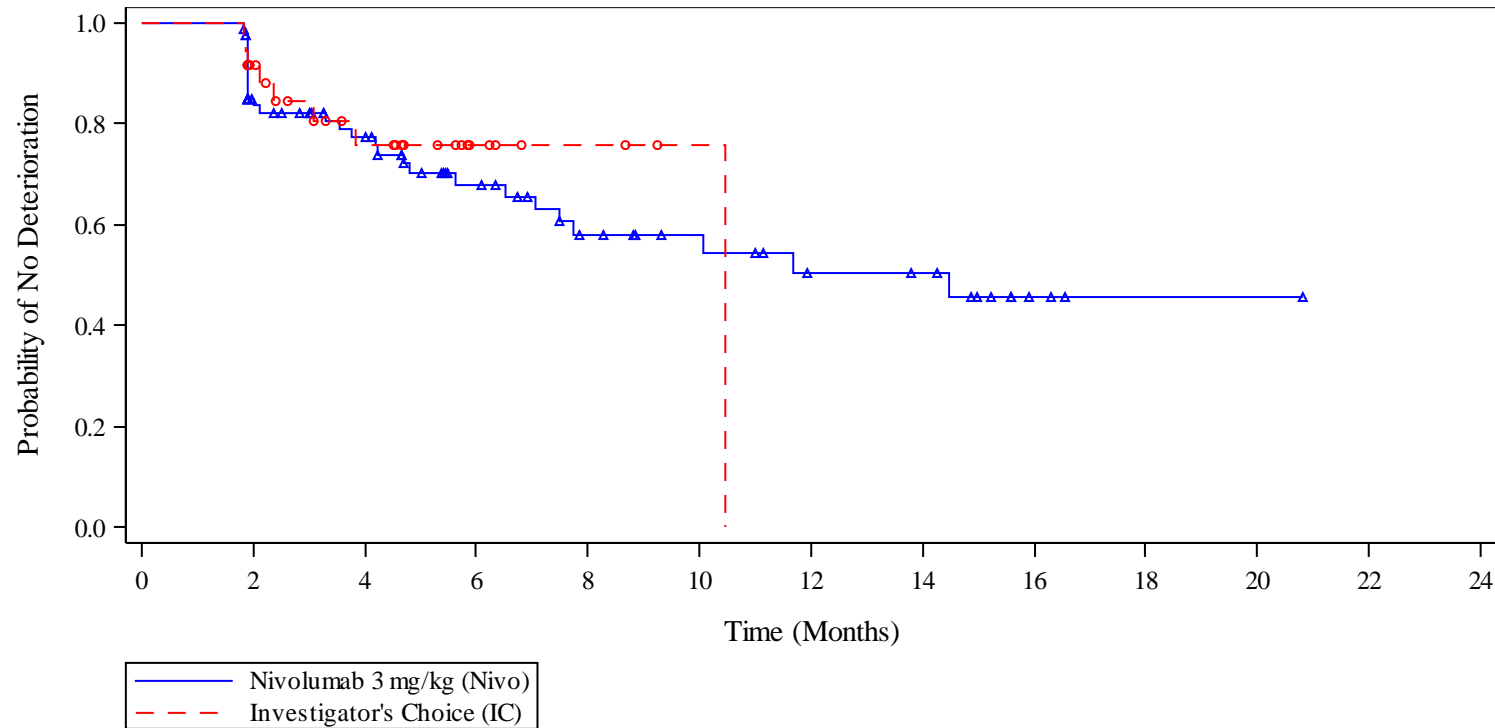
Figure 4.1.14: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Diarrhea



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo	90	65	51	31	21	15	10	7	2	0	
IC	36	27	14	6	3	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

**Figure 4.1.15: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Financial Difficulties**



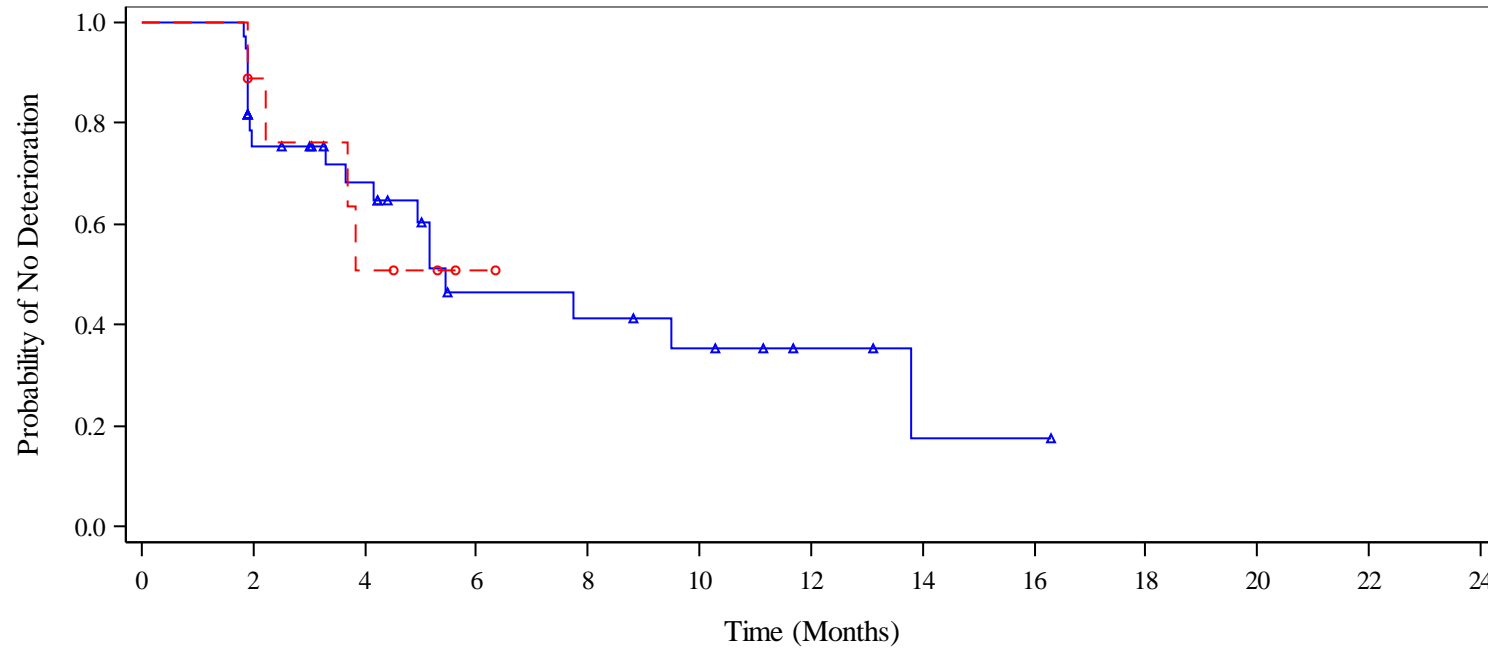
		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	90	60	47	31	21	17	12	11	3	1	1	0		
IC	36	27	16	6	3	1	0							

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Abbildung 3: Kaplan-Meier-Kurven der Endpunkte Morbidität (Krankheitsbedingte Symptome gemäß EORTC QLQ-C30) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

**MTX-Teilpopulation**

**Figure 4.1.7: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Fatigue (MTX)**



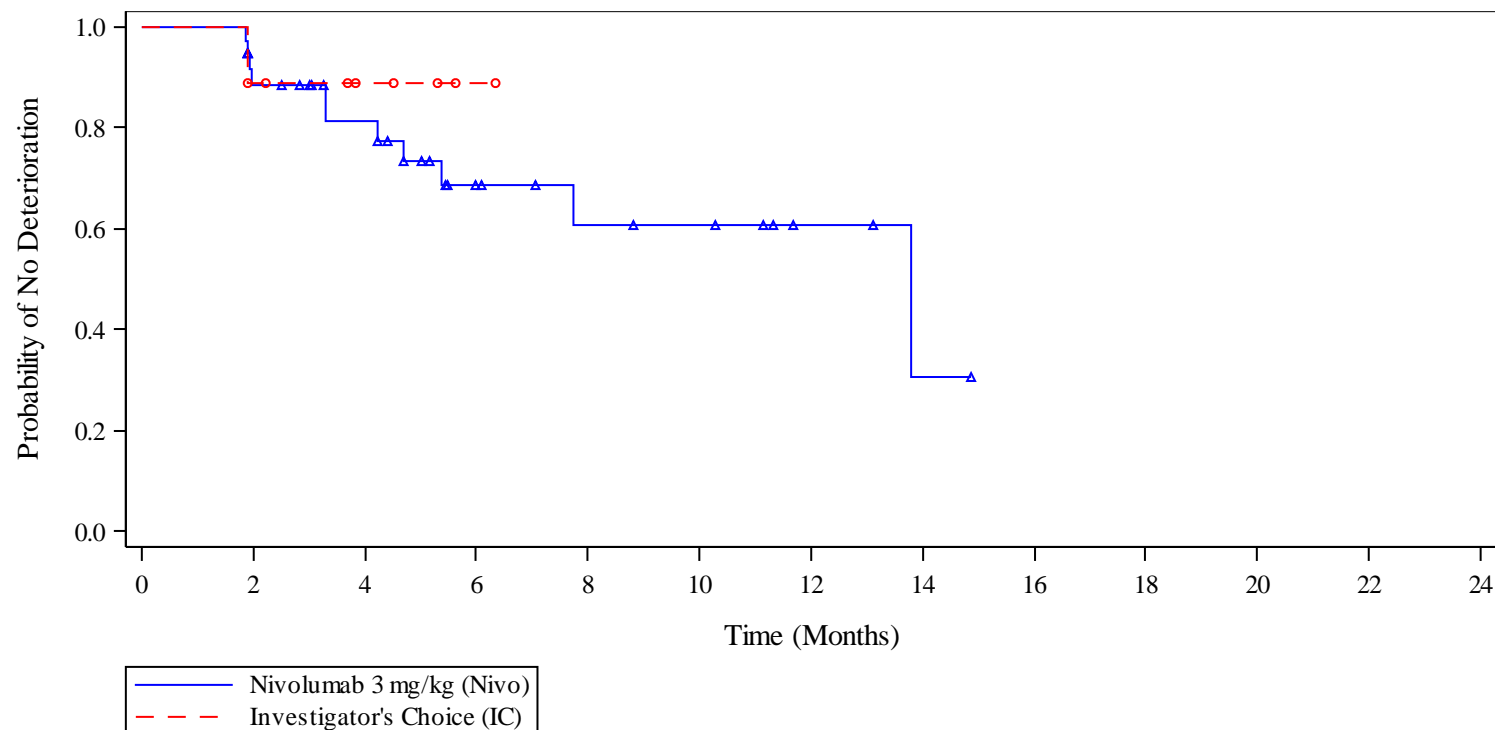
—▲— Nivolumab 3 mg/kg (Nivo)  
- -○- - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	38	25	19	9	8	6	3	1	1	0
IC	9	7	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

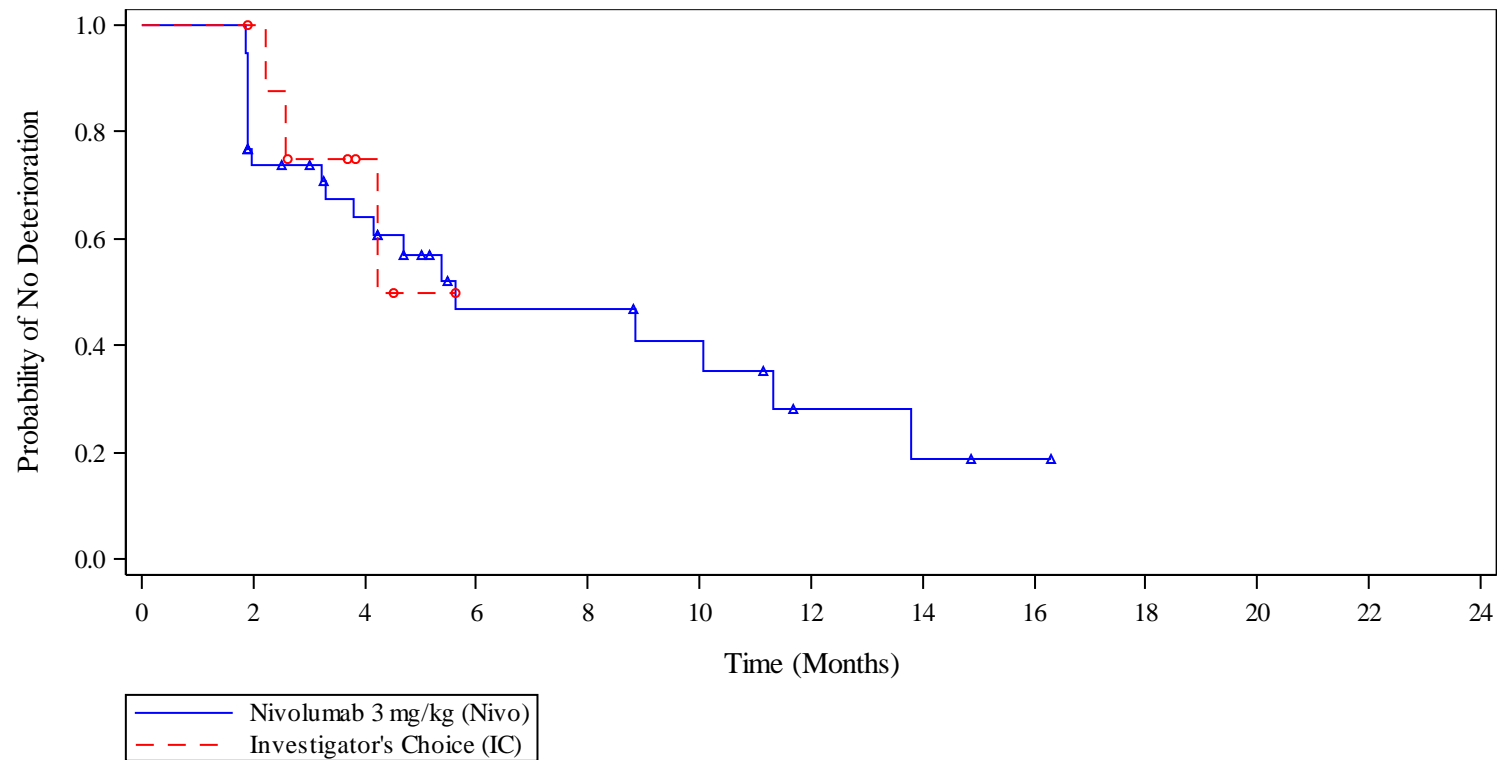
**Figure 4.1.8: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Nausea and Vomiting (MTX)**



		Number of Subjects at Risk								
		0	2	4	6	8	10	12	14	16
Nivo		38	29	22	12	8	7	3	1	0
IC		9	7	4	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

Figure 4.1.9: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Pain (MTX)

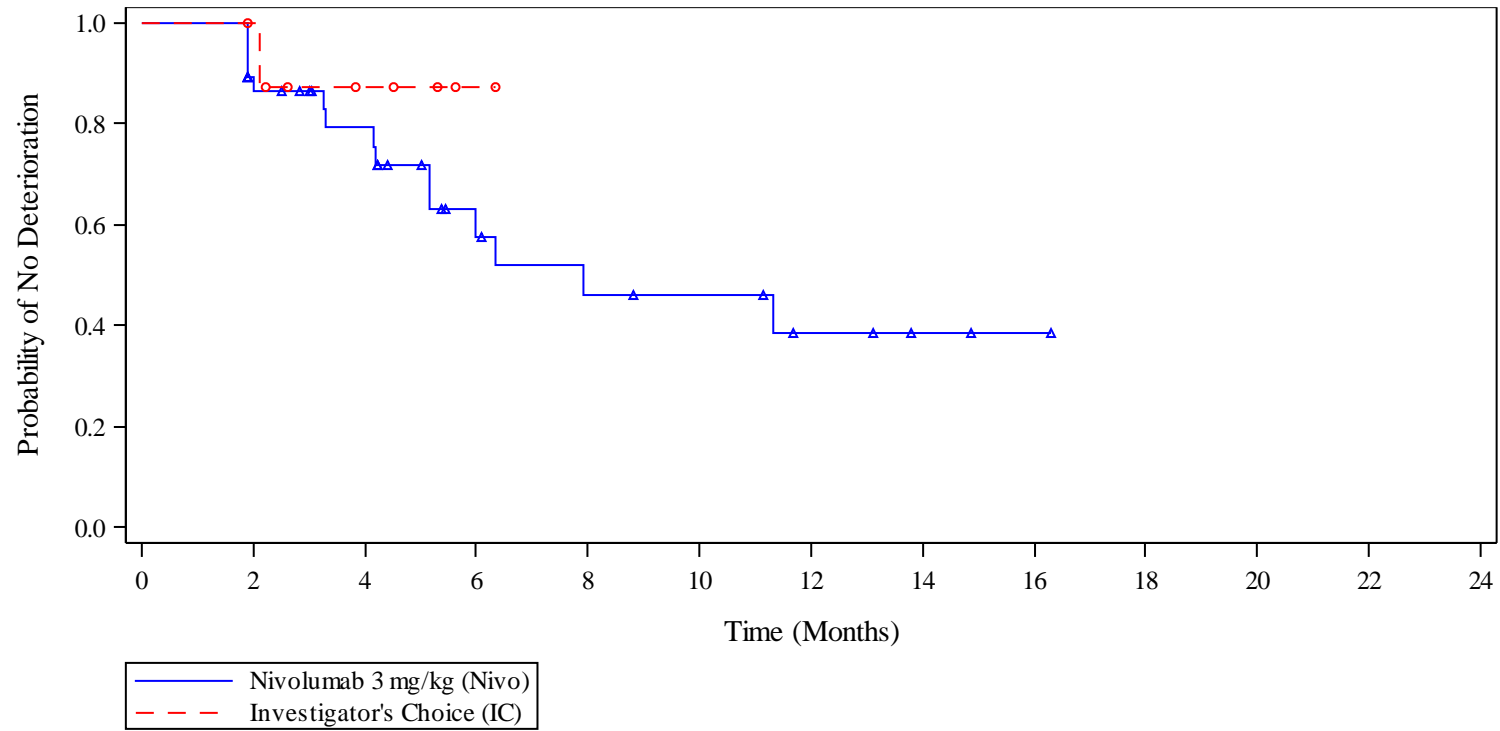


		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo	39	25	19	9	9	7	3	2	1	0	
IC	9	8	3	0							

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe



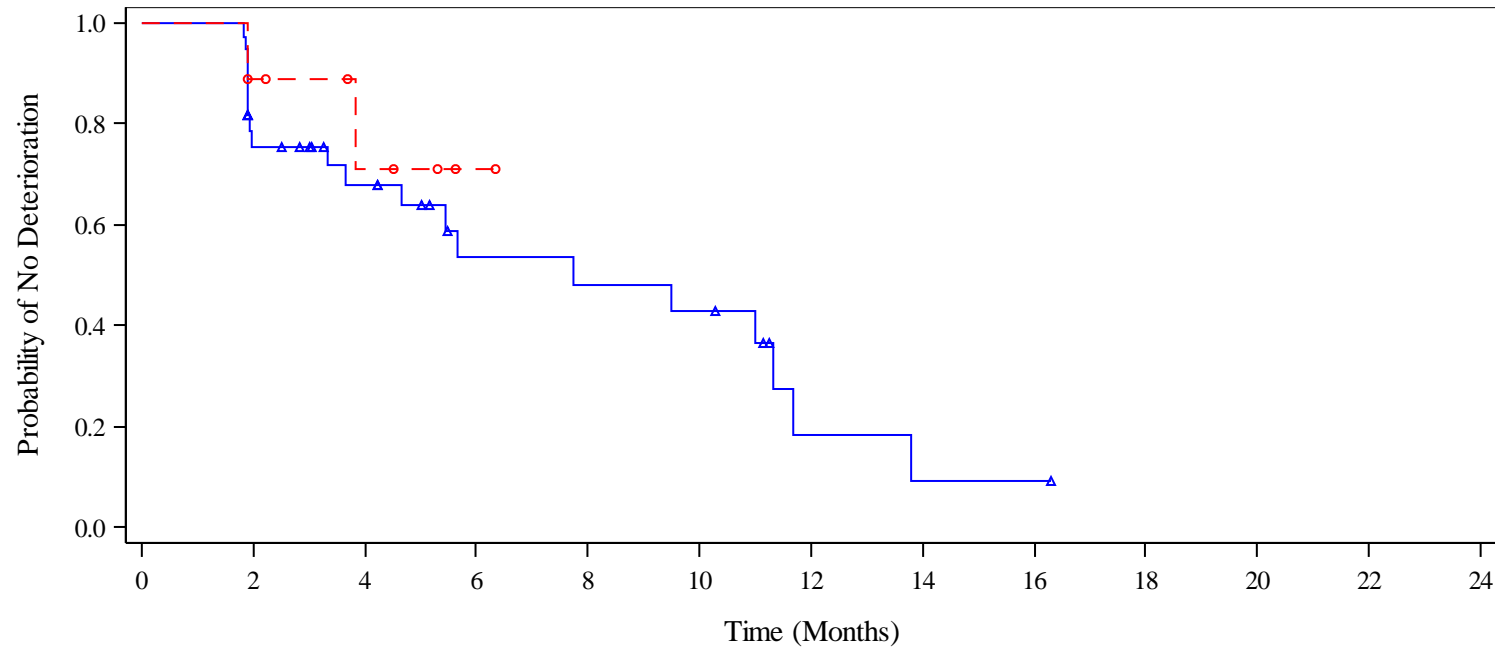
**Figure 4.1.10: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Dyspnea (MTX)**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		38	29	22	12	8	7	4	2	1	0
IC		9	8	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

**Figure 4.1.11: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Insomnia (MTX)**



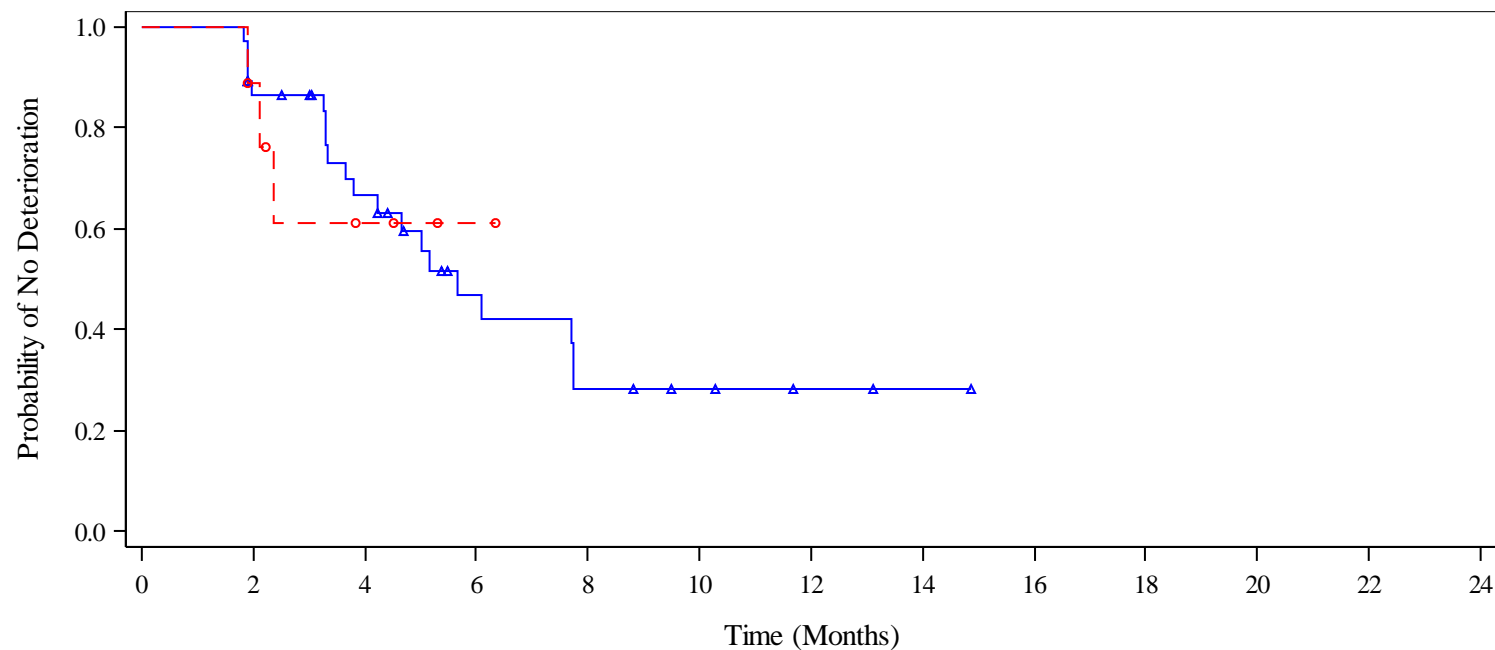
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	38	25	18	10	9	8	2	1	1	0
IC	9	7	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

**Figure 4.1.12: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Appetite Loss (MTX)**



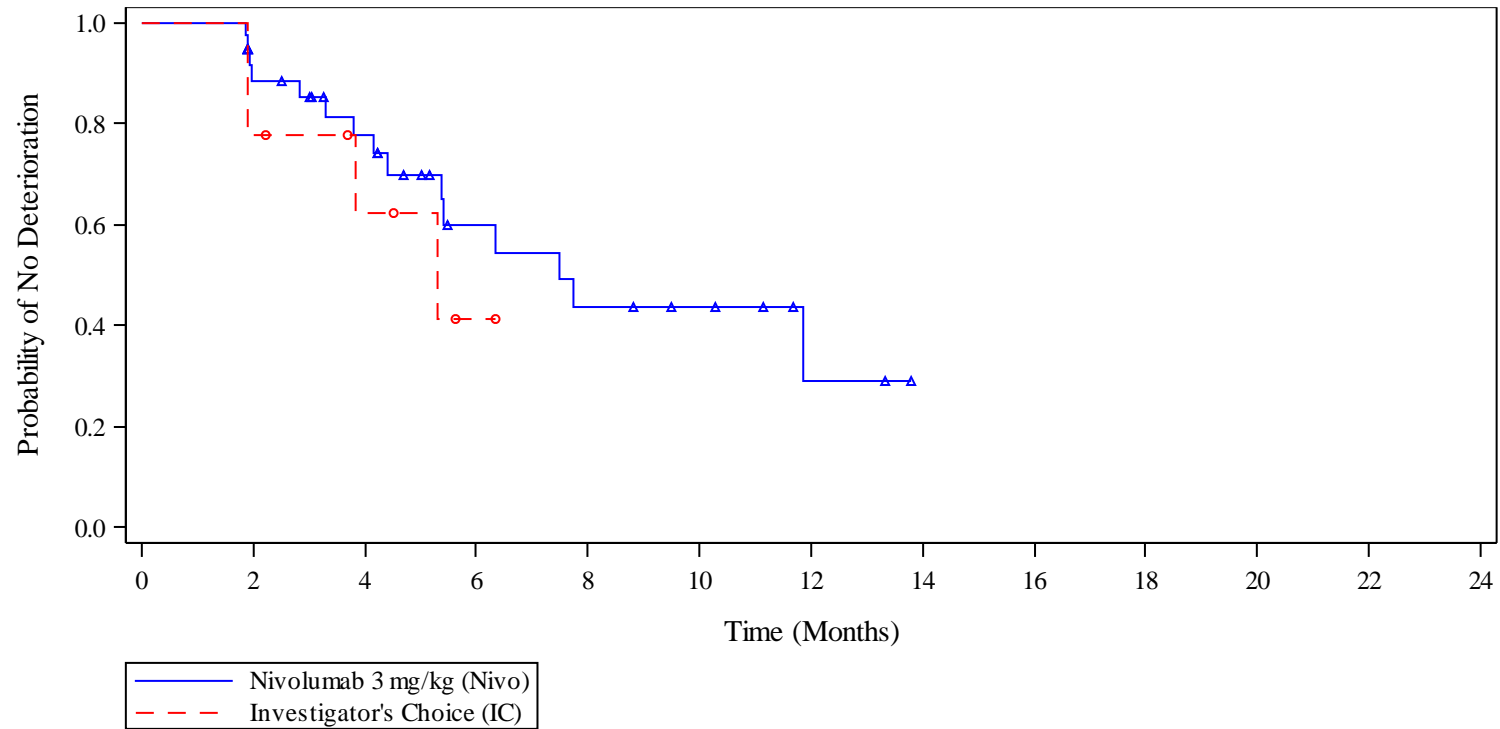
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	38	29	20	10	6	4	2	1	0
IC	9	7	3	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

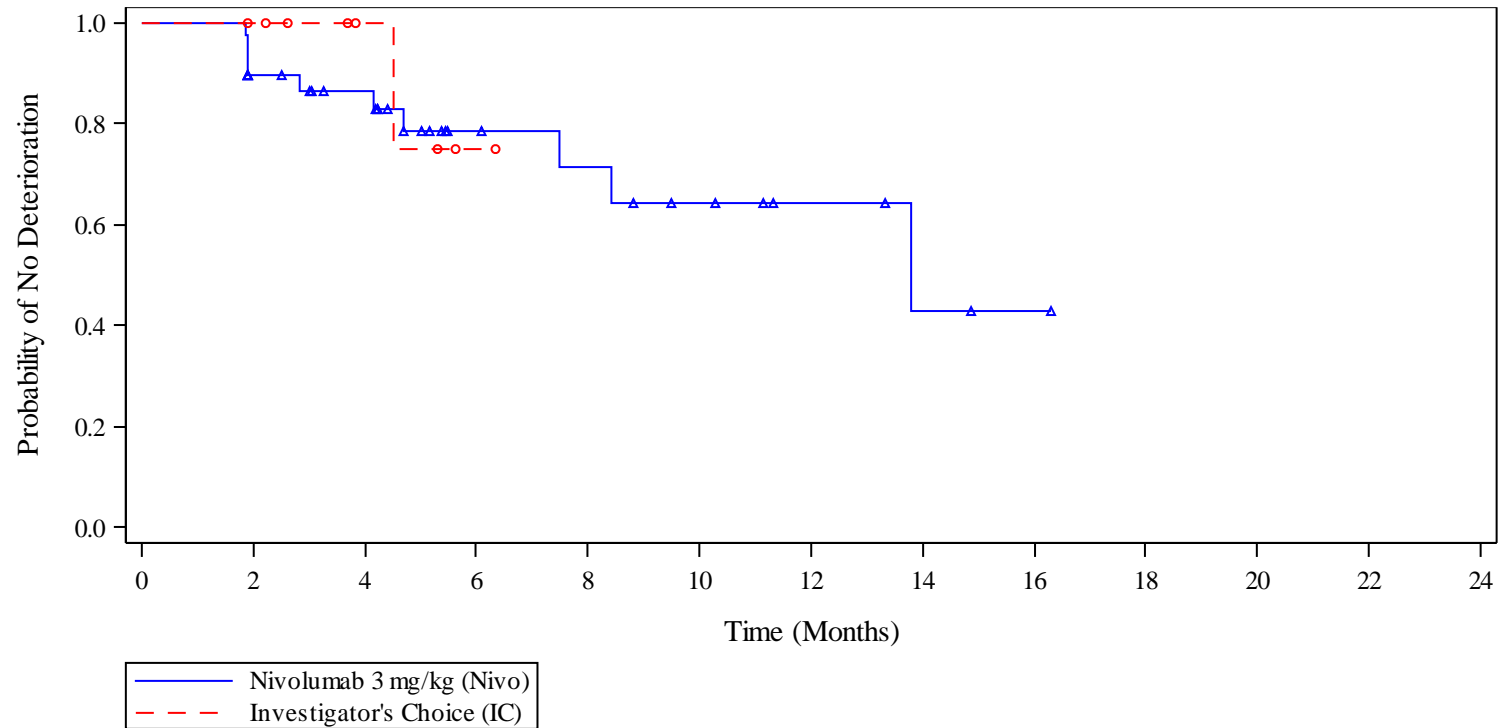
**Figure 4.1.13: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Constipation (MTX)**



		Number of Subjects at Risk							
		0	2	4	6	8	10	12	14
Nivo		39	28	21	11	8	6	2	0
IC		9	7	4	1	0			

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

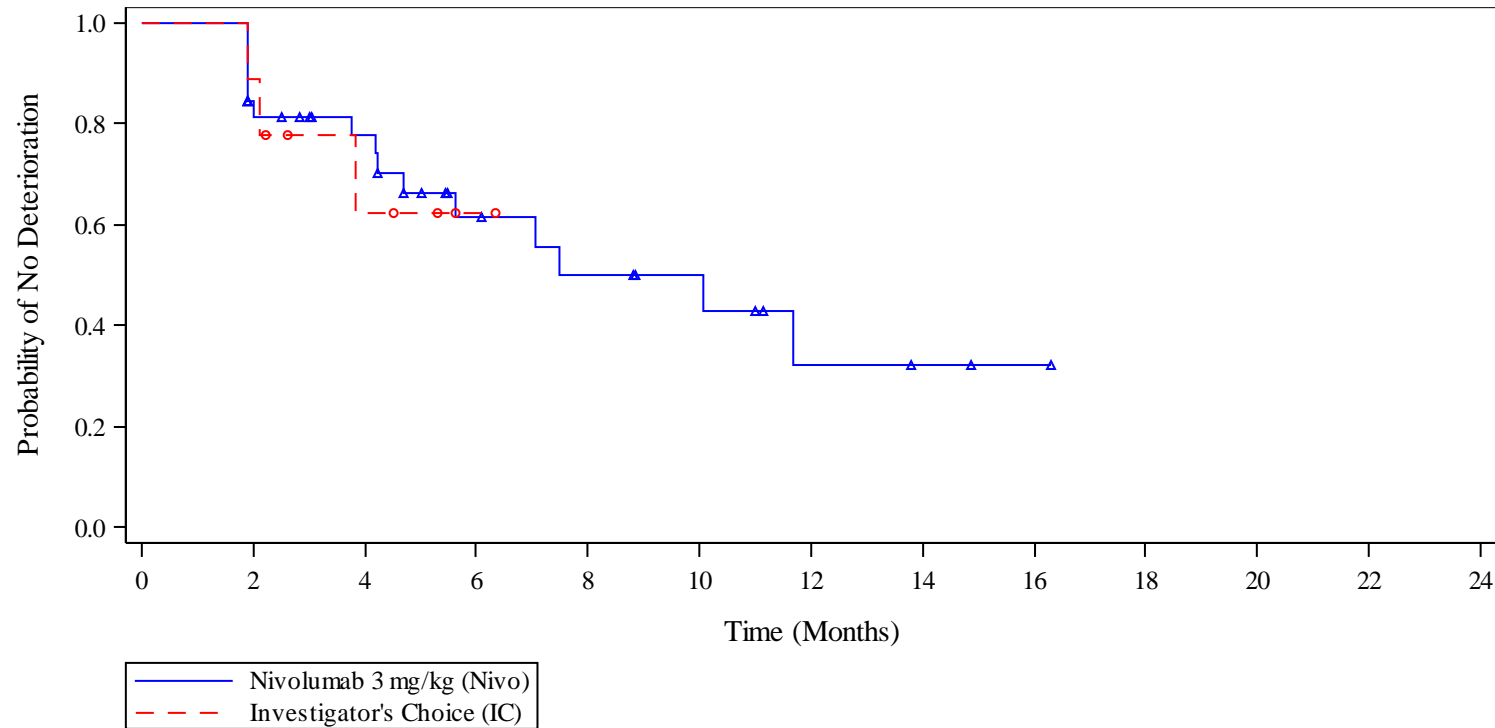
Figure 4.1.14: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Diarrhea (MTX)



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		39	29	24	12	10	7	4	2	1	0
IC		9	8	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

Figure 4.1.15: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Financial Difficulties (MTX)



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		39	27	21	12	9	7	3	2	1	0
IC		9	8	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

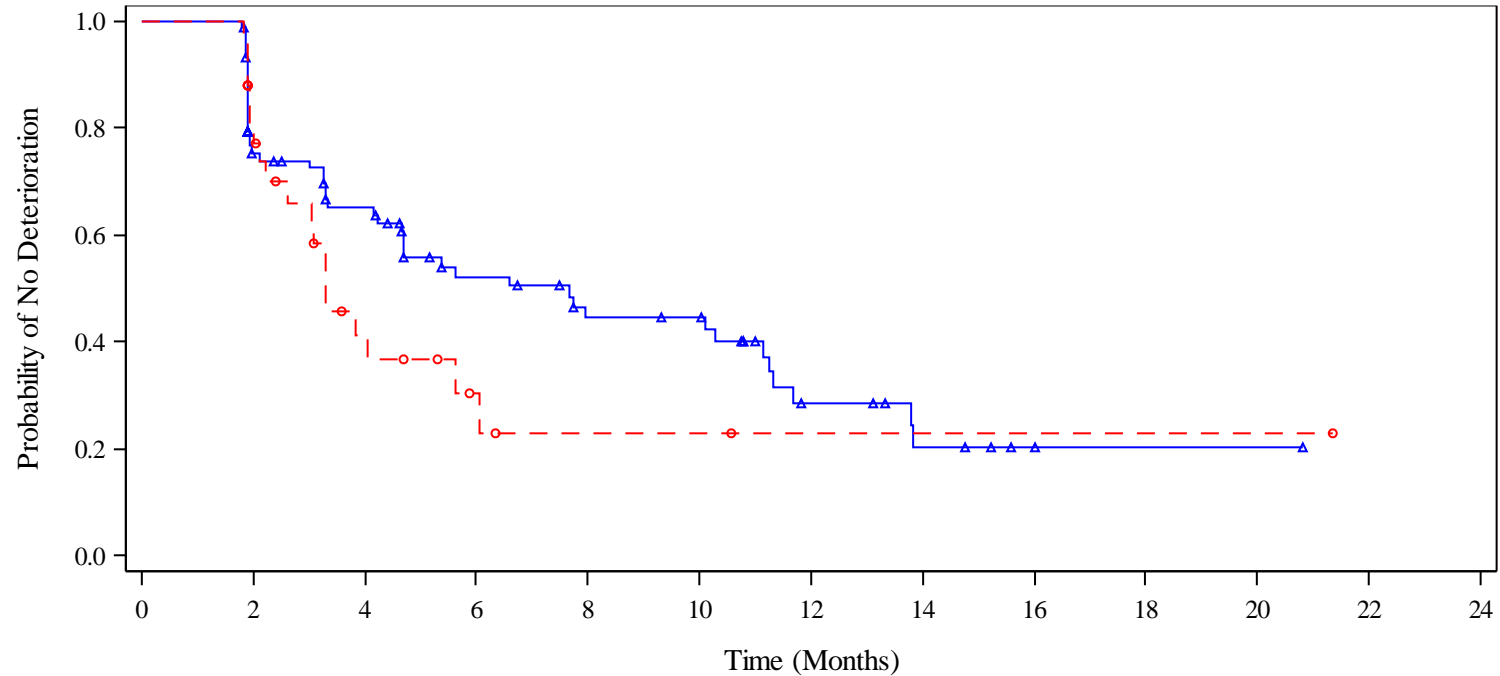
Abbildung 4: Kaplan-Meier-Kurven der Endpunkte Morbidität (Krankheitsbedingte Symptome gemäß EORTC QLQ-C30) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

**4.3.1.3.1.4 Endpunkte Morbidität – Gesundheitszustand gemäß EQ-5D-VAS**

Ergänzung der Kaplan-Meier-Kurven (MID 7 mm und 10 mm)

**Gesamtpopulation**

Figure 4.3.2: Time to First Disease-Related Deterioration and Number at Risk on EQ-5D VAS



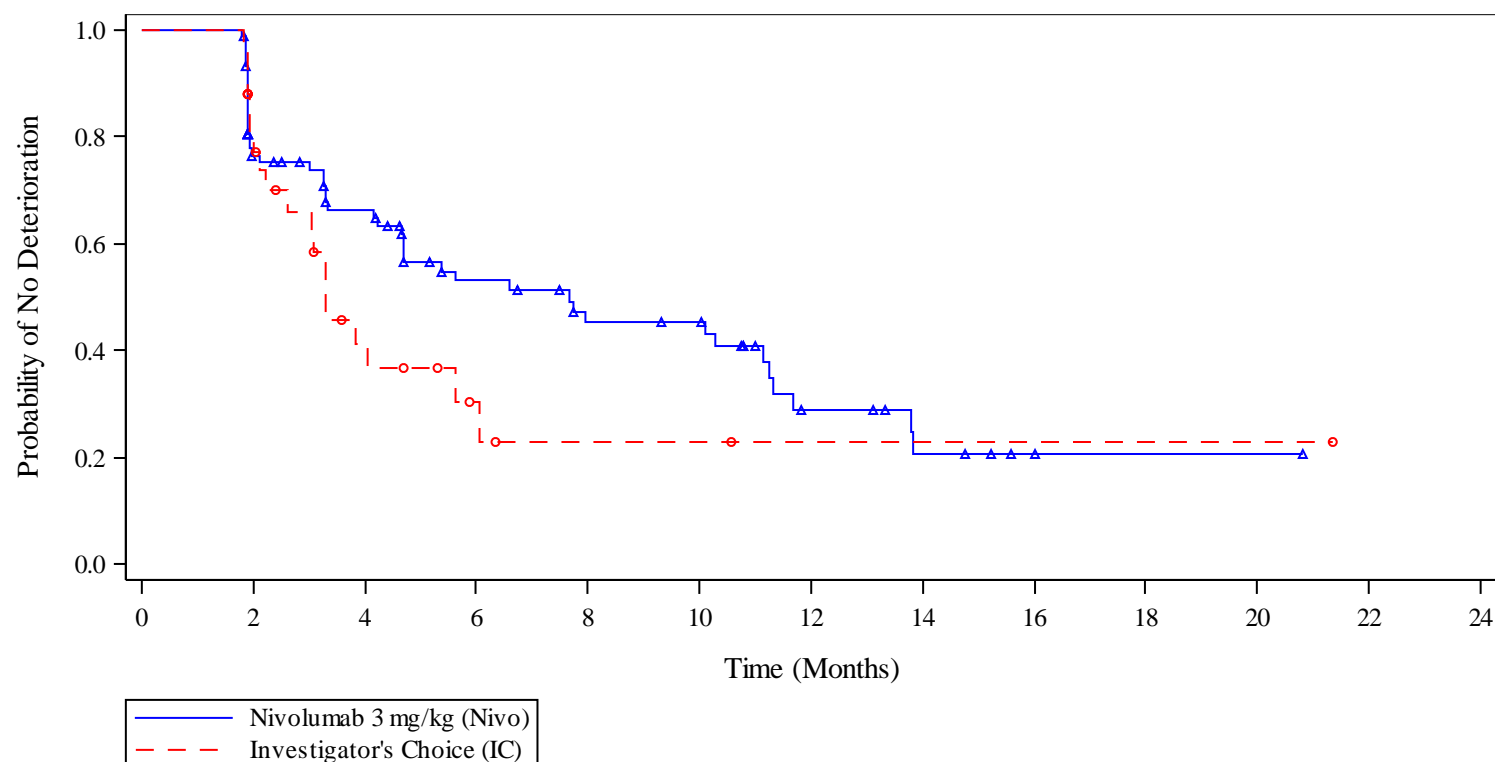
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	89	55	44	29	22	21	9	5	2	1	1	0
IC	33	23	9	4	2	2	1	1	1	1	1	0

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Figure 4.3.3: Time to First Disease-Related Deterioration and Number at Risk on EQ-5D VAS (MID = 10)



		Number of Subjects at Risk											
		0	2	4	6	8	10	12	14	16	18	20	24
Nivo	89	56	44	29	22	21	9	5	2	1	1	0	
IC	33	23	9	4	2	2	1	1	1	1	1	0	

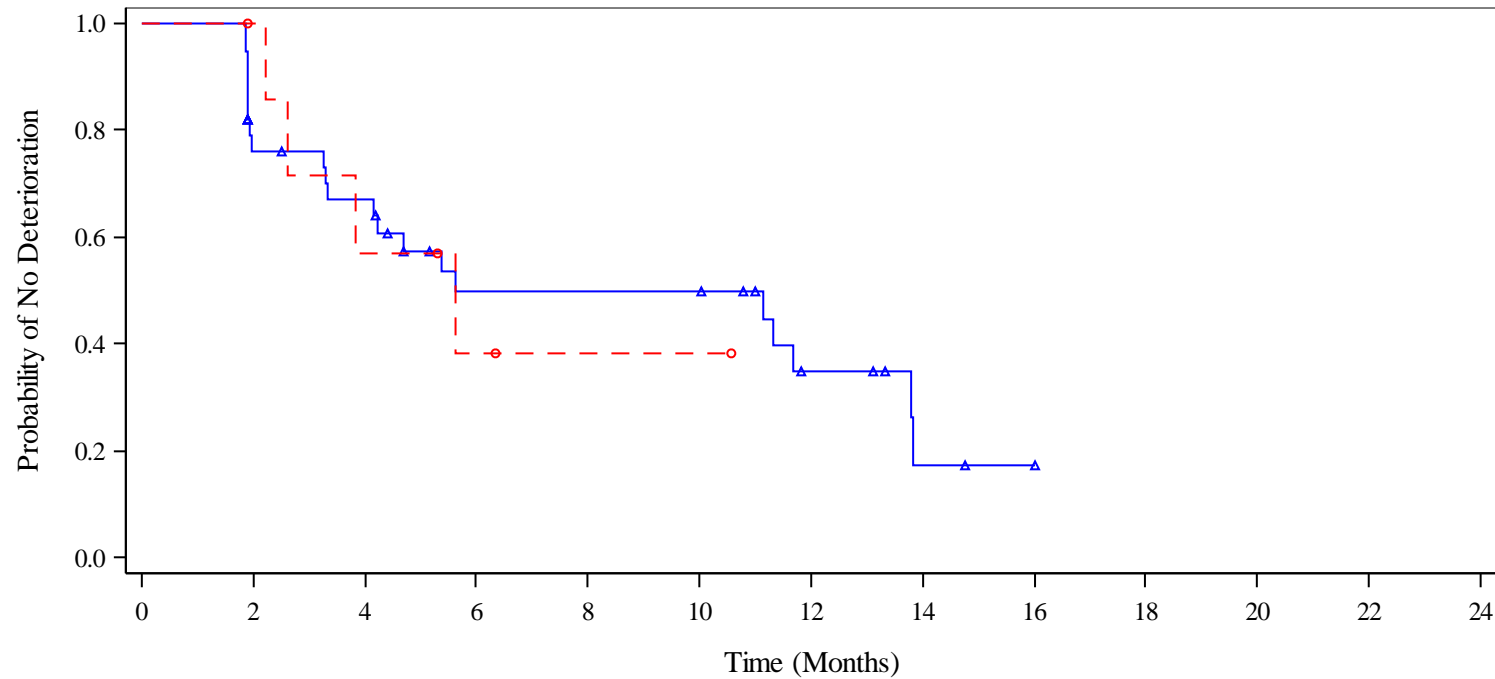
Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Abbildung 5: Kaplan-Meier-Kurven des Endpunkts Gesundheitszustand gemäß EQ-5D-VAS aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)



**MTX-Teilpopulation**

Figure 4.3.2: Time to First Disease-Related Deterioration and Number at Risk on EQ-5D VAS (MTX)



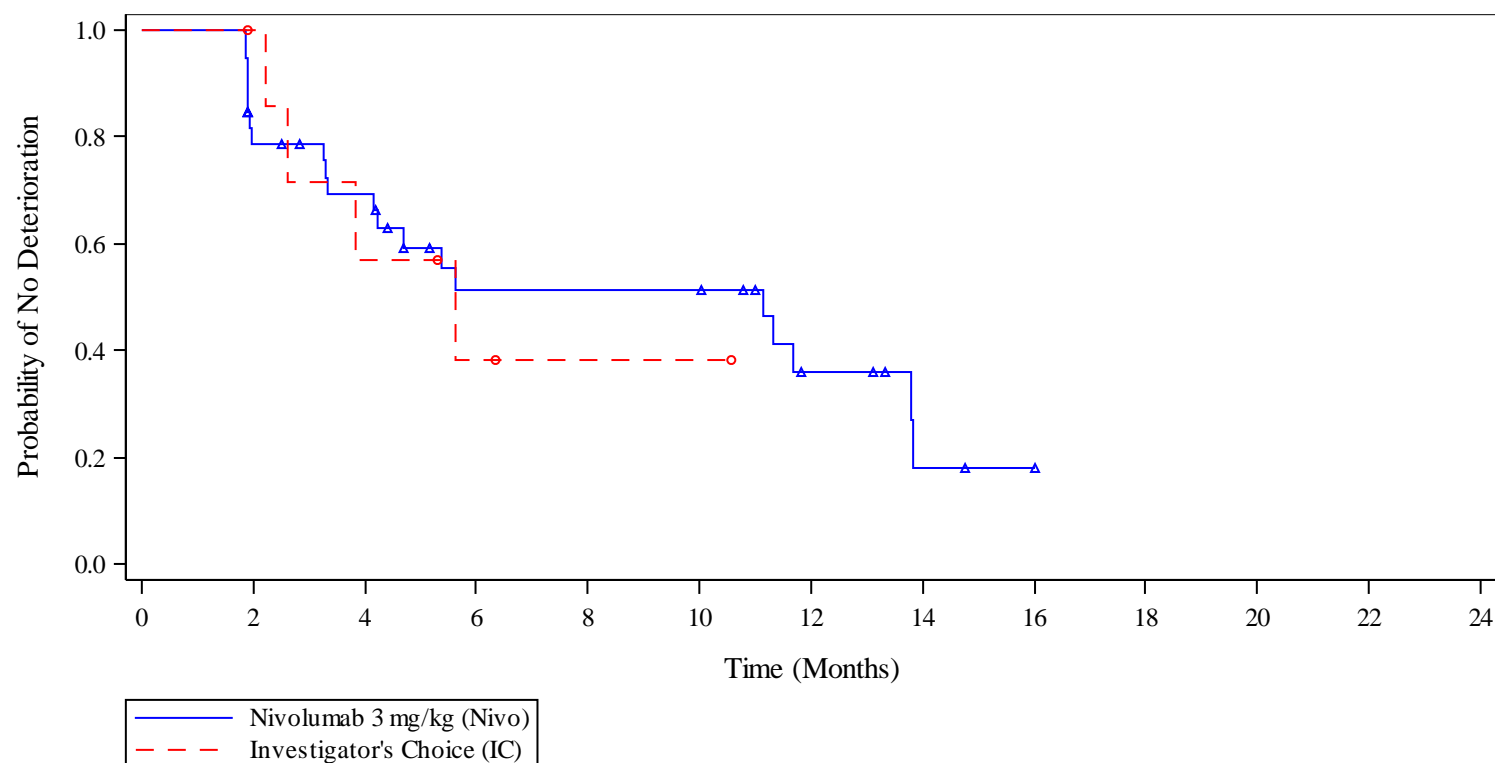
— Nivolumab 3 mg/kg (Nivo)  
- - - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	39	26	22	13	13	13	6	2	1
IC	8	7	4	2	1	1	0		

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

Figure 4.3.3: Time to First Disease-Related Deterioration and Number at Risk on EQ-5D VAS (MID = 10) (MTX)



		Number of Subjects at Risk								
		0	2	4	6	8	10	12	14	16
Nivo		39	27	22	13	13	13	6	2	1
IC		8	7	4	2	1	1	0		

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

Abbildung 6: Kaplan-Meier-Kurven des Endpunkts Gesundheitszustand gemäß EQ-5D-VAS aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

#### **4.3.1.3.1.5 Endpunkte gesundheitsbezogener Lebensqualität gemäß EORTC QLQ-C30**

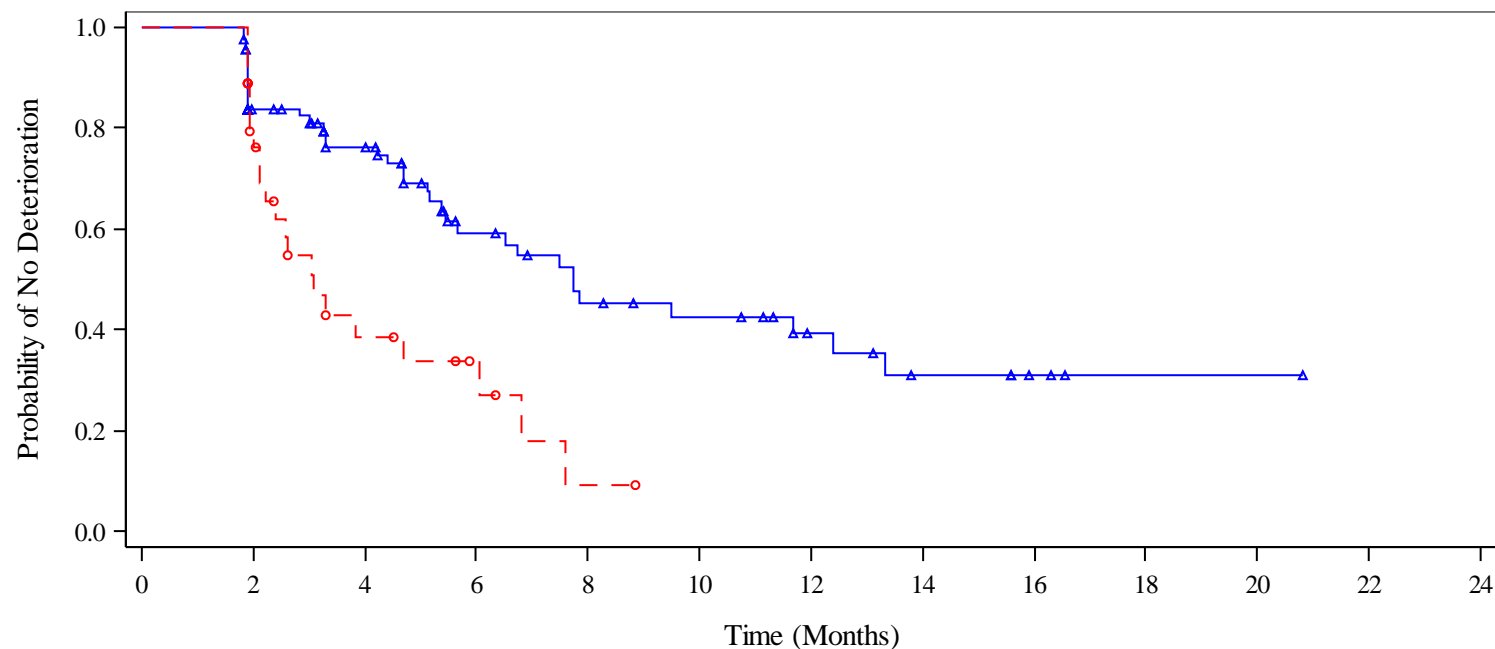
##### Ergänzung der Kaplan-Meier-Kurven

Nachfolgend werden die Kaplan-Meier-Kurven für die Lebensqualitätsskalen des EORTC QLQ-C30 jeweils für die Gesamtpopulation und die MTX-Teilpopulation dargestellt:

Gesundheitlicher Status insgesamt, Physikalische Funktion, Rollenfunktion, Emotionale Funktion, Kognitive Funktion, Soziale Funktion

**Gesamtpopulation**

**Figure 4.1.1: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Global Health Status**



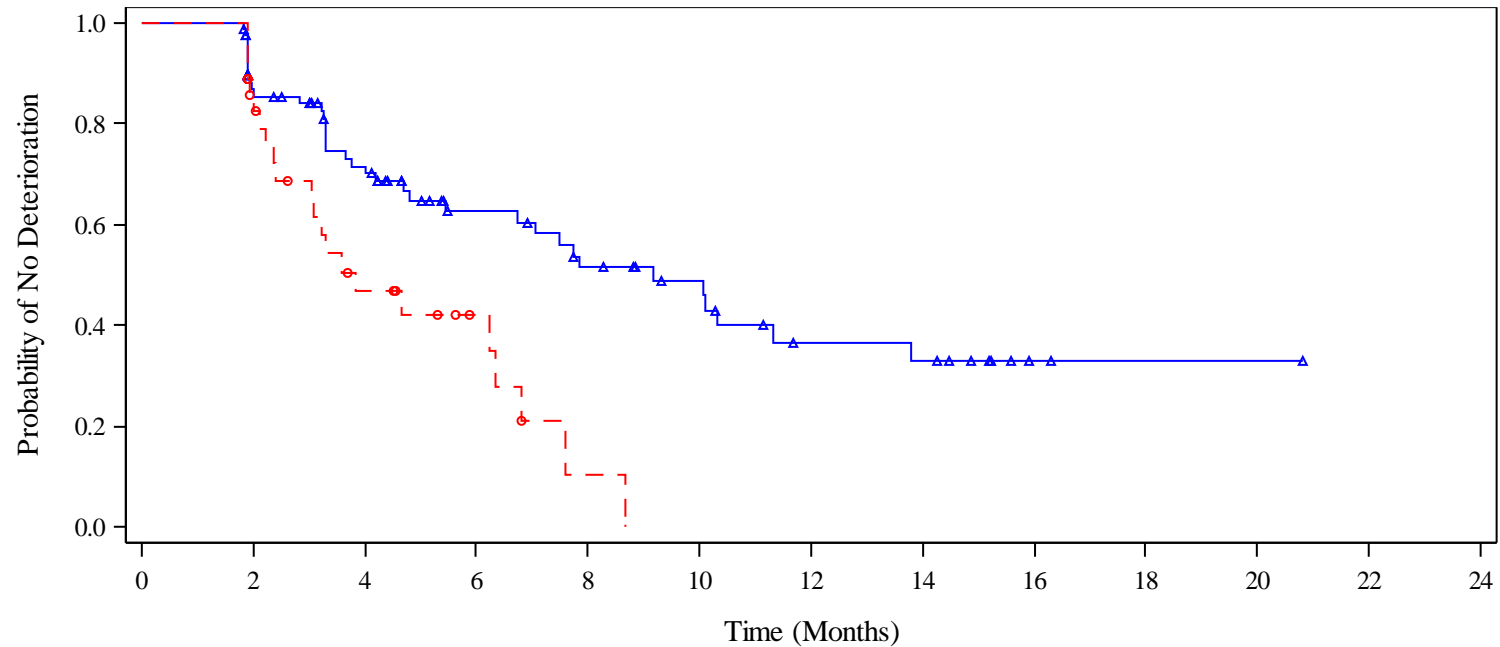
—▲— Nivolumab 3 mg/kg (Nivo)  
- -○- - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	89	61	47	27	19	16	10	6	3	1	1	0
IC	36	24	9	5	1	0						

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

**Figure 4.1.2: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Physical Functioning**



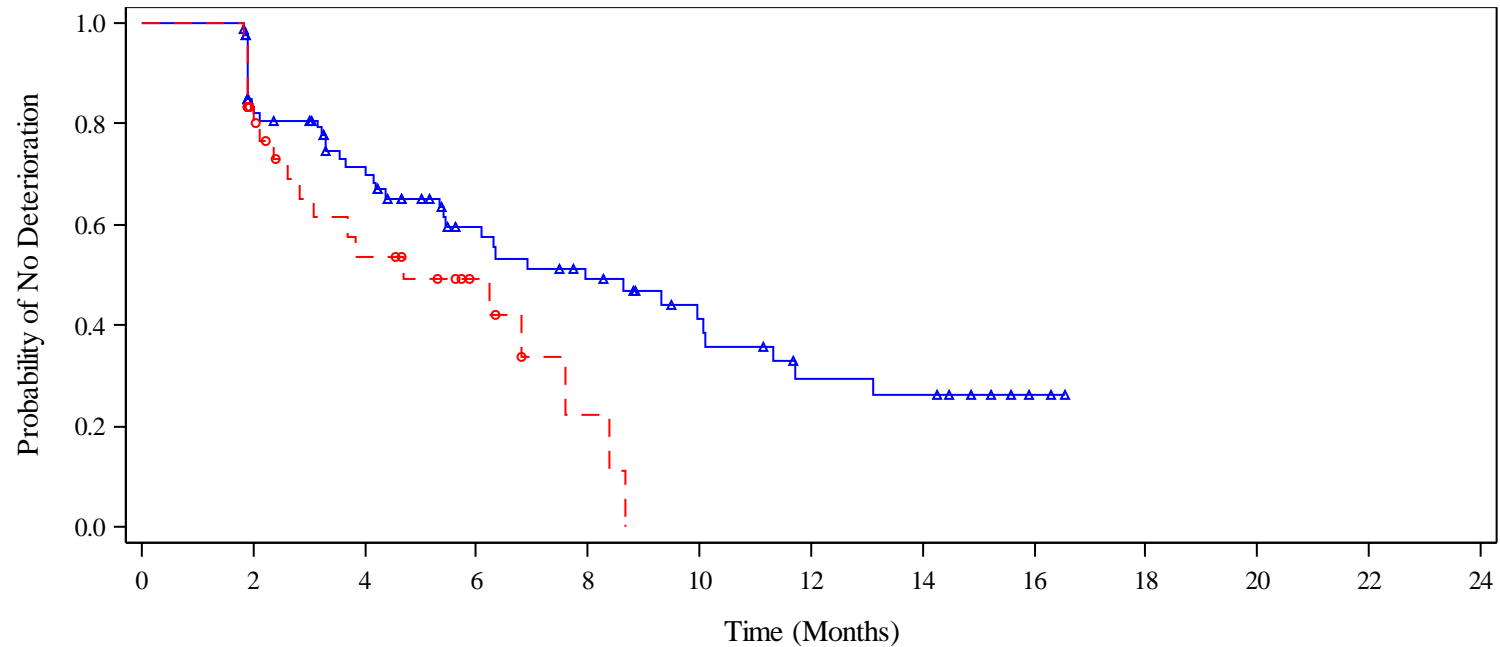
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	89	63	46	29	22	17	10	9	2	1	1	0
IC	36	26	12	6	1	0						

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

**Figure 4.1.3: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Role Functioning**



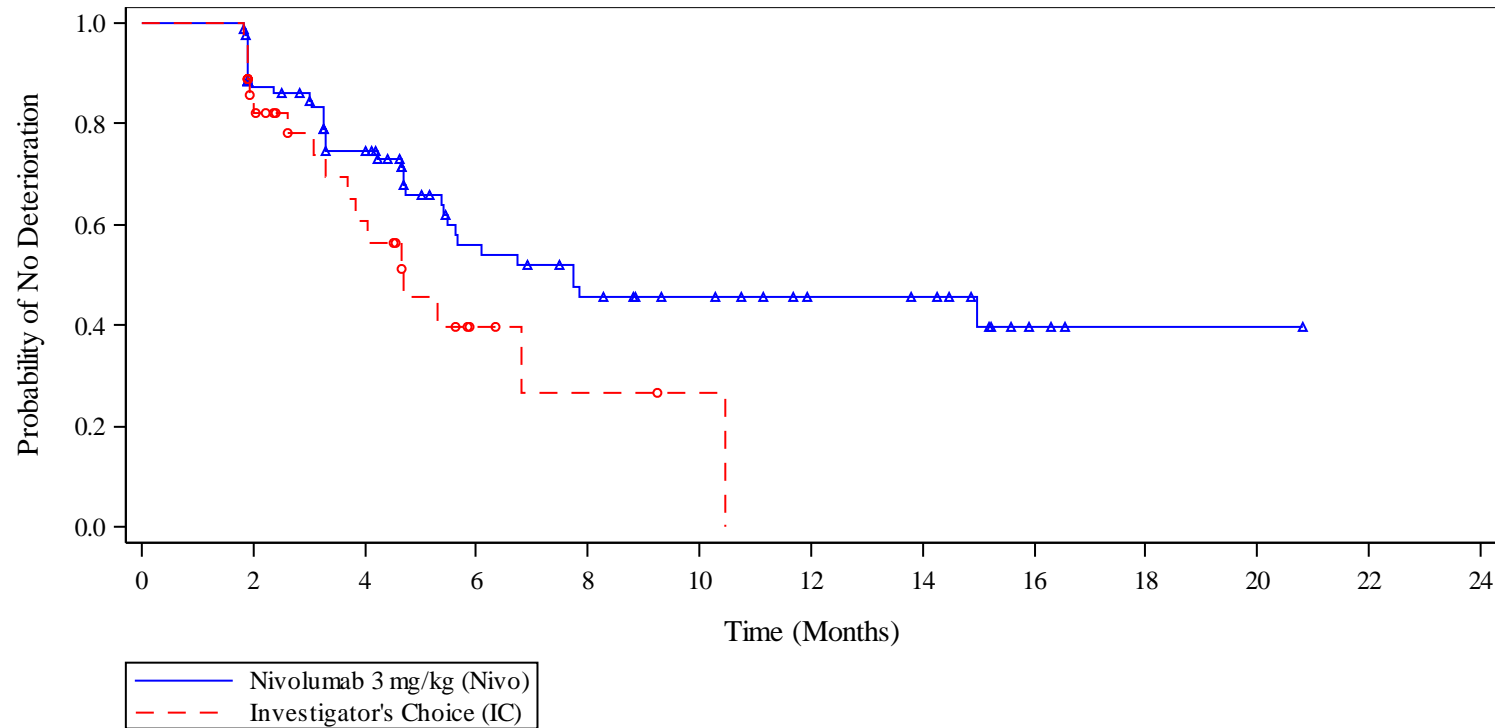
—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	88	61	46	29	22	15	9	8	2	0
IC	36	25	14	7	2	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

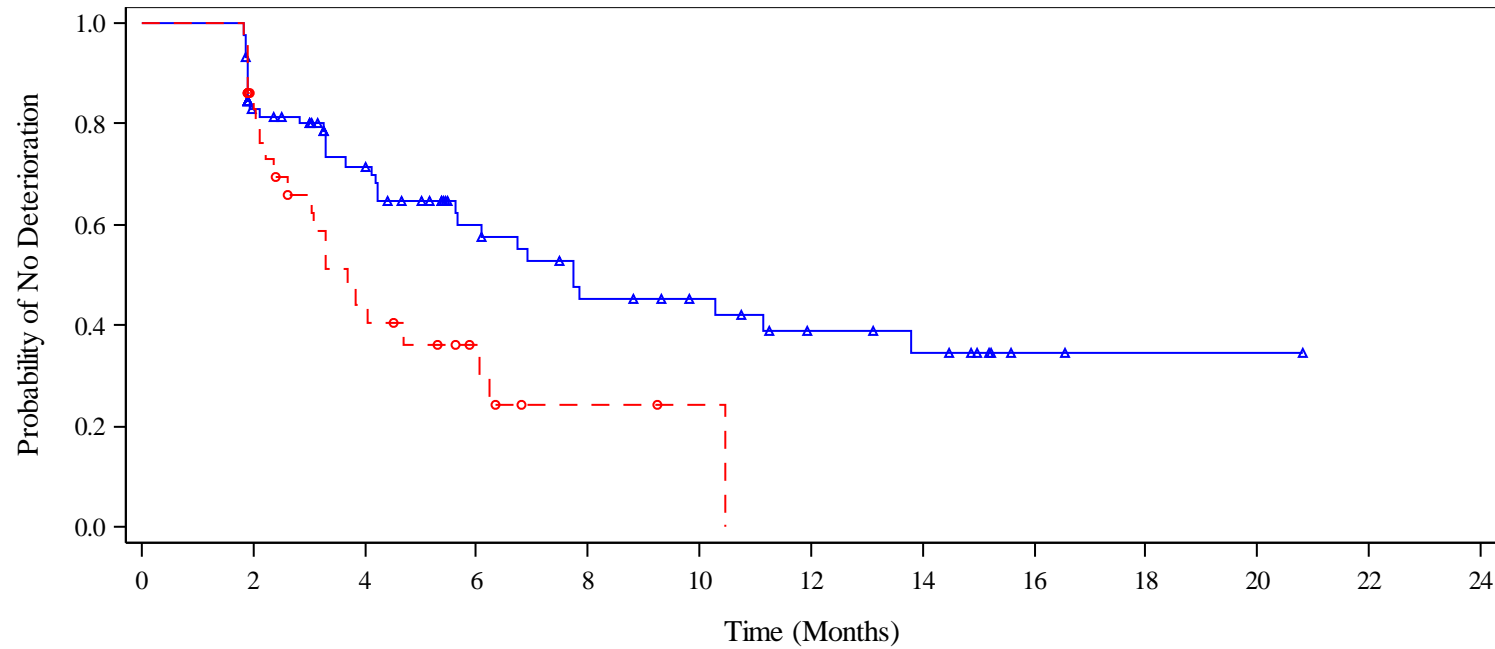
**Figure 4.1.4: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Emotional Functioning**



		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	90	66	50	28	21	17	12	11	3	1	1	0		
IC	36	25	14	4	2	1	0							

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

**Figure 4.1.5: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Cognitive Functioning**



—▲ Nivolumab 3 mg/kg (Nivo)  
- -○ Investigator's Choice (IC)

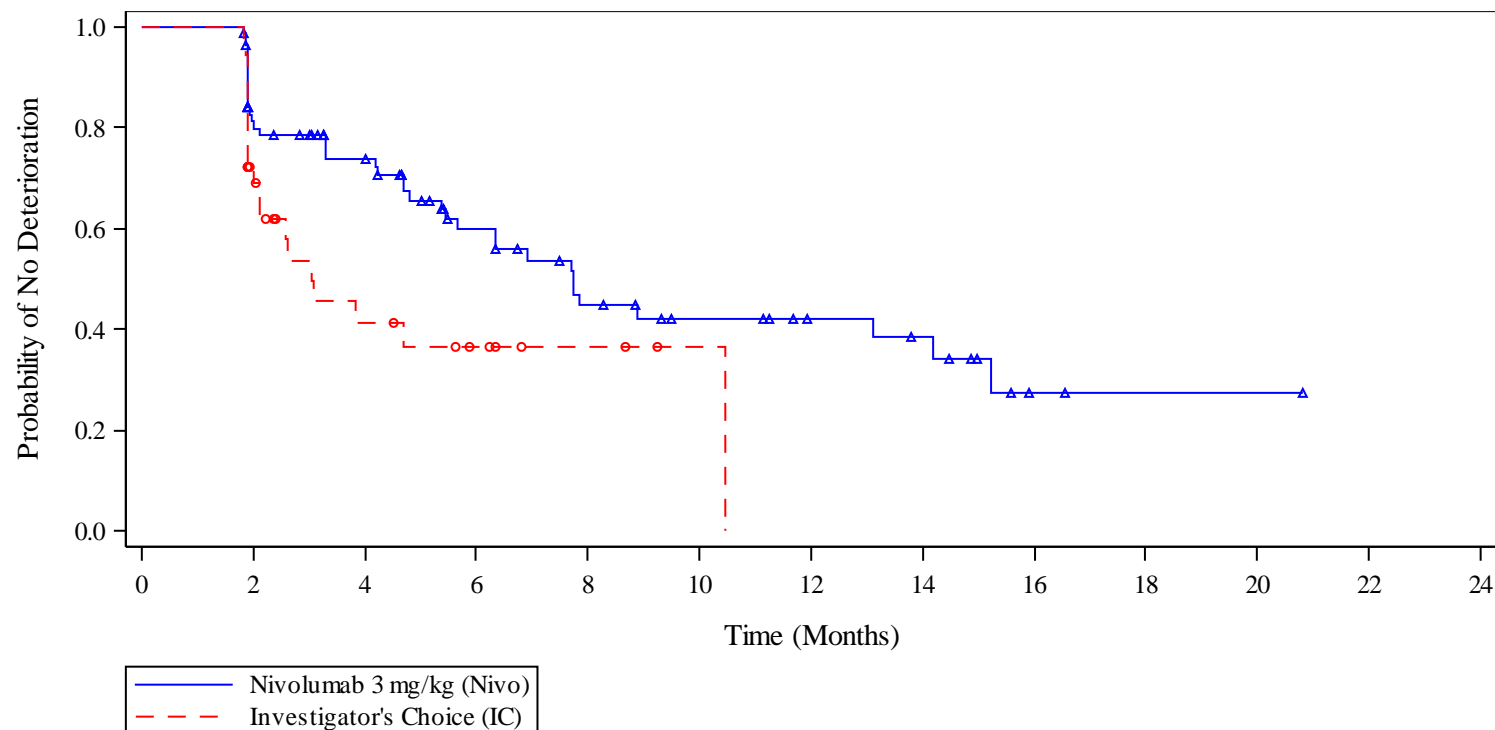
Number of Subjects at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo	90	58	42	26	18	15	10	8	2	1	1	0	
IC	36	26	12	6	2	1	0						

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe



Figure 4.1.6: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Social Functioning



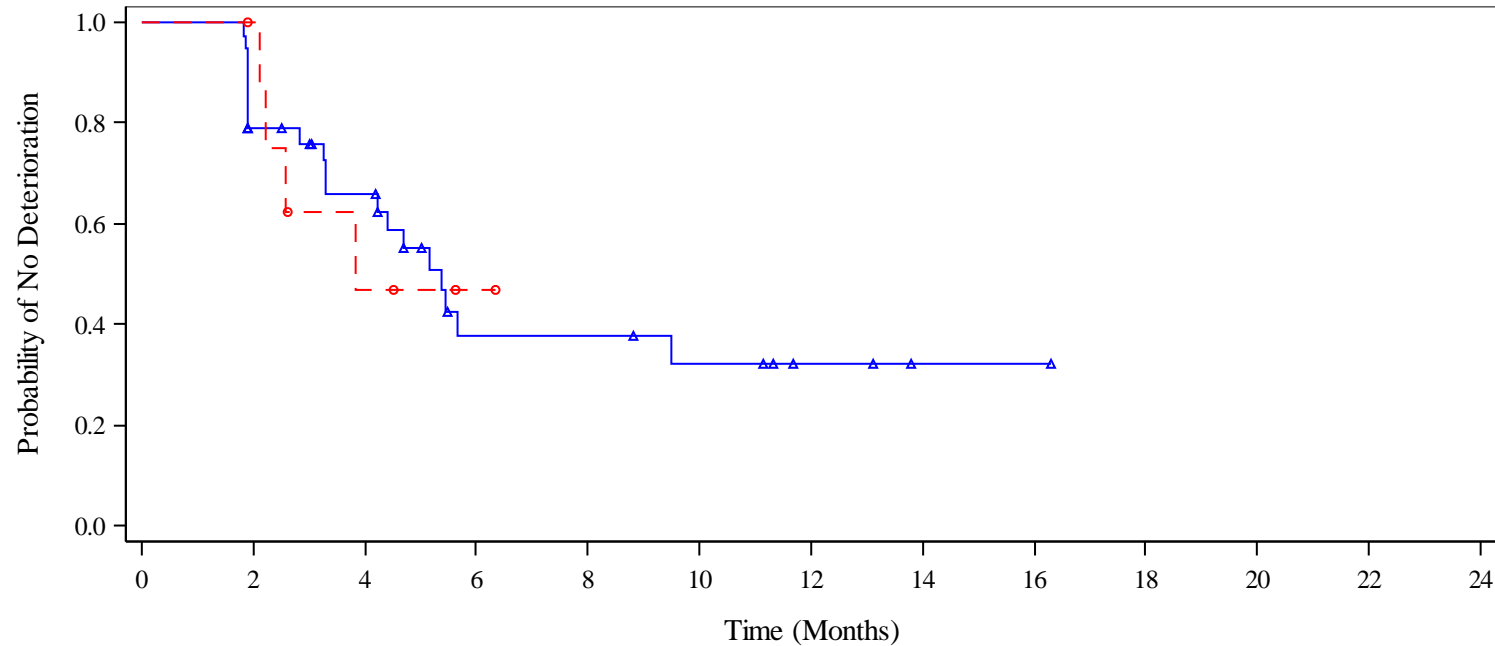
		Number of Subjects at Risk												
		0	2	4	6	8	10	12	14	16	18	20	22	24
Nivo		89	61	48	30	20	15	11	9	2	1	1	0	
IC		36	22	10	6	3	1	0						

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Abbildung 7: Kaplan-Meier-Kurven der Endpunkte gesundheitsbezogener Lebensqualität gemäß EORTC QLQ-C30 aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

**MTX-Teilpopulation**

**Figure 4.1.1: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Global Health Status (MTX)**



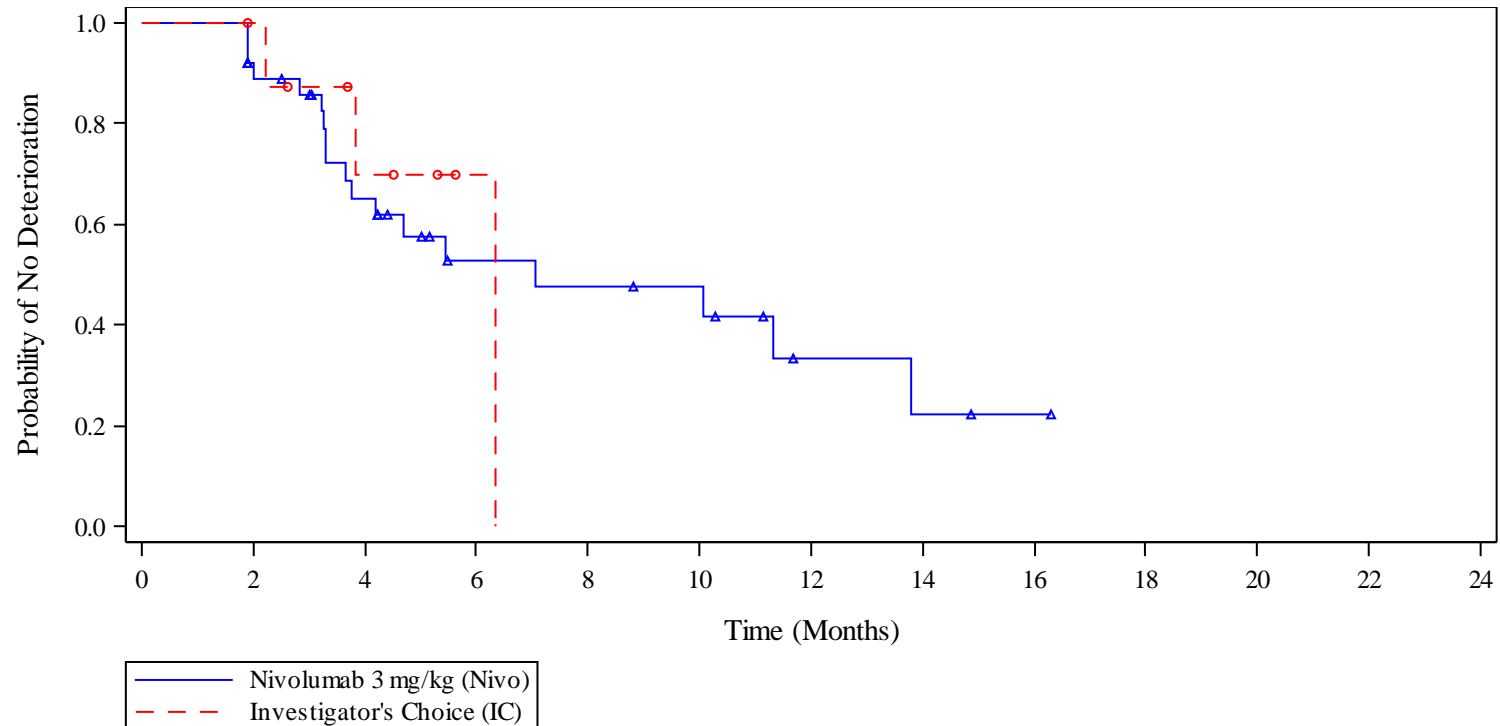
—▲— Nivolumab 3 mg/kg (Nivo)  
- -○- - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	38	27	20	8	8	6	3	1	1	0
IC	9	8	3	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

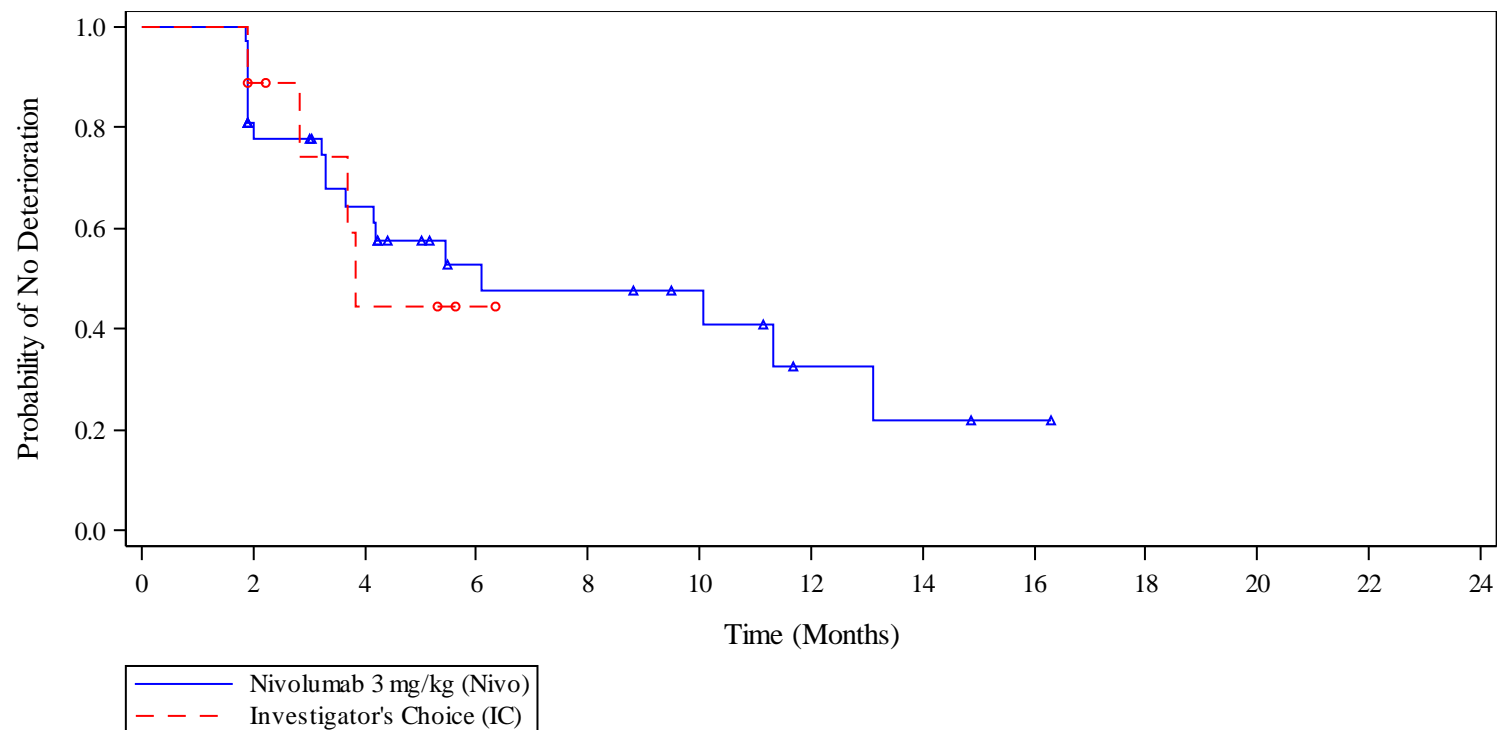
**Figure 4.1.2: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Physical Functioning (MTX)**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		38	30	19	10	9	8	3	2	1	0
IC		9	8	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

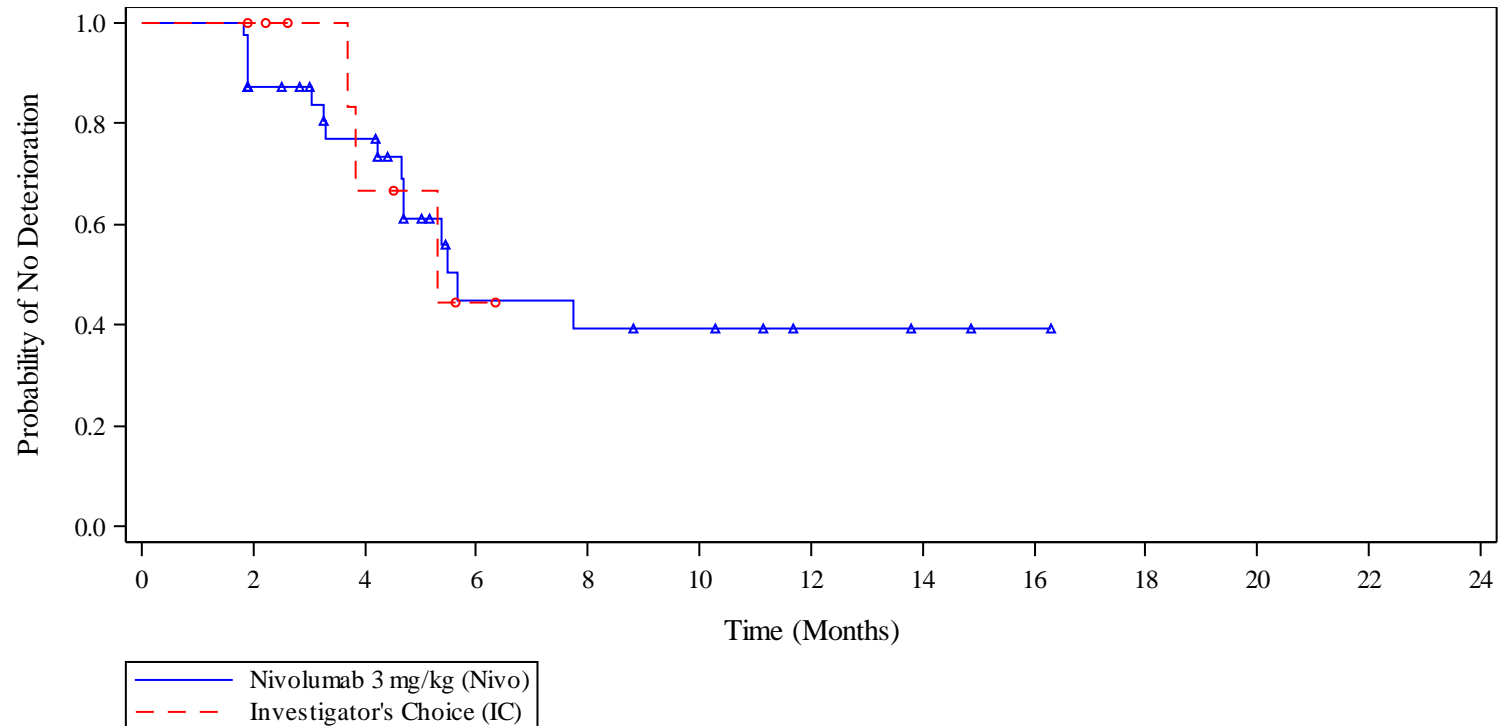
**Figure 4.1.3: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Role Functioning (MTX)**



	Number of Subjects at Risk									
	0	2	3	4	5	6	9	10	11	12
Nivo	37	26	19	10	9	7	3	2	1	0
IC	9	7	3	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

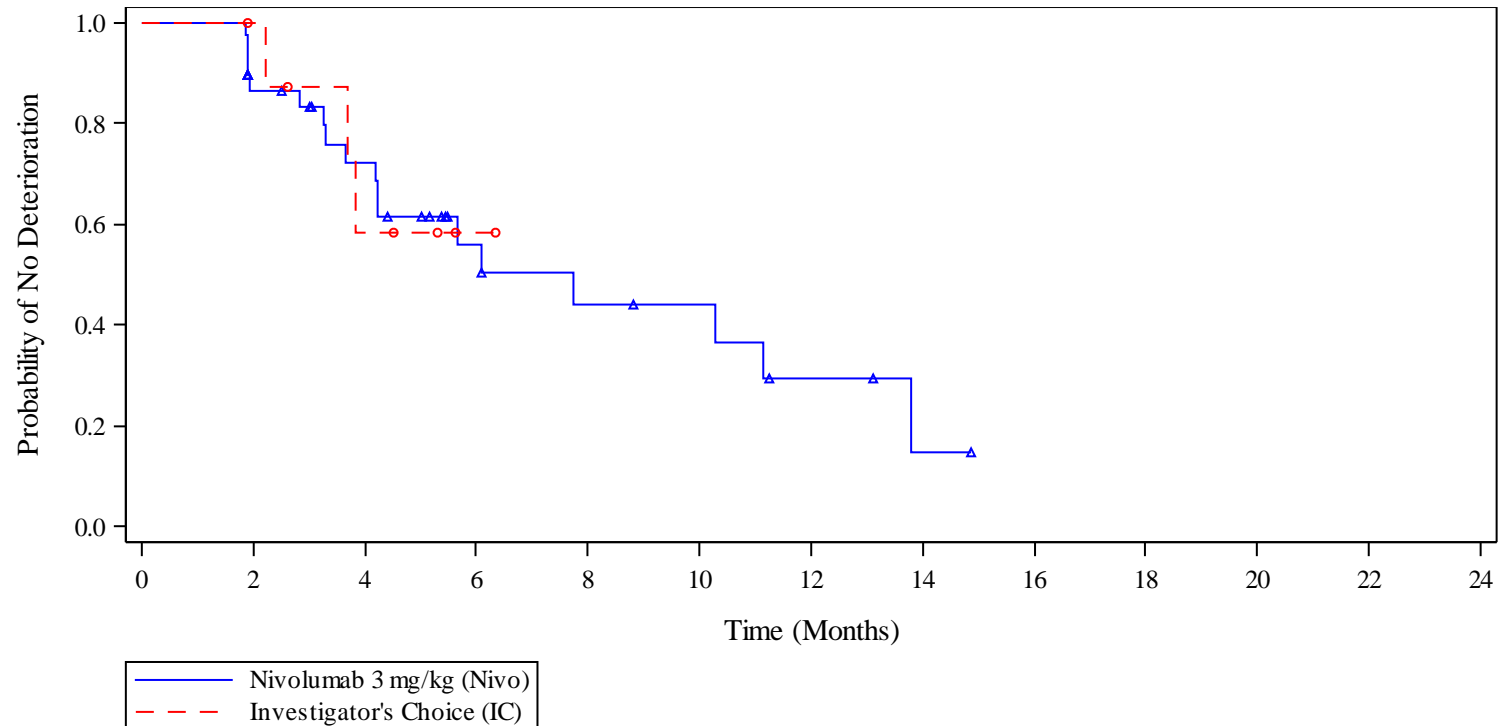
**Figure 4.1.4: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Emotional Functioning (MTX)**



		Number of Subjects at Risk									
		0	2	4	6	8	10	12	14	16	18
Nivo		39	29	22	8	7	6	3	2	1	0
IC		9	8	4	1	0					

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

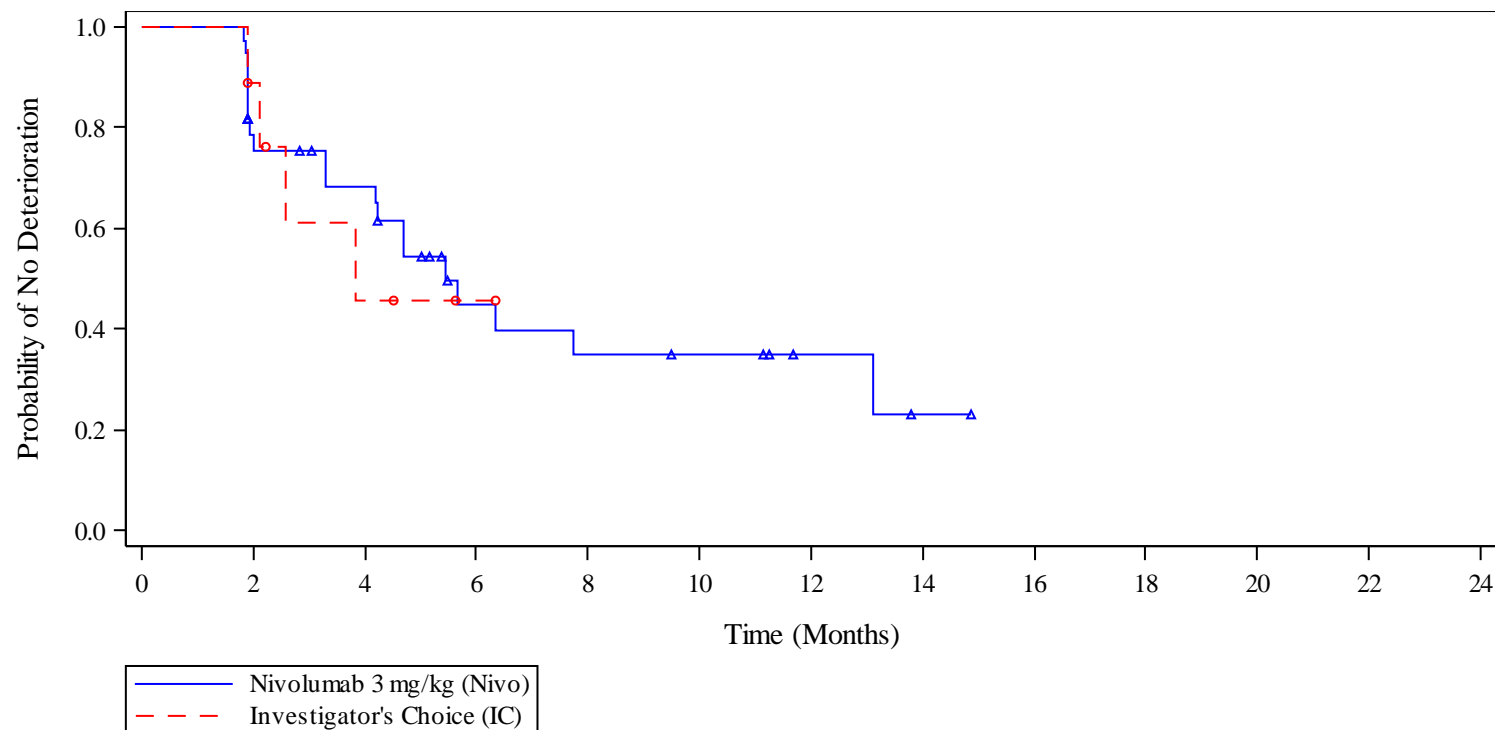
**Figure 4.1.5: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Cognitive Functioning (MTX)**



		Number of Subjects at Risk								
		0	2	4	6	8	10	12	14	16
Nivo		39	27	20	10	7	6	3	1	0
IC		9	8	4	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

**Figure 4.1.6: Time to First Disease-Related Deterioration and Number at Risk on EORTC QLQ C30 Social Functioning (MTX)**



		Number of Subjects at Risk								
		0	2	4	6	8	10	12	14	15
Nivo		38	25	20	9	7	6	3	1	0
IC		9	7	3	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\DataSets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

Abbildung 8: Kaplan-Meier-Kurven der Endpunkte gesundheitsbezogener Lebensqualität gemäß EORTC QLQ-C30 aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

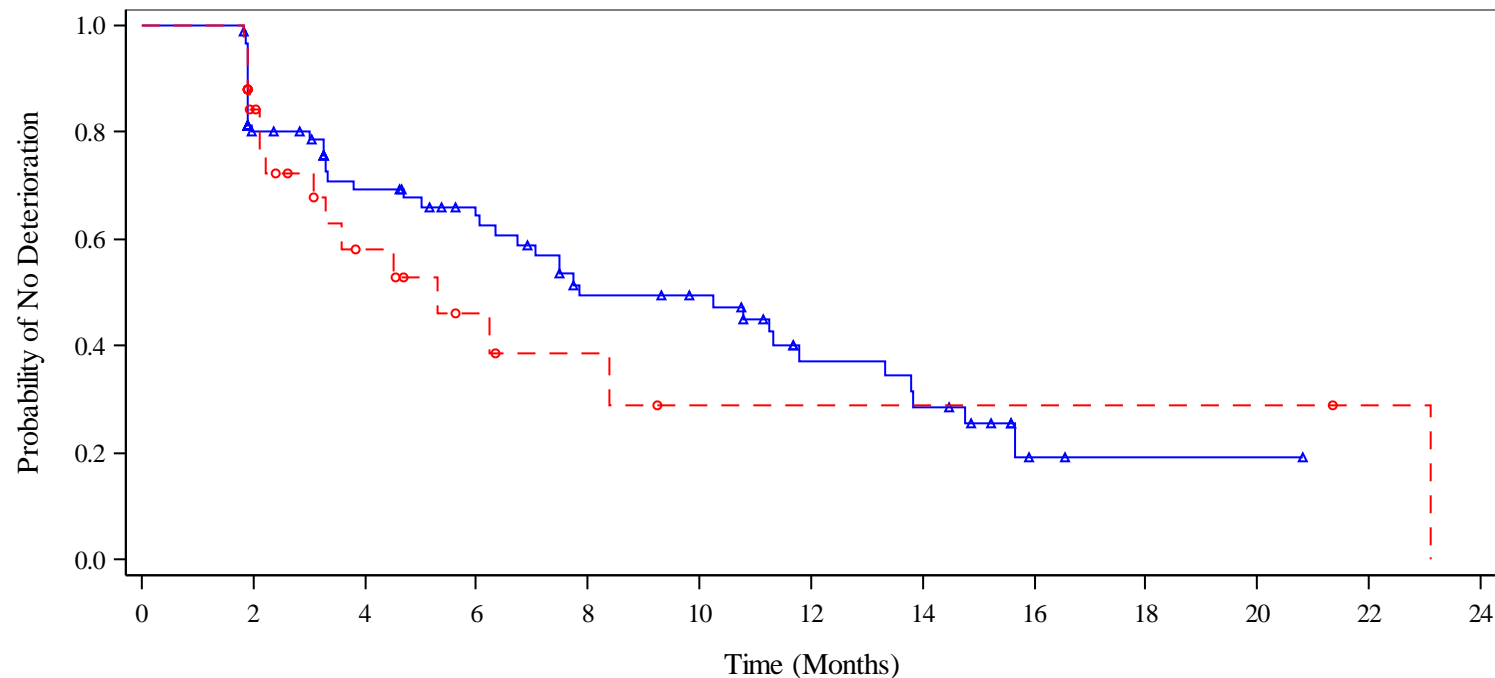
#### **4.3.1.3.1.6 Endpunkte generischer Lebensqualität gemäß EQ-5D**

##### Ergänzung der Kaplan-Meier-Kurven



**Gesamtpopulation**

Figure 4.3.1: Time to First Disease-Related Deterioration and Number at Risk on EQ-5D Utility Index



— Nivolumab 3 mg/kg (Nivo)  
 - - - Investigator's Choice (IC)

Number of Subjects at Risk

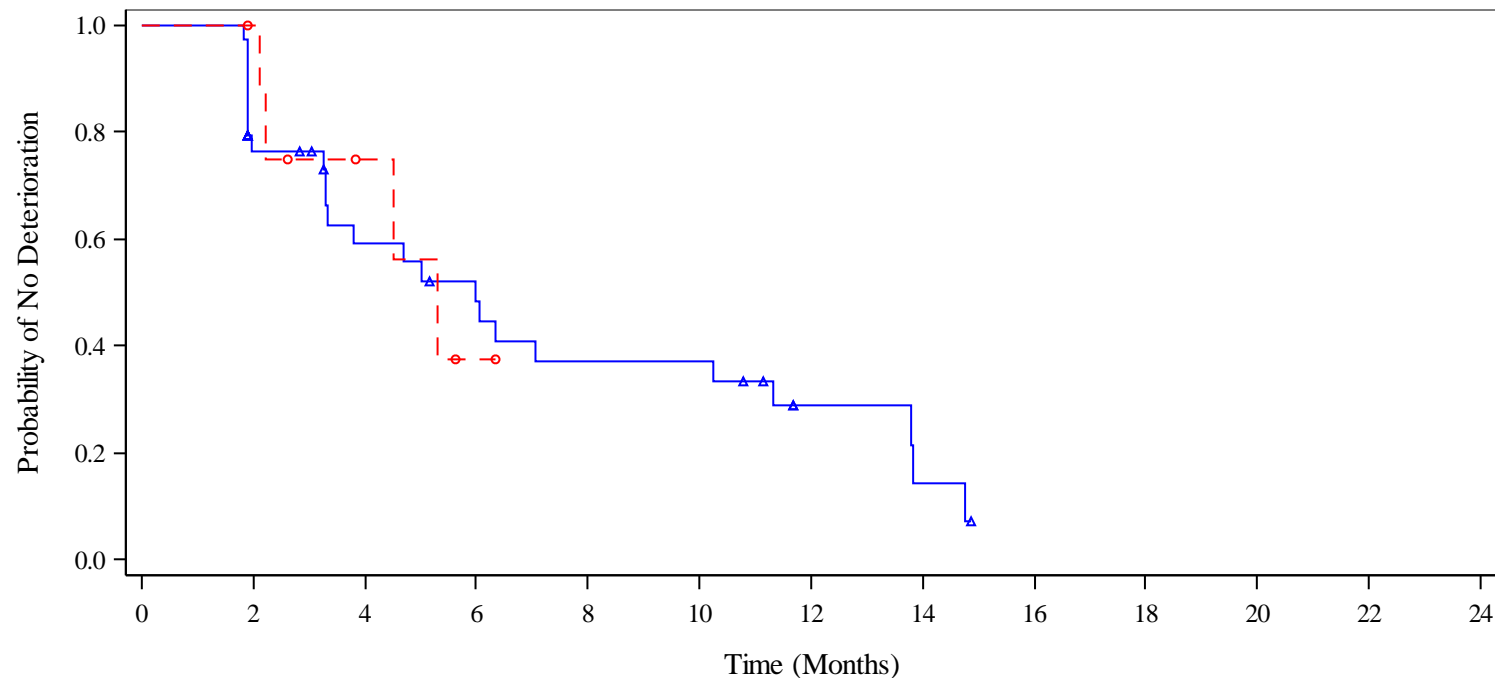
Nivo	87	58	44	37	25	23	13	10	2	1	1	0	
IC	33	22	11	6	4	2	2	2	2	2	2	1	0

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_4.sas EXECUTED: June 22, 2017 at 10:10 by alejandro.moreno-koe

Abbildung 9: Kaplan-Meier-Kurve des Endpunkts generischer Lebensqualität gemäß EQ-5D-Index-Wert aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

**MTX-Teilpopulation**

Figure 4.3.1: Time to First Disease-Related Deterioration and Number at Risk on EQ-5D Utility Index (MTX)



—▲— Nivolumab 3 mg/kg (Nivo)  
- -○- - Investigator's Choice (IC)

Number of Subjects at Risk

Nivo	39	25	17	14	10	10	4	2	0
IC	9	8	4	1	0				

Includes subjects with data at baseline and at least one post-baseline on treatment visit with non-missing PRO data  
 PROGRAM: \\global\av\SHARED\Projs\US\BS7006A QoS Stat Analyses\Datasets\141\Round3\Analysis\Programs\AMNOG\BS7006A 141  
 AMNOG KM Plots\_RND3\_v0\_5.sas EXECUTED: June 26, 2017 at 08:17 by alejandro.moreno-koe

Abbildung 10: Kaplan-Meier-Kurve des Endpunkts generischer Lebensqualität gemäß EQ-5D-Index-Wert aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

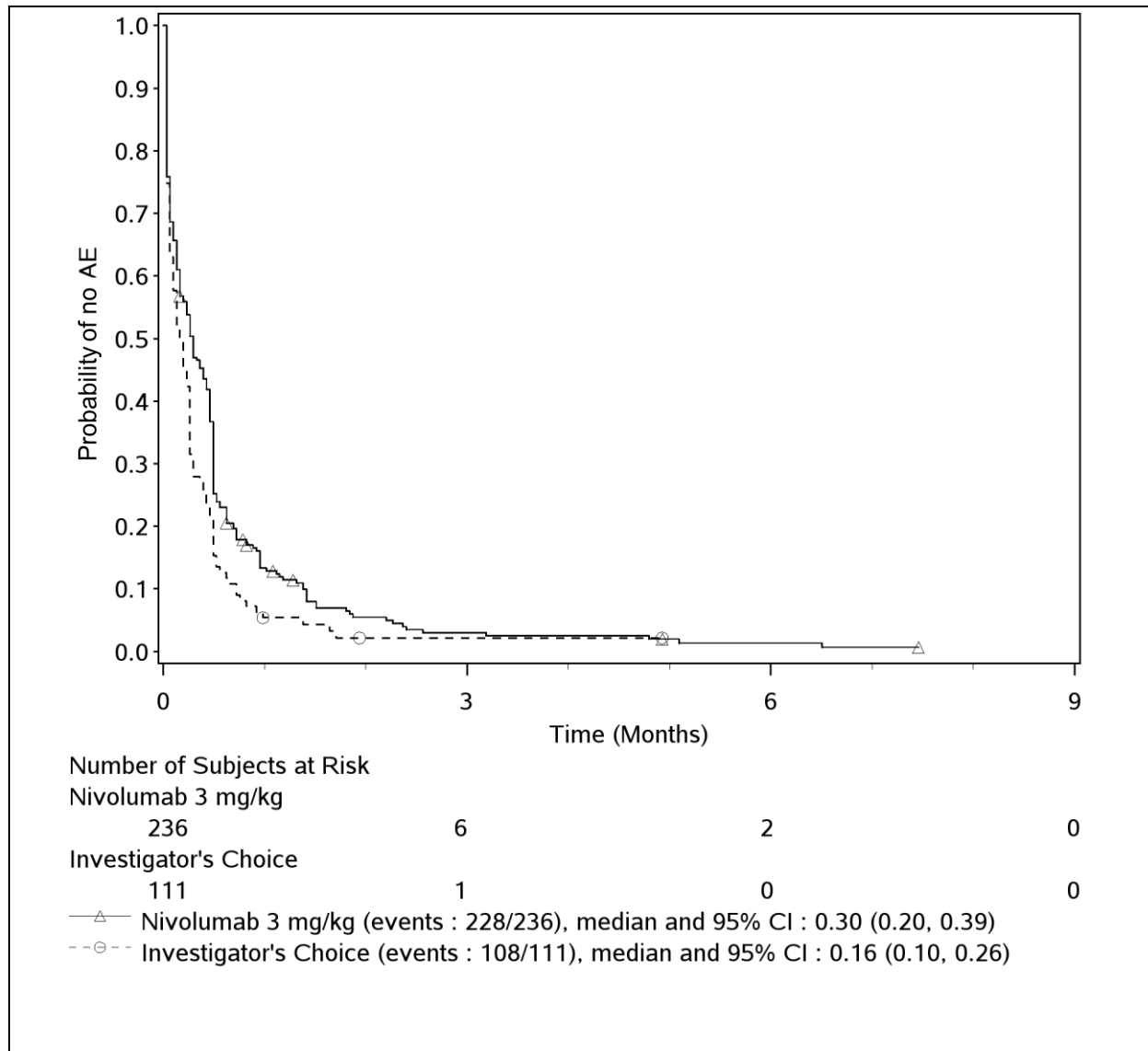
**4.3.1.3.1.7 Endpunkte Verträglichkeit**Ergänzung der Kaplan-Meier-Kurven***Gesamtpopulation***

Abbildung 11: Kaplan-Meier-Kurve des Endpunkts jegliches UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

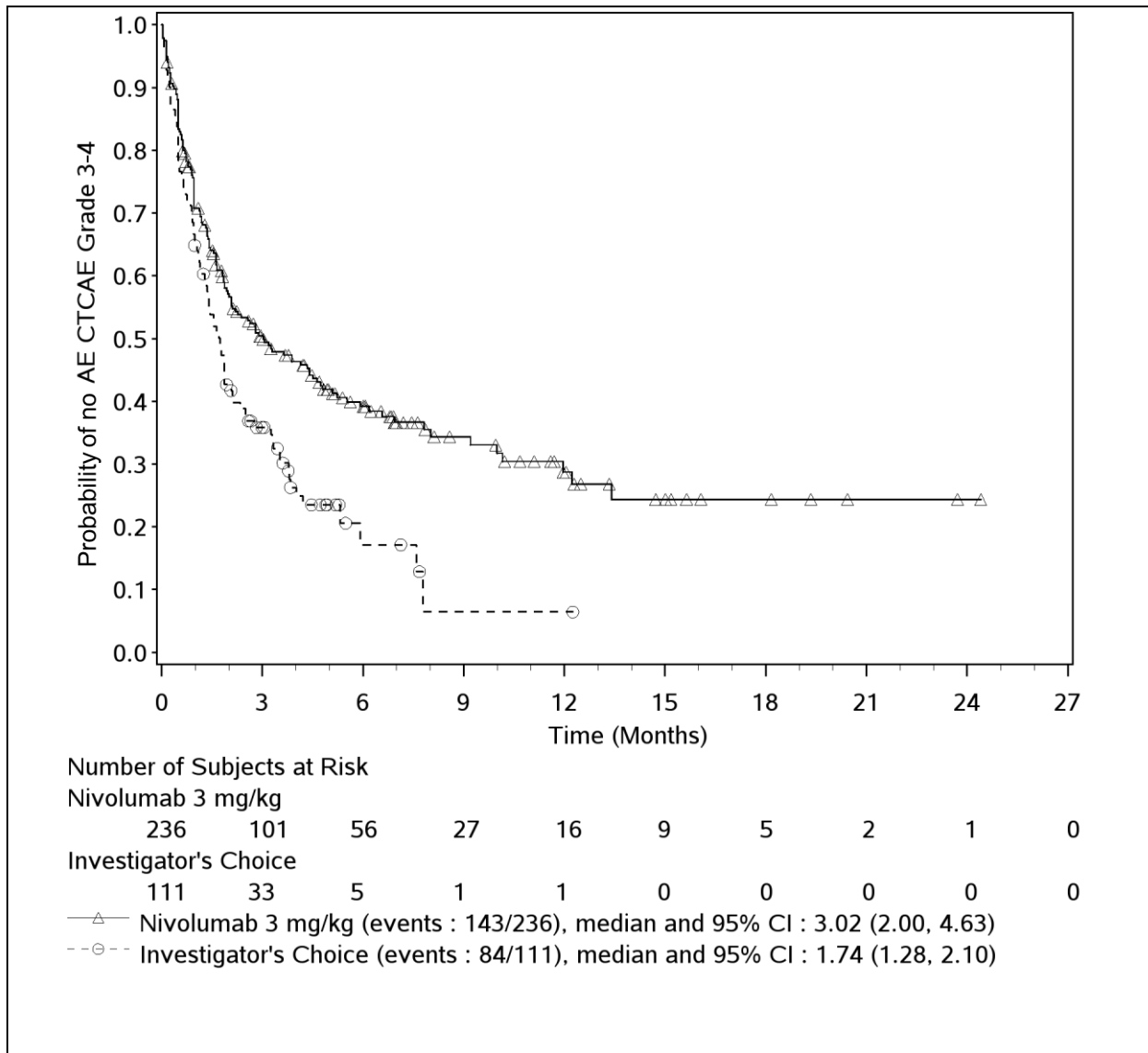


Abbildung 12: Kaplan-Meier-Kurve des Endpunkts UE Grad 3-4 ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

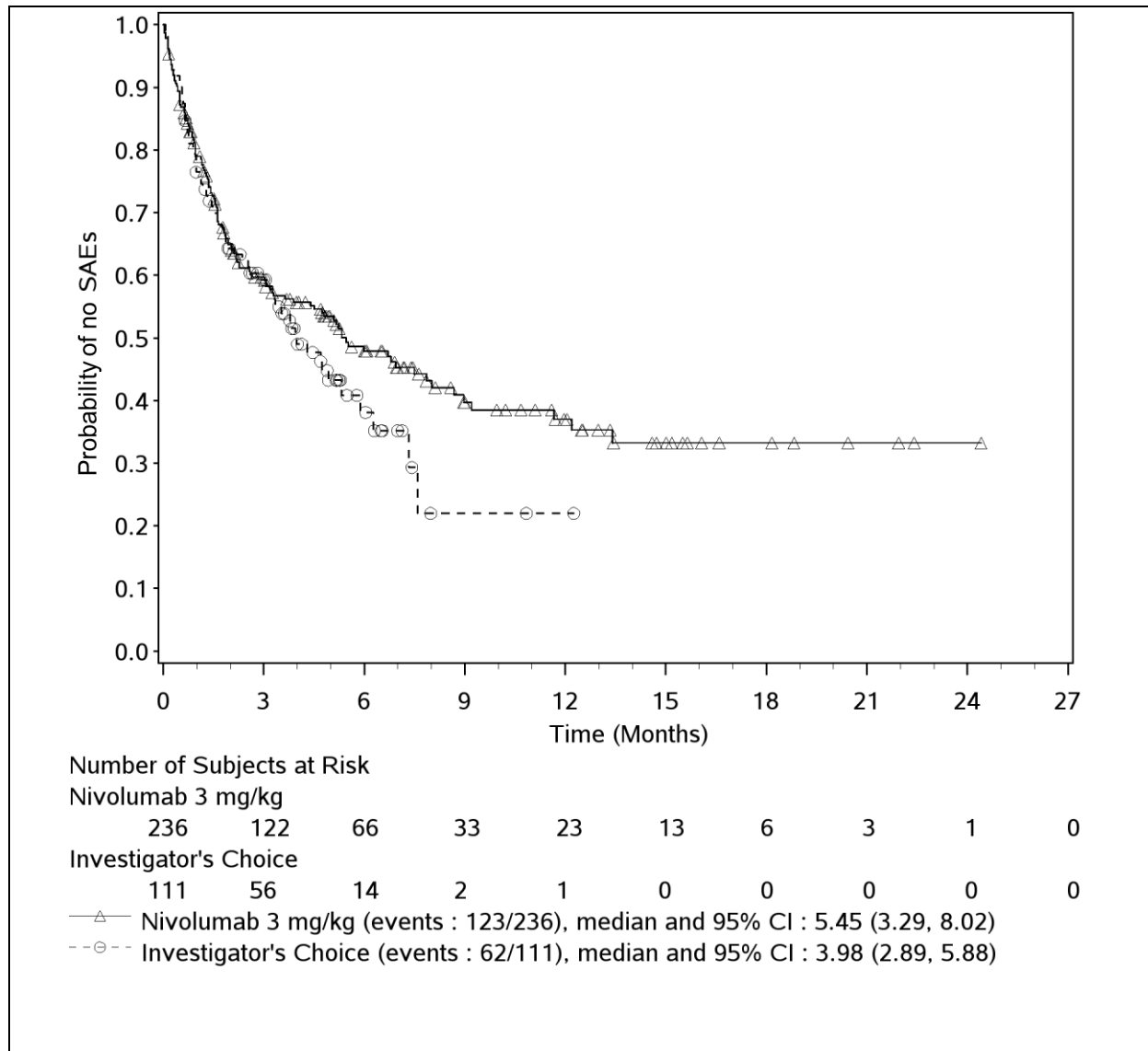


Abbildung 13: Kaplan-Meier-Kurve des Endpunkts schwerwiegende UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

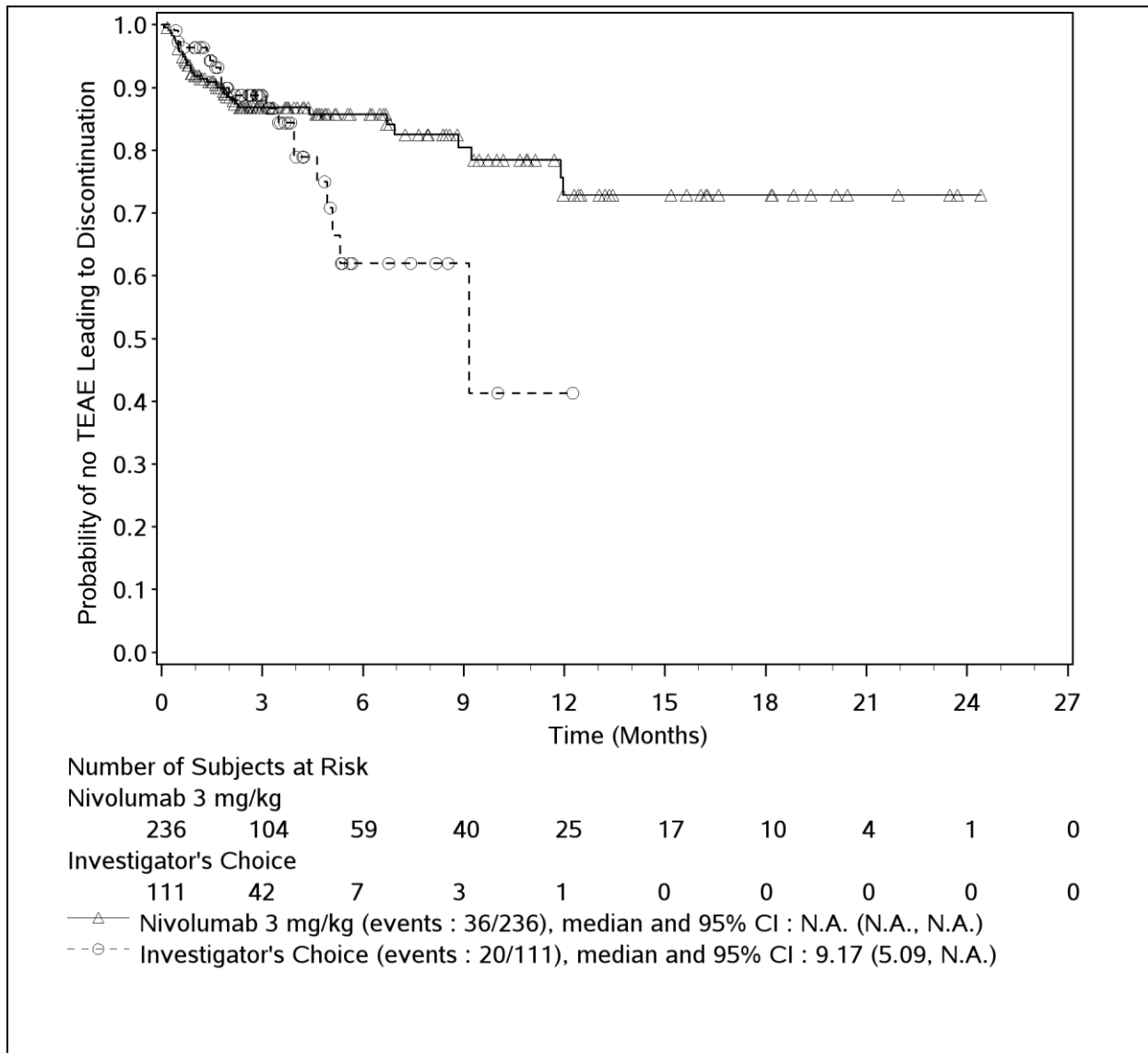


Abbildung 14: Kaplan-Meier-Kurve des Endpunkts Therapieabbruch wegen UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

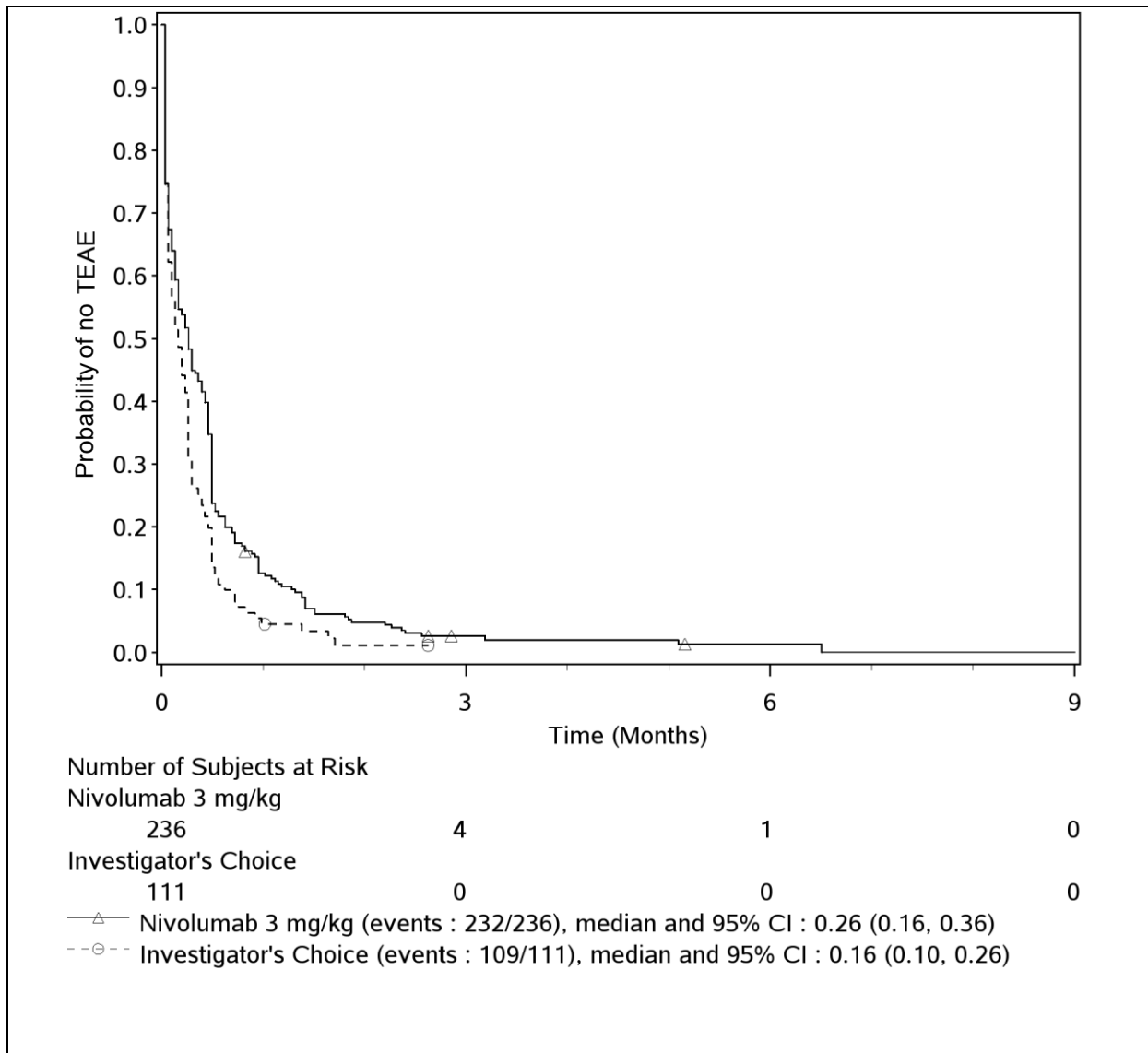


Abbildung 15: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts jegliches UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

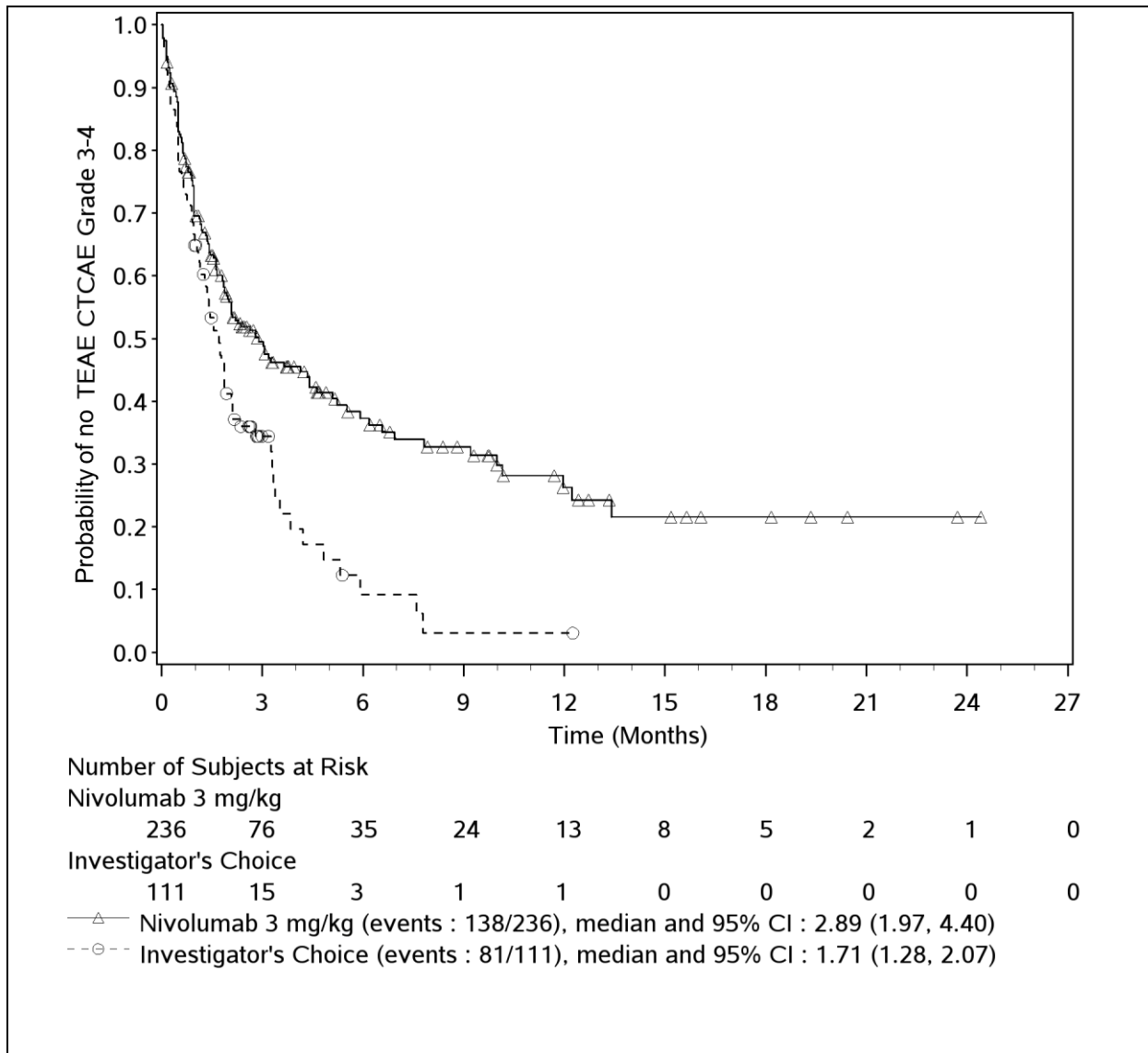


Abbildung 16: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts UE Grad 3-4 (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)



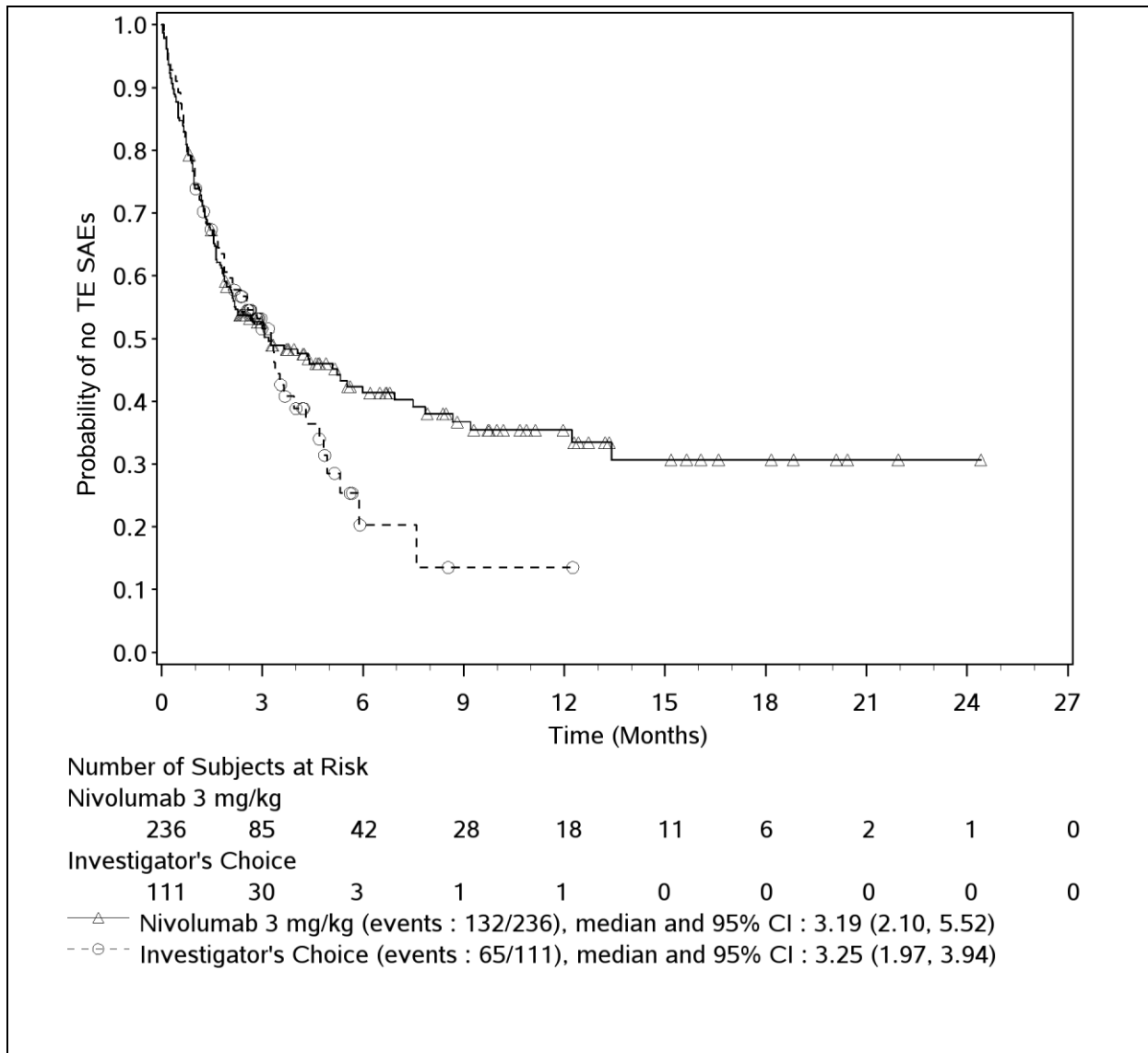


Abbildung 17: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts schwerwiegende UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

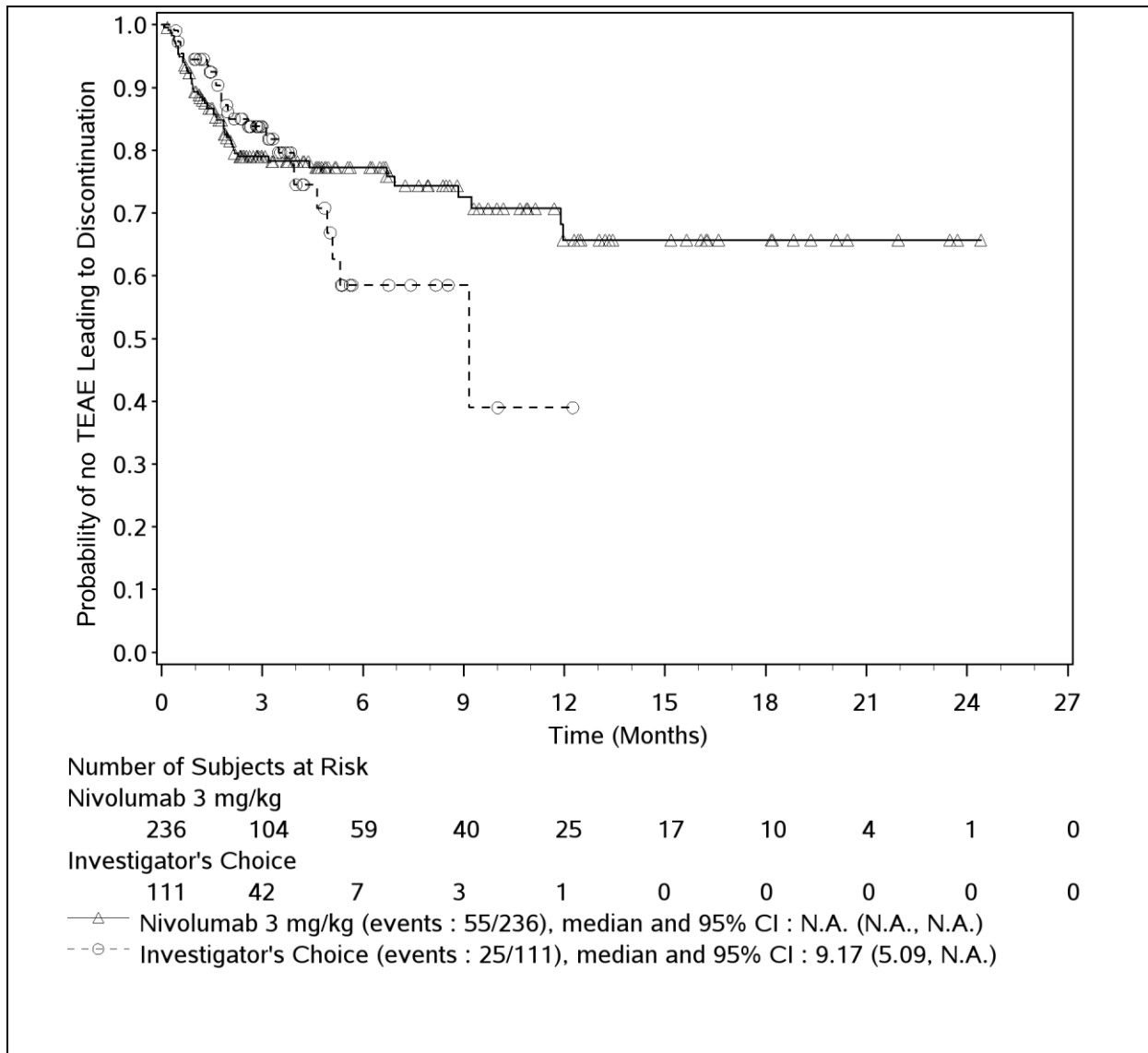


Abbildung 18: Sensitivitätsanalyse:Kaplan-Meier-Kurve des Endpunkts Therapieabbruch wegen UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

**MTX-Teilpopulation**

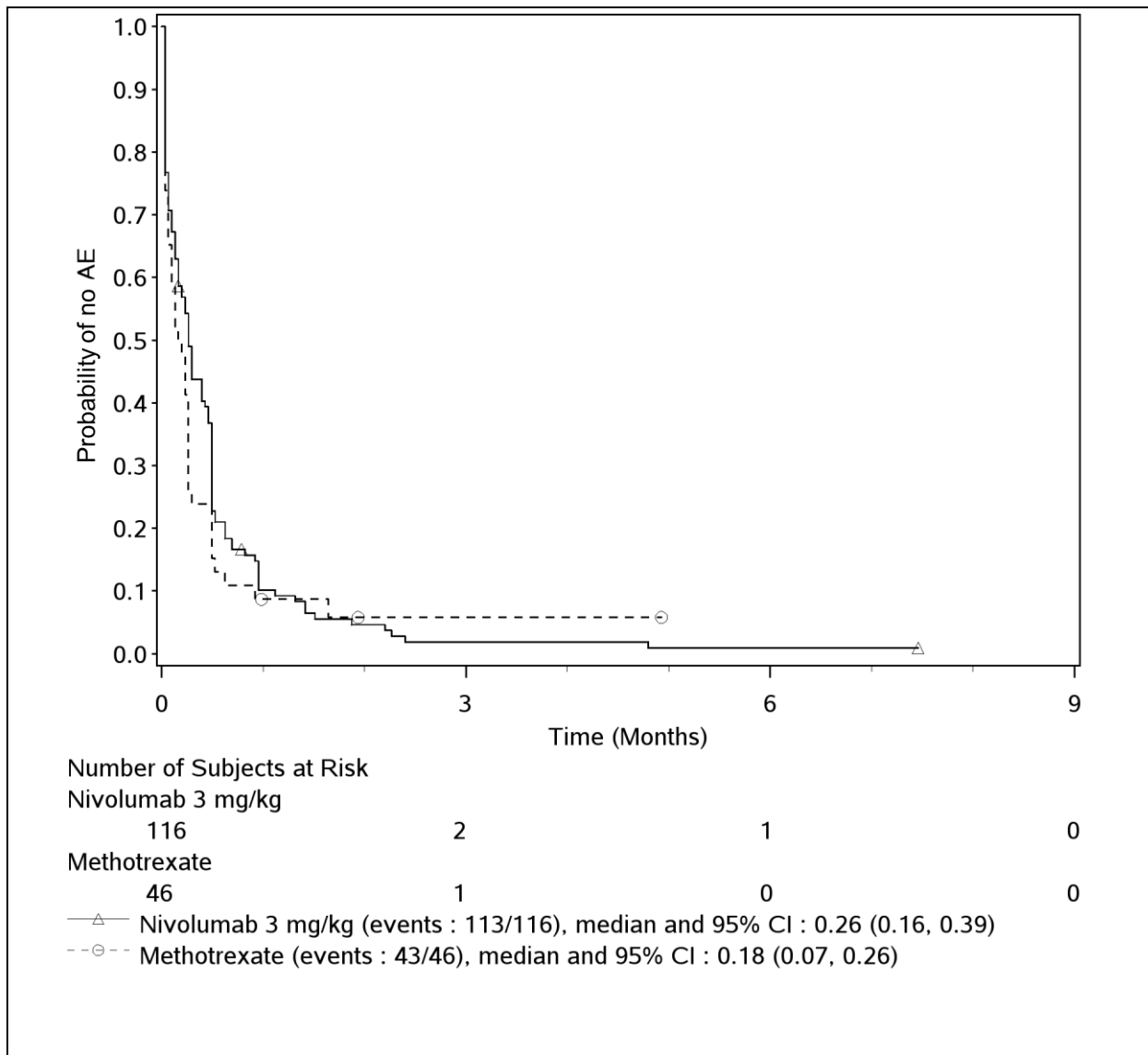


Abbildung 19: Kaplan-Meier-Kurve des Endpunkts jegliches UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

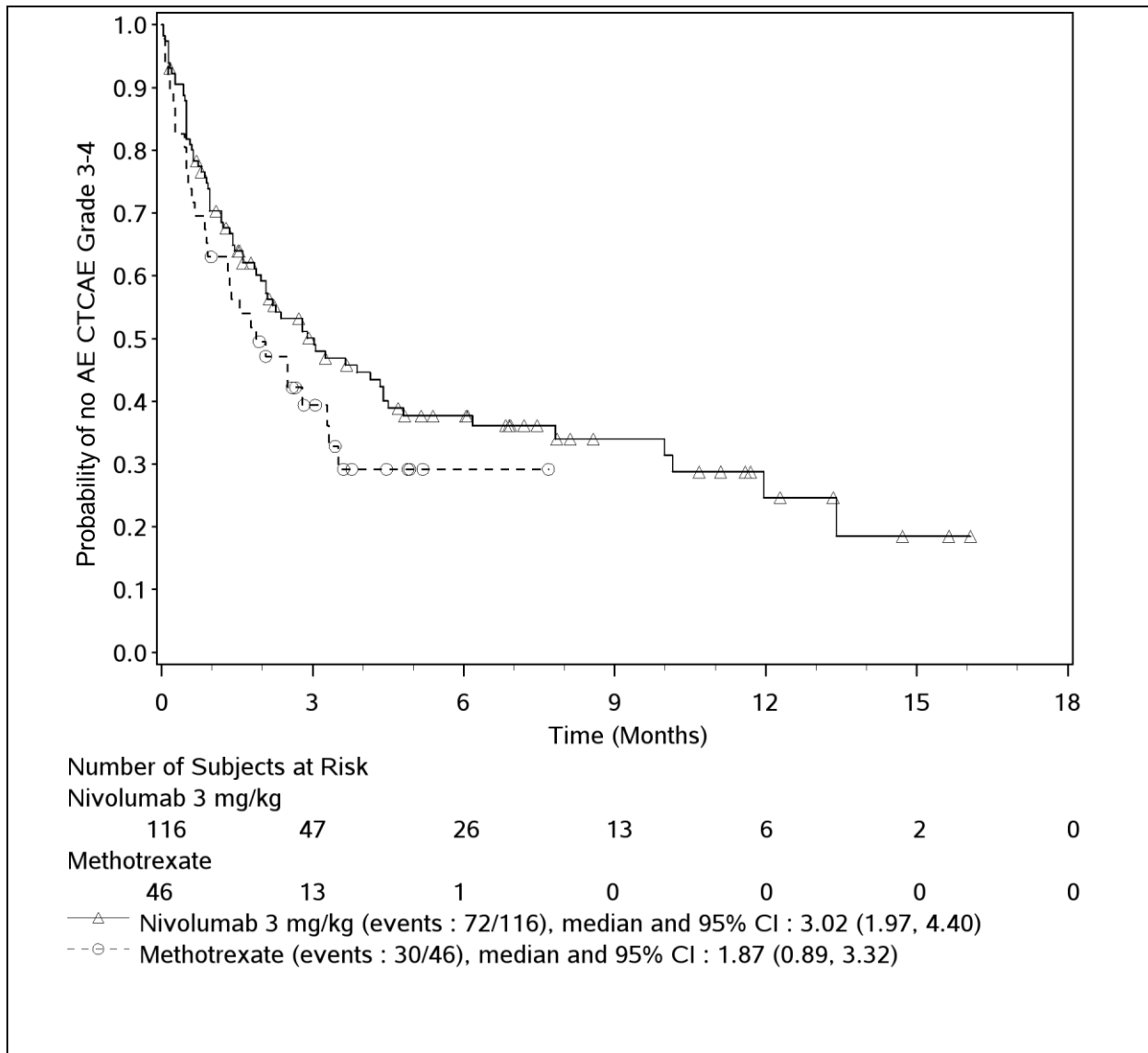


Abbildung 20: Kaplan-Meier-Kurve des Endpunkts UE Grad 3-4 ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

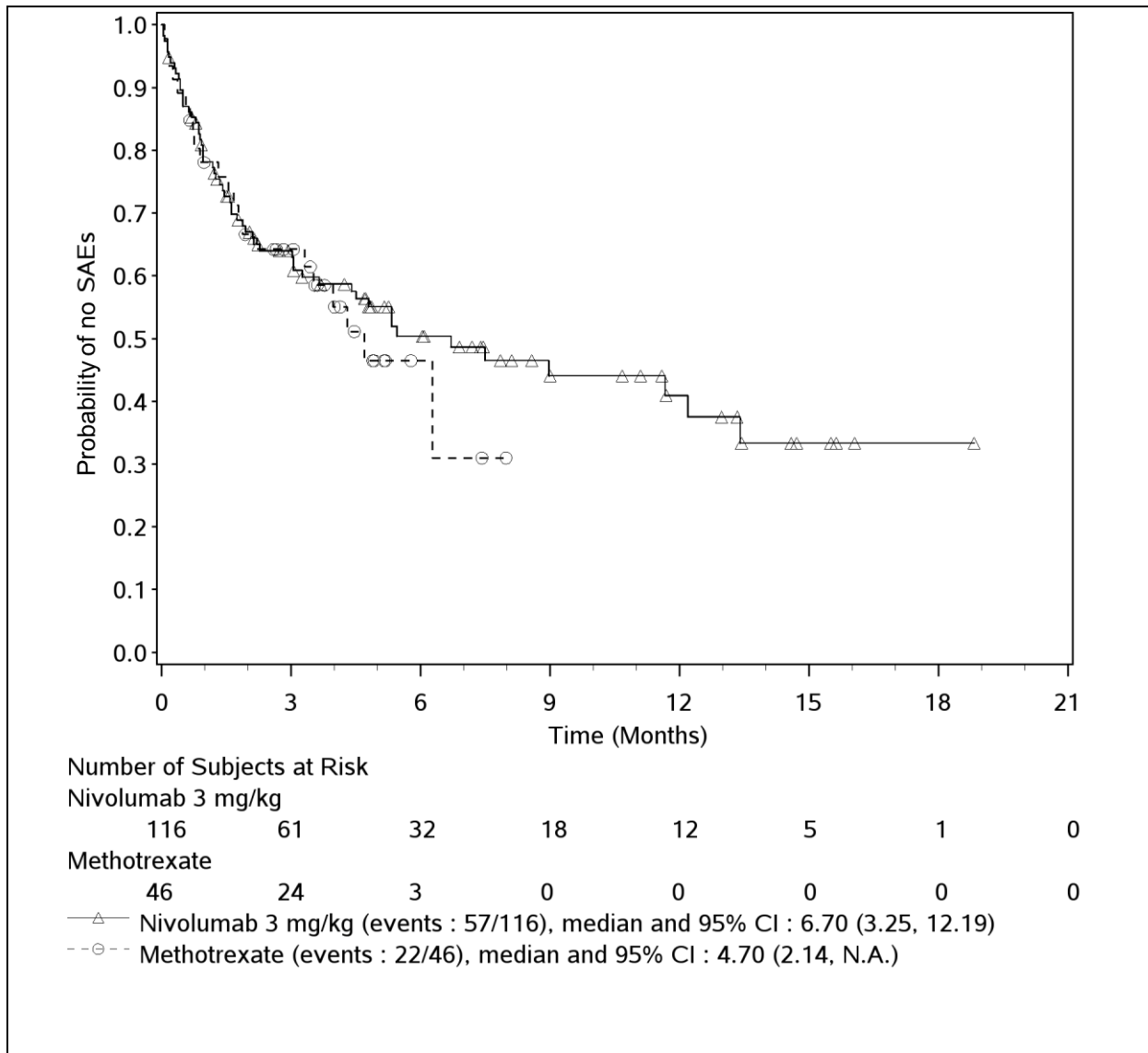


Abbildung 21: Kaplan-Meier-Kurve des Endpunkts schwerwiegende UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

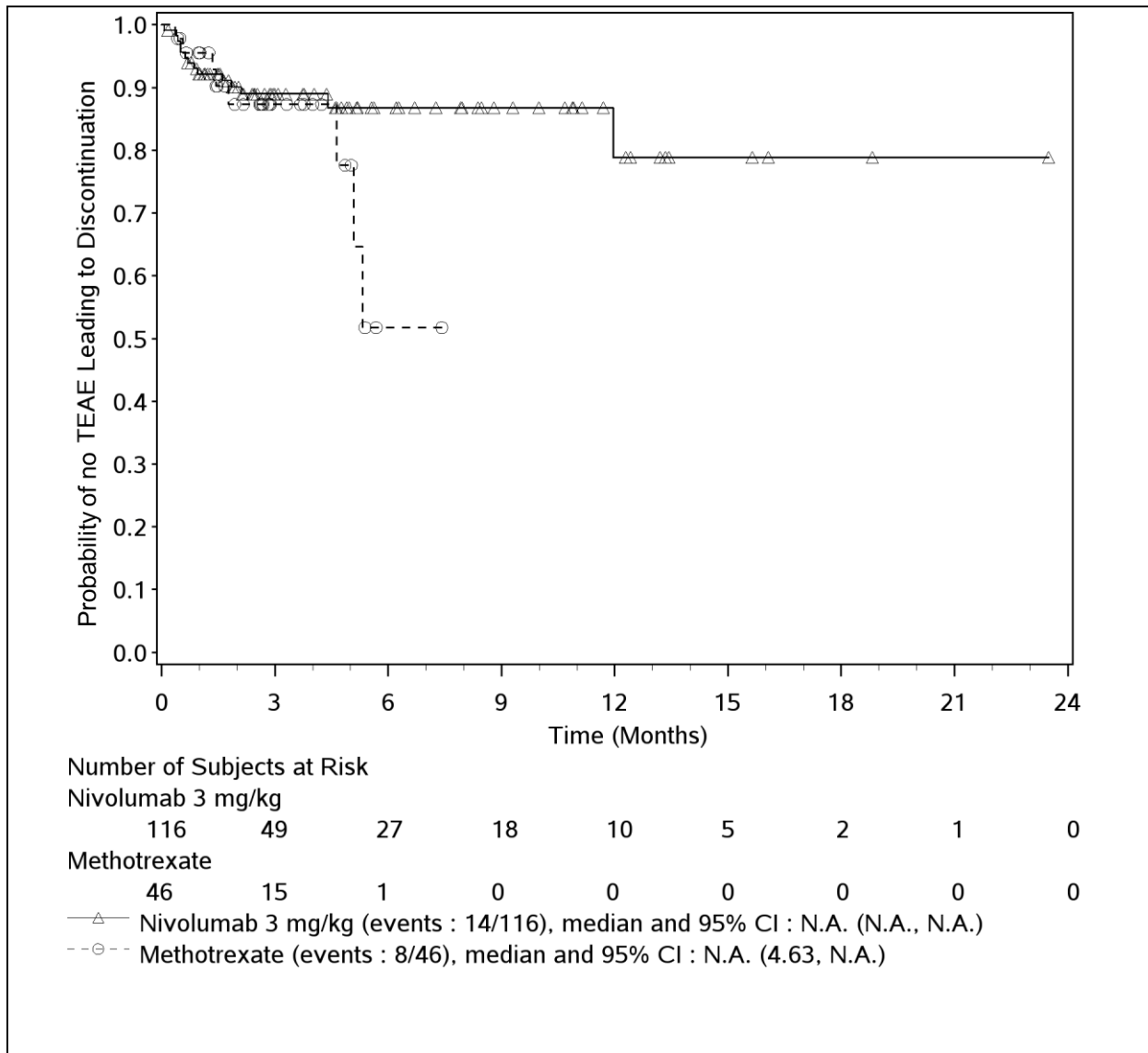


Abbildung 22: Kaplan-Meier-Kurve des Endpunkts Therapieabbruch wegen UE ohne Erfassung des Progresses der Grunderkrankung aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

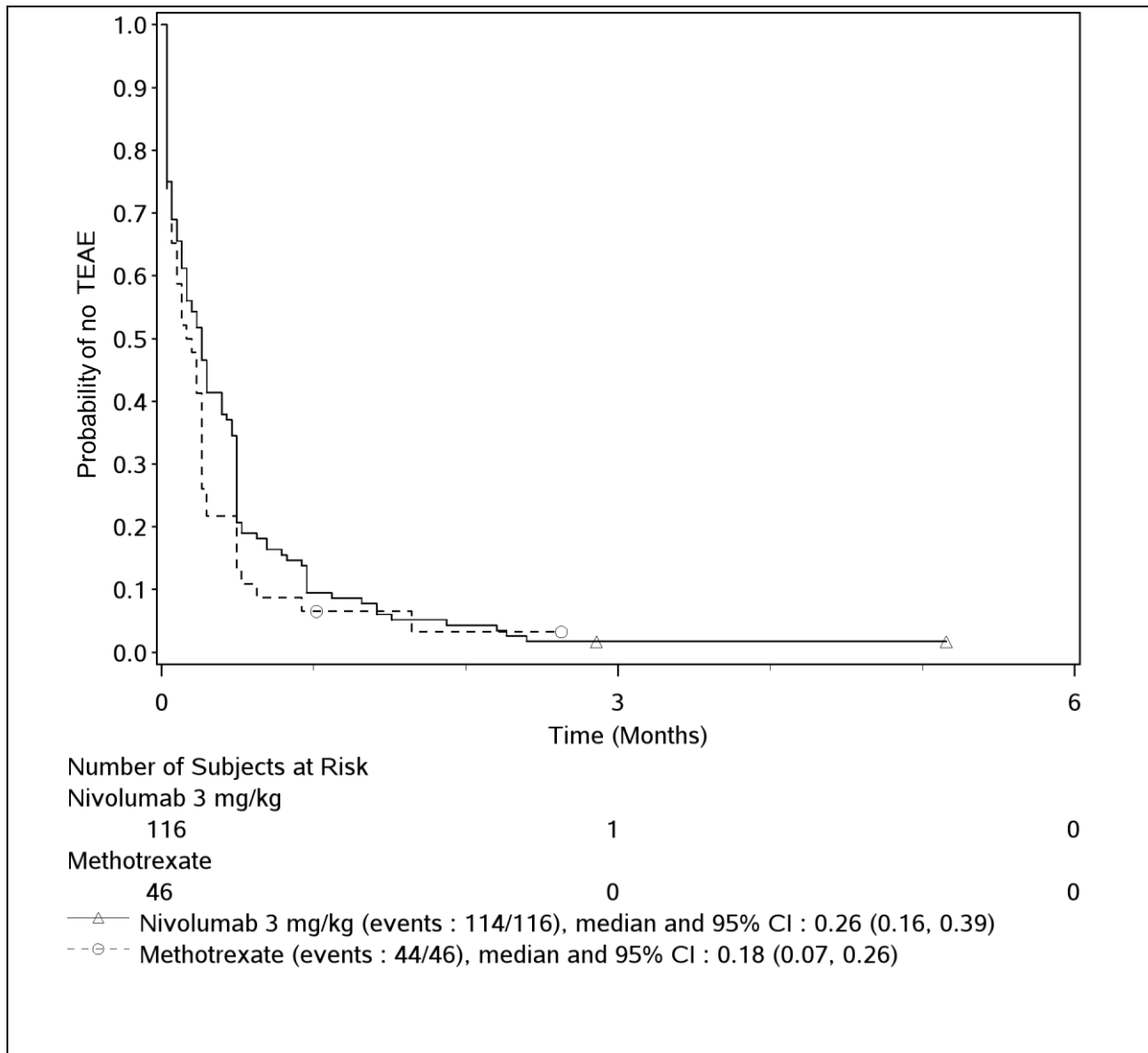


Abbildung 23: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts jegliches UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

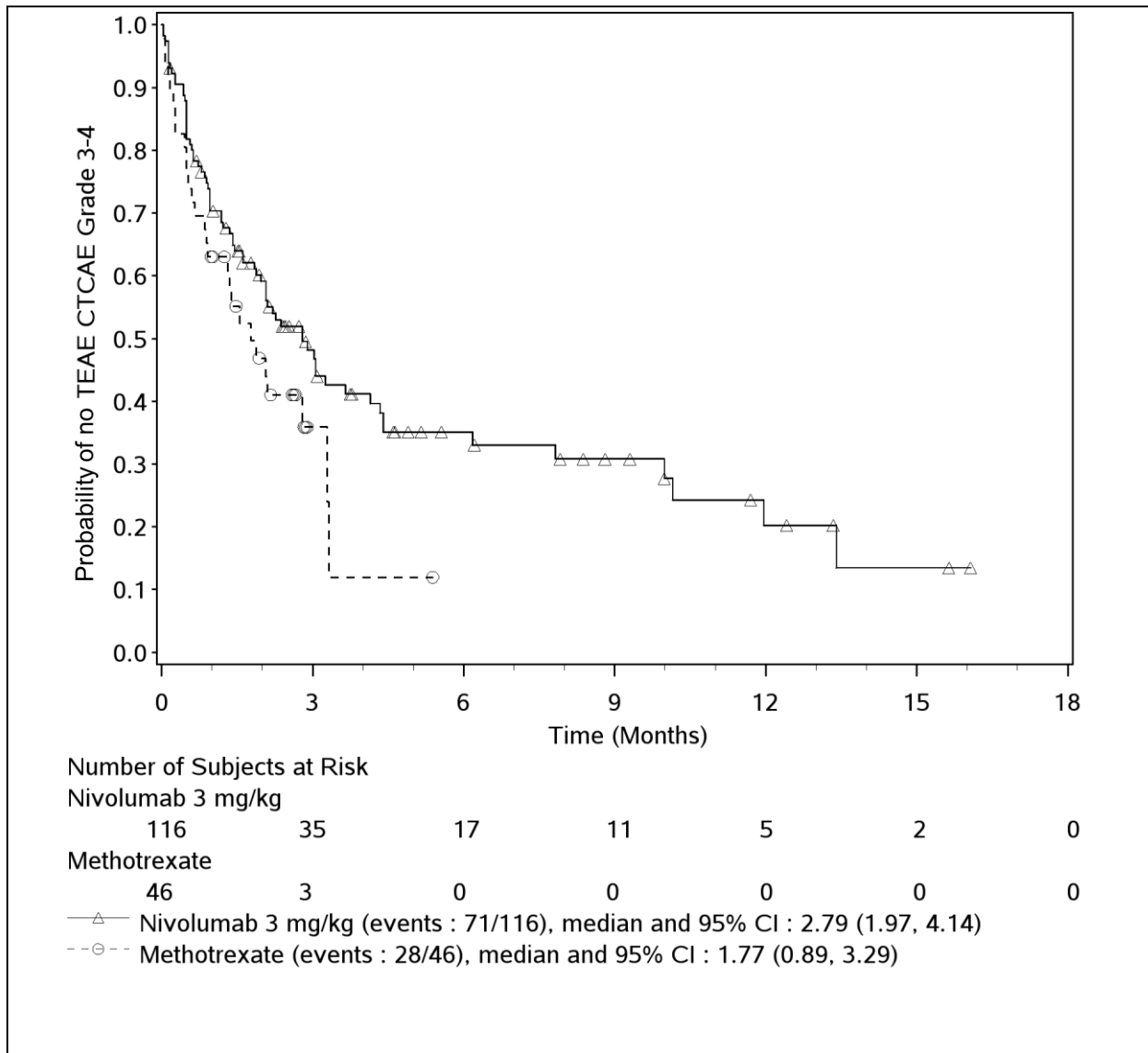


Abbildung 24: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts UE Grad 3-4 (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)



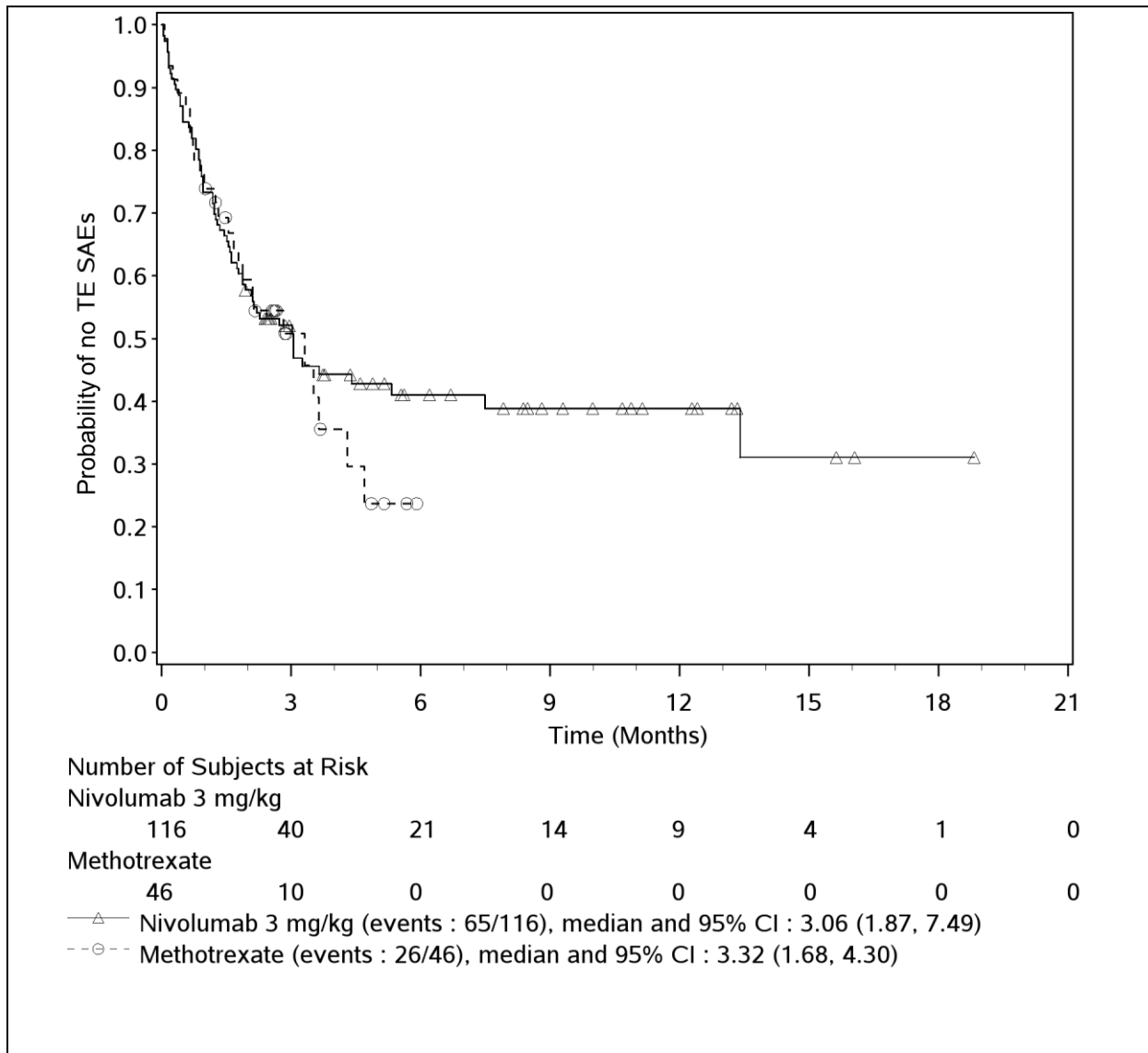


Abbildung 25: Sensitivitätsanalyse: Kaplan-Meier-Kurve des Endpunkts schwerwiegende UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

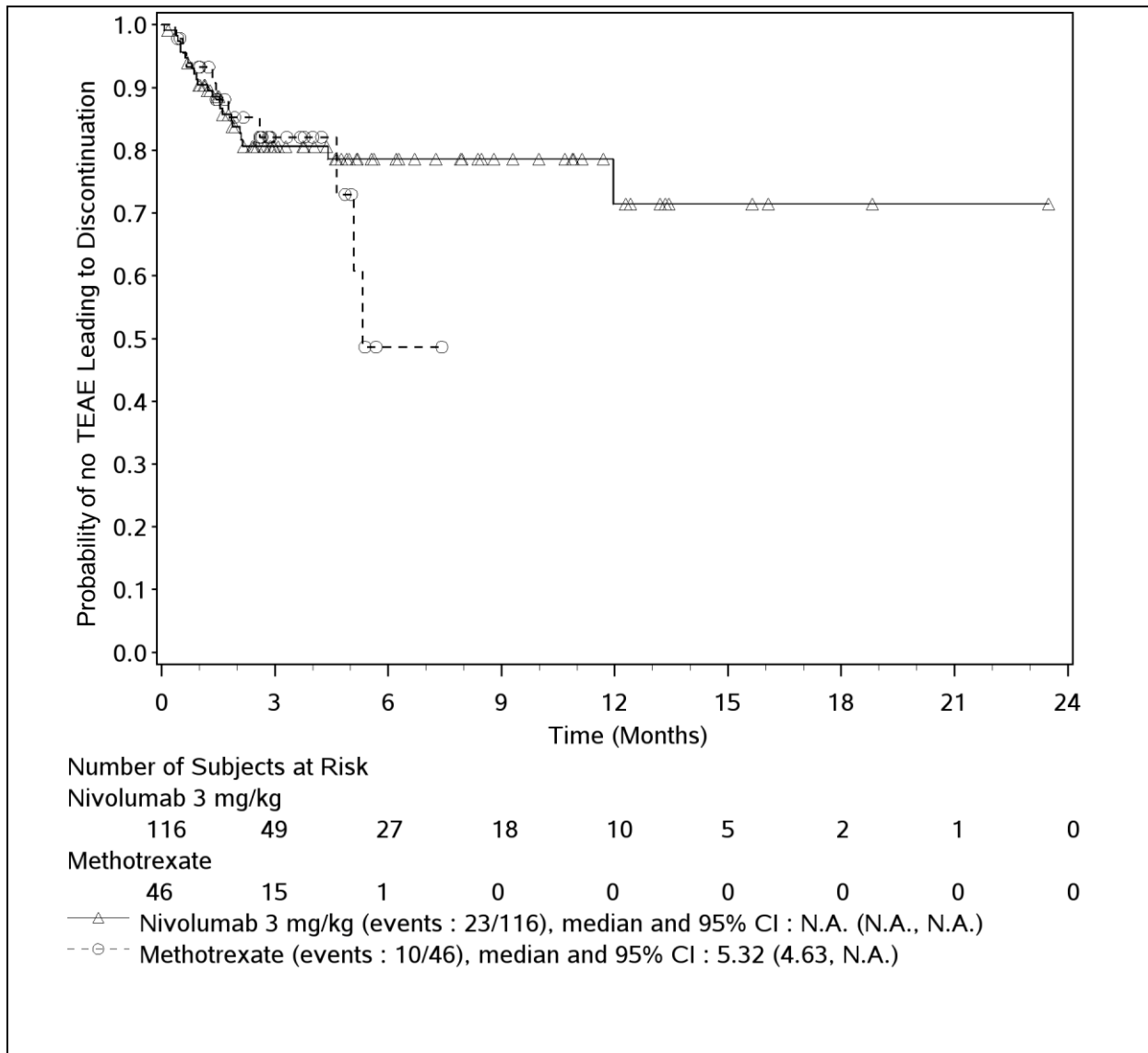


Abbildung 26: Sensitivitätsanalyse:Kaplan-Meier-Kurve des Endpunkts Therapieabbruch wegen UE (Analyse aller erfassten UE (inkl. Progress)) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

### 4.3.1.3.2 Subgruppenanalysen – CA209-141

Nachfolgend werden die Kaplan-Meier-Kurven für die dargestellten Subgruppenanalysen, für die sich ein Beleg für eine Interaktion zeigte, ergänzt. Dieses Vorgehen entspricht der Diskussion der Subgruppenanalysen im Abschnitt 4.3.1.3.3 des Moduls 4 G mit dem Fokus auf die Subgruppenanalysen mit einem Beleg für eine Interaktion.

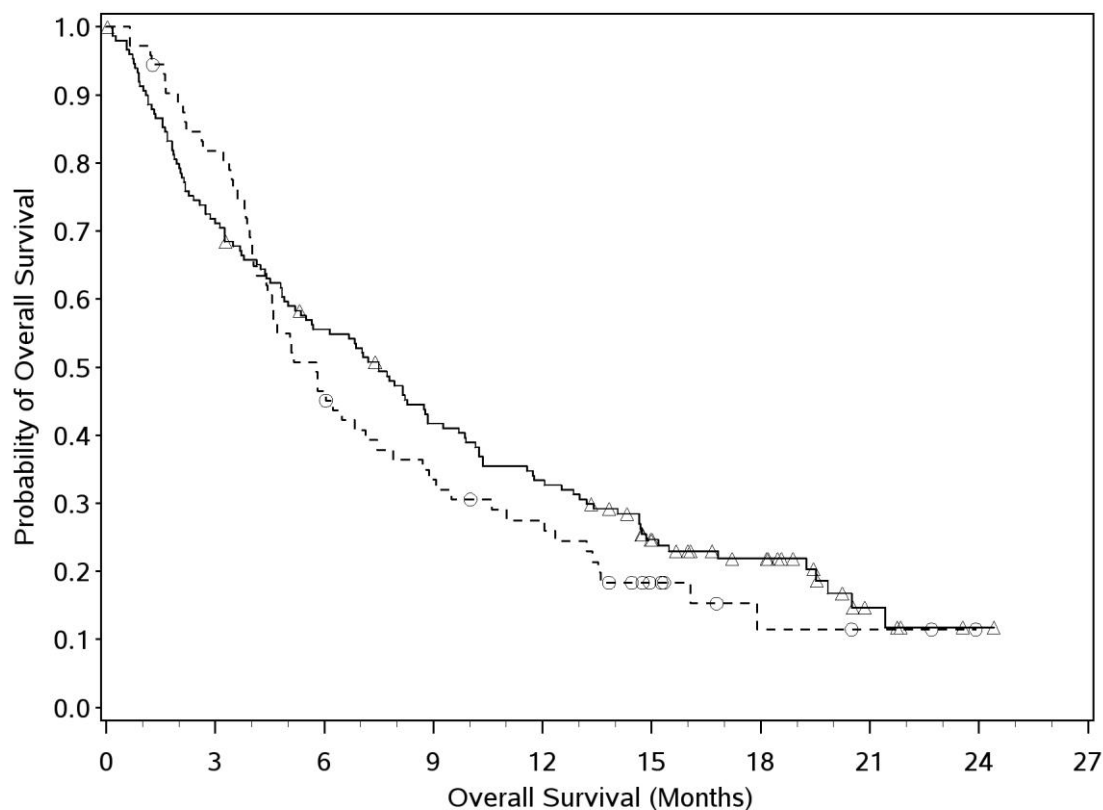
#### 4.3.1.3.2.1 Subgruppenanalysen für Endpunkt Mortalität – Gesamtüberleben (OS)

##### Ergänzung der Kaplan-Meier-Kurven

##### **Gesamtpopulation**

*Subgruppenmerkmal: Vorherige Therapie mit Cetuximab lt. CRF*

Subgruppe ja



Number of Subjects at Risk

Nivolumab 3 mg/kg

150 106 81 60 48 30 19 5 1 0

Investigator's Choice

72 58 33 23 18 8 3 2 0 0

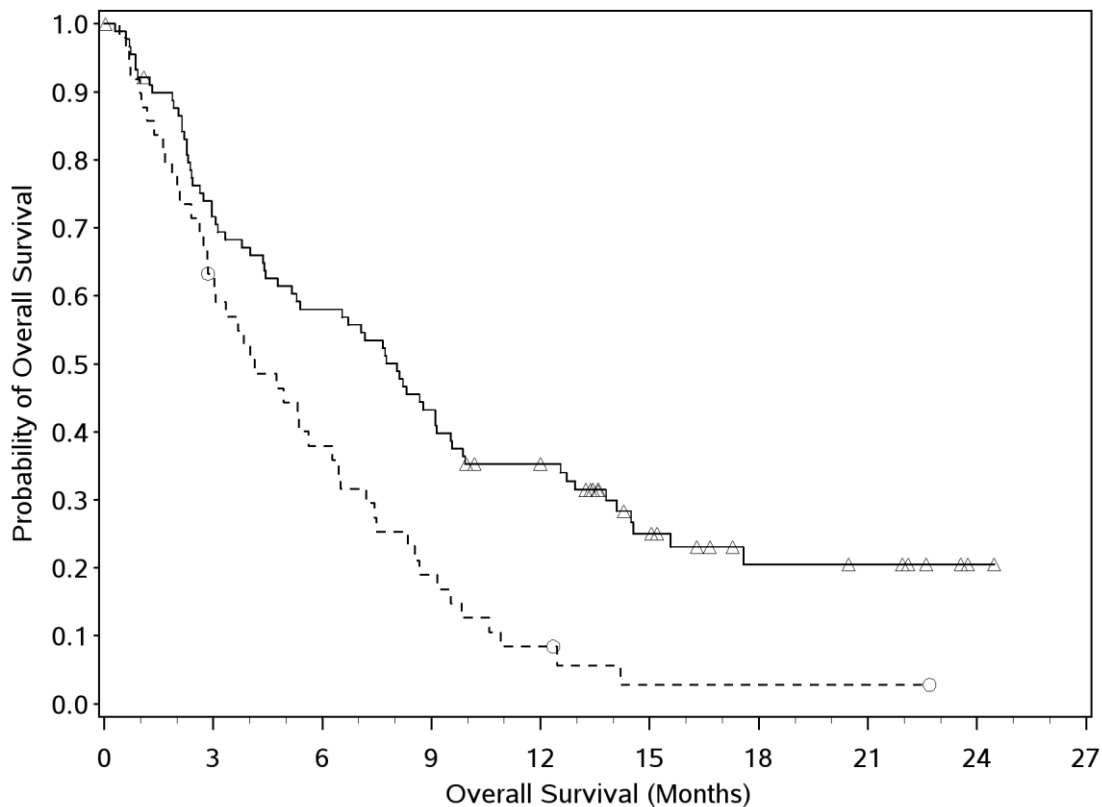
—△— Nivolumab 3 mg/kg (events : 118/150), median and 95% CI : 7.49 (5.19, 8.84)

--○-- Investigator's Choice (events : 59/72), median and 95% CI : 5.78 (4.40, 7.46)

Hazard Ratio (Nivolumab 3 mg/kg over Inv. Choice) and 95% CI: 0.86 (0.63, 1.18)

Unstratified log-rank p-value: 0.3625

Subgruppe nein



Number of Subjects at Risk

Nivolumab 3 mg/kg	90	63	51	38	28	15	8	7	2	0
Investigator's Choice	49	30	18	9	4	1	1	1	0	0

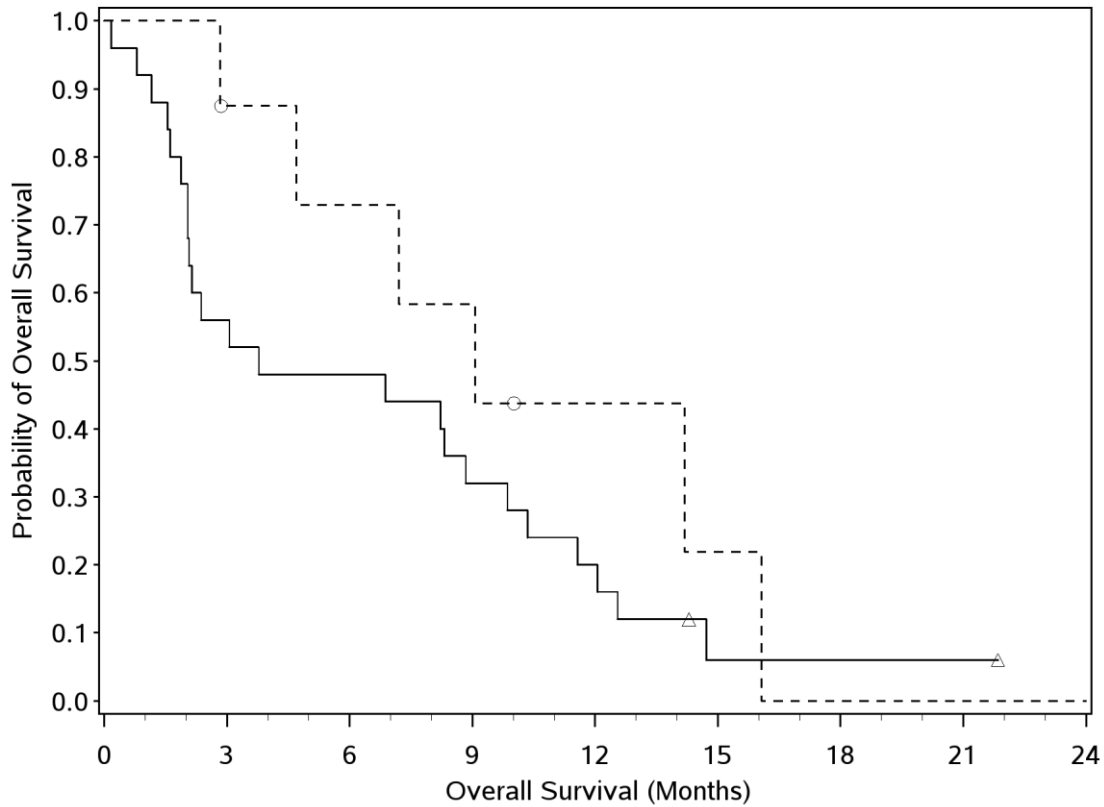
—△— Nivolumab 3 mg/kg (events : 66/90), median and 95% CI : 8.05 (5.16, 9.13)  
 ---○--- Investigator's Choice (events : 46/49), median and 95% CI : 4.14 (2.86, 6.28)  
 Hazard Ratio (Nivolumab 3 mg/kg over Inv. Choice) and 95% CI: 0.50 (0.34, 0.74)  
 Unstratified log-rank p-value: 0.000339

Abbildung 27: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt Gesamtüberleben (OS) aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

**MTX-Teilpopulation**

Subgruppenmerkmal: Dauer von der Diagnose bis zur Randomisierung

Subgruppe < 1 Jahr



Number of Subjects at Risk

Nivolumab 3 mg/kg

25 14 12 8 5 1 1 1 0

Methotrexate

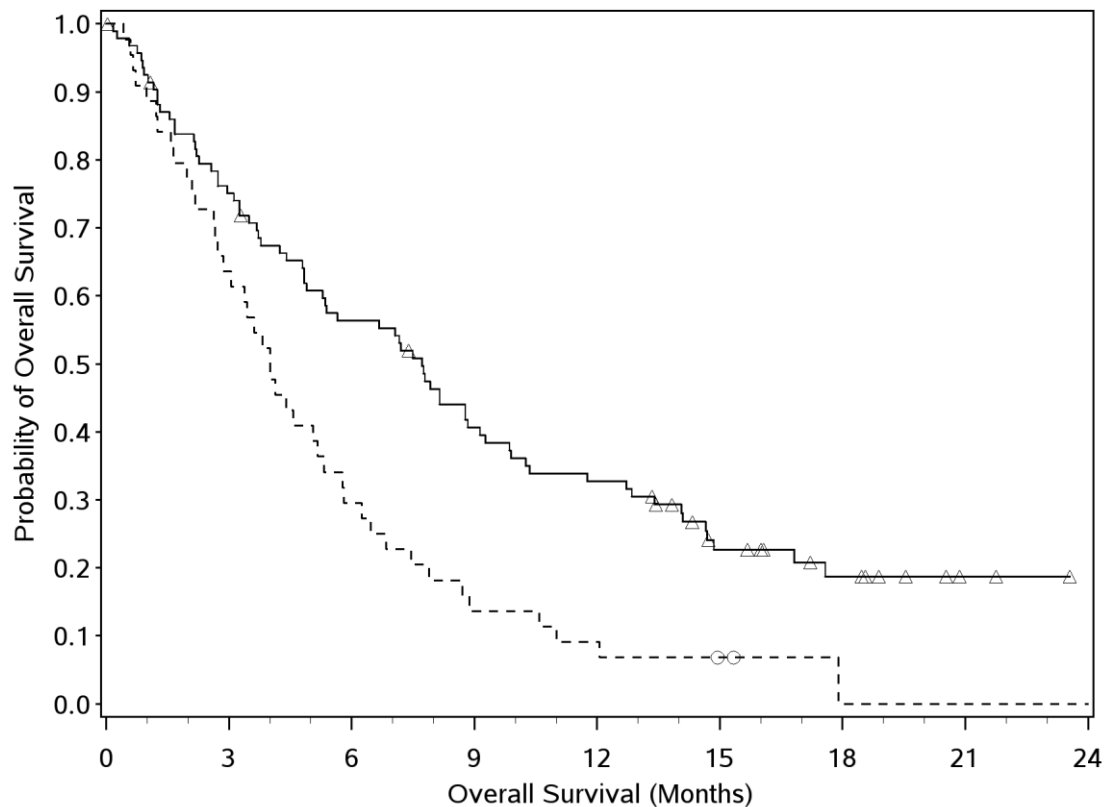
8 6 5 4 2 1 0 0 0

—△— Nivolumab 3 mg/kg (events : 23/25), median and 95% CI : 3.78 (2.04, 9.86)

--○-- Methotrexate (events : 6/8), median and 95% CI : 9.07 (2.83, 16.07)

Hazard Ratio (Nivolumab 3 mg/kg over Methotrexate) and 95% CI: 1.71 (0.69, 4.21)

Unstratified log-rank p-value: 0.2418

Subgruppe  $\geq 1$  Jahr

## Number of Subjects at Risk

## Nivolumab 3 mg/kg

94	69	51	36	29	16	9	3	0
----	----	----	----	----	----	---	---	---

## Methotrexate

44	28	13	6	4	2	0	0	0
----	----	----	---	---	---	---	---	---

—△— Nivolumab 3 mg/kg (events : 71/94), median and 95% CI : 7.72 (4.90, 9.13)

--○-- Methotrexate (events : 42/44), median and 95% CI : 4.01 (2.73, 5.32)

Hazard Ratio (Nivolumab 3 mg/kg over Methotrexate) and 95% CI: 0.51 (0.34, 0.75)

Unstratified log-rank p-value: 0.000464

Abbildung 28: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt Gesamtüberleben (OS) aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

#### 4.3.1.3.2.2 Subgruppenanalysen für Endpunkte Verträglichkeit

##### Ergänzung der Kaplan-Meier-Kurven für jegliches UE

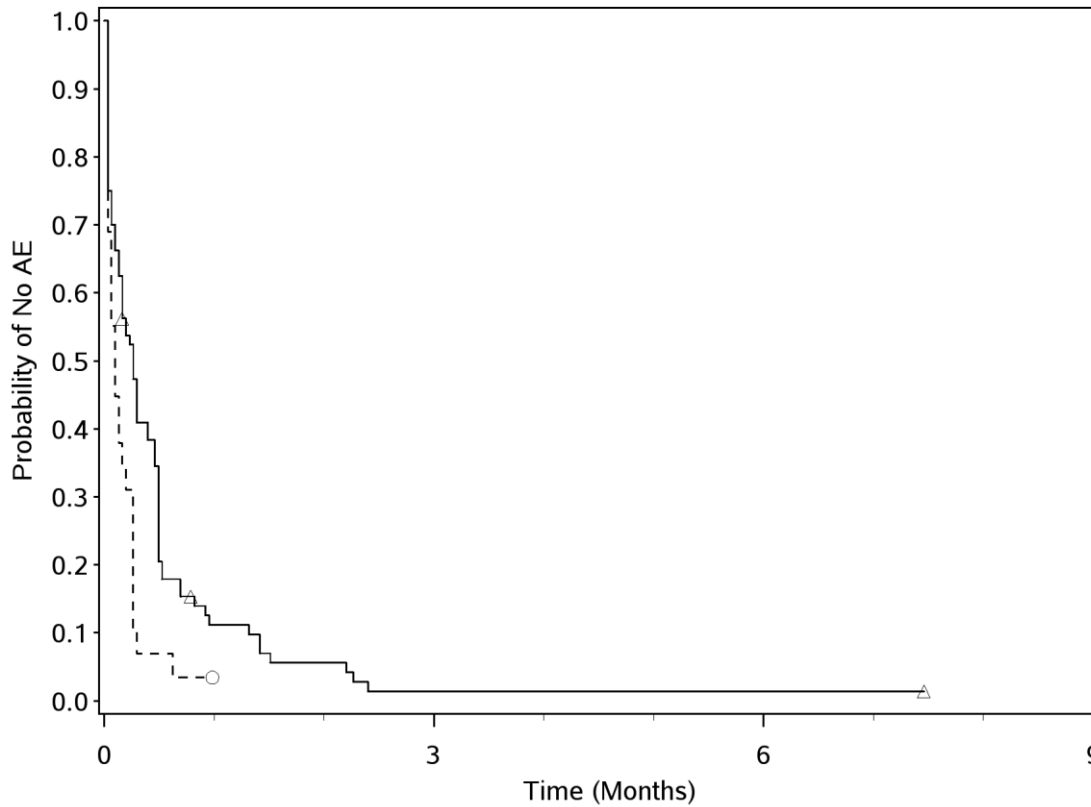
##### *Gesamtpopulation*

Keine Subgruppen mit Beleg auf Interaktion

**MTX-Teilpopulation**

Subgruppenmerkmal: Altersgruppe I

Subgruppe < 65 Jahre



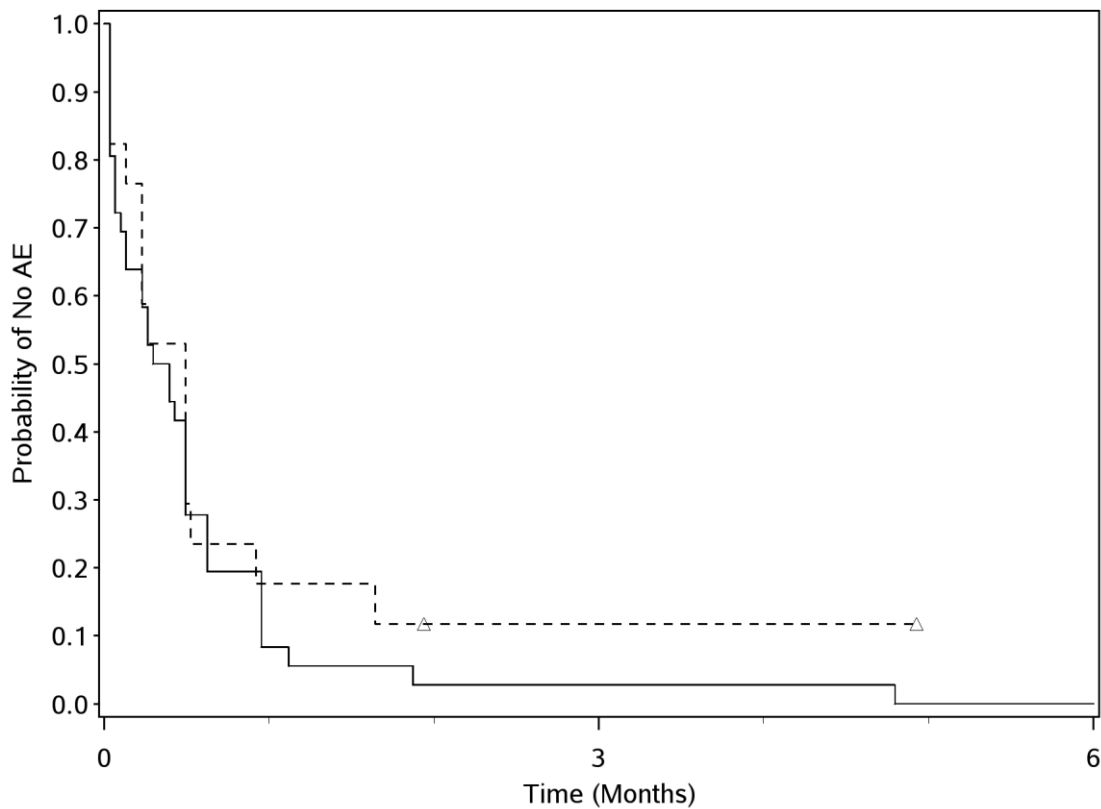
Number of Subjects at Risk

Time (Months)	0	0.26	0.10	3	6	9
Nivolumab 3 mg/kg	80	1	1	0	0	0
Methotrexate	29	0	0	0	0	0

—△— Nivolumab 3 mg/kg (events : 77/80), median and 95% CI : 0.26 (0.16, 0.39)

--○-- Methotrexate (events : 28/29), median and 95% CI : 0.10 (0.03, 0.20)

Subgruppe  $\geq 65$  Jahre



Number of Subjects at Risk

Nivolumab 3 mg/kg

36

1

0

Methotrexate

17

1

0

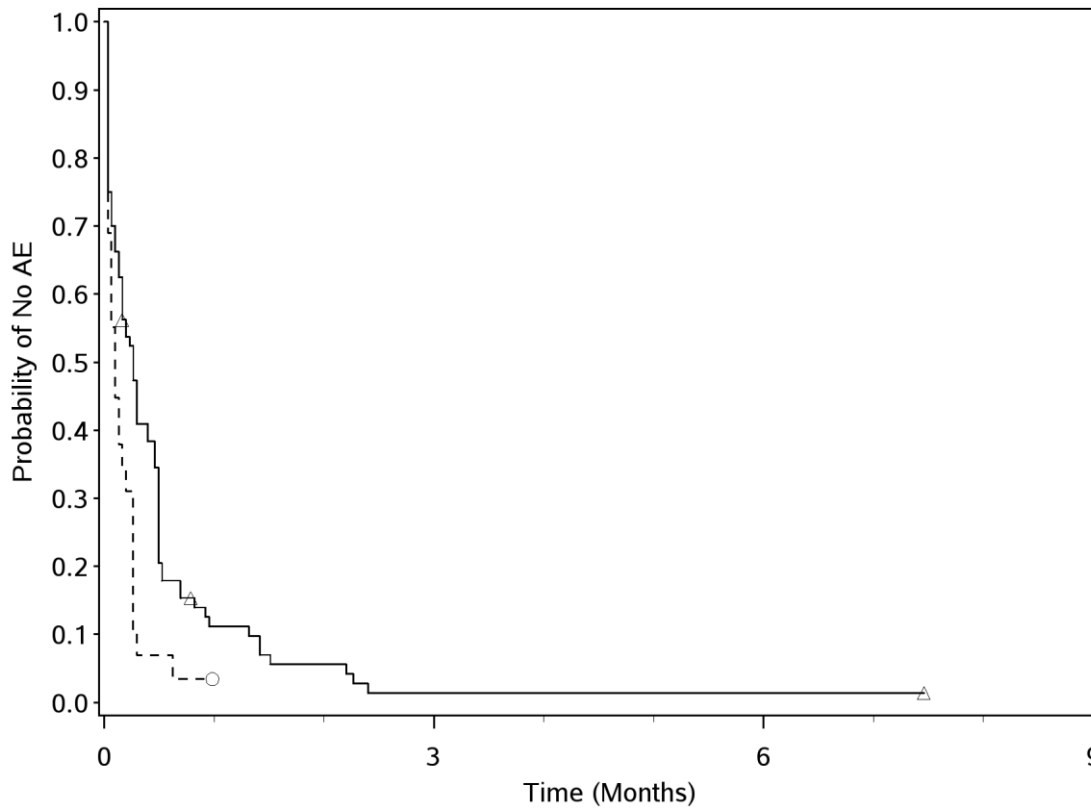
—△— Nivolumab 3 mg/kg (events : 36/36), median and 95% CI : 0.34 (0.13, 0.49)

--○-- Methotrexate (events : 15/17), median and 95% CI : 0.49 (0.13, 0.53)



*Subgruppenmerkmal: Altersgruppe III*

Subgruppe < 65 Jahre



Number of Subjects at Risk

Nivolumab 3 mg/kg

80	1	1	0
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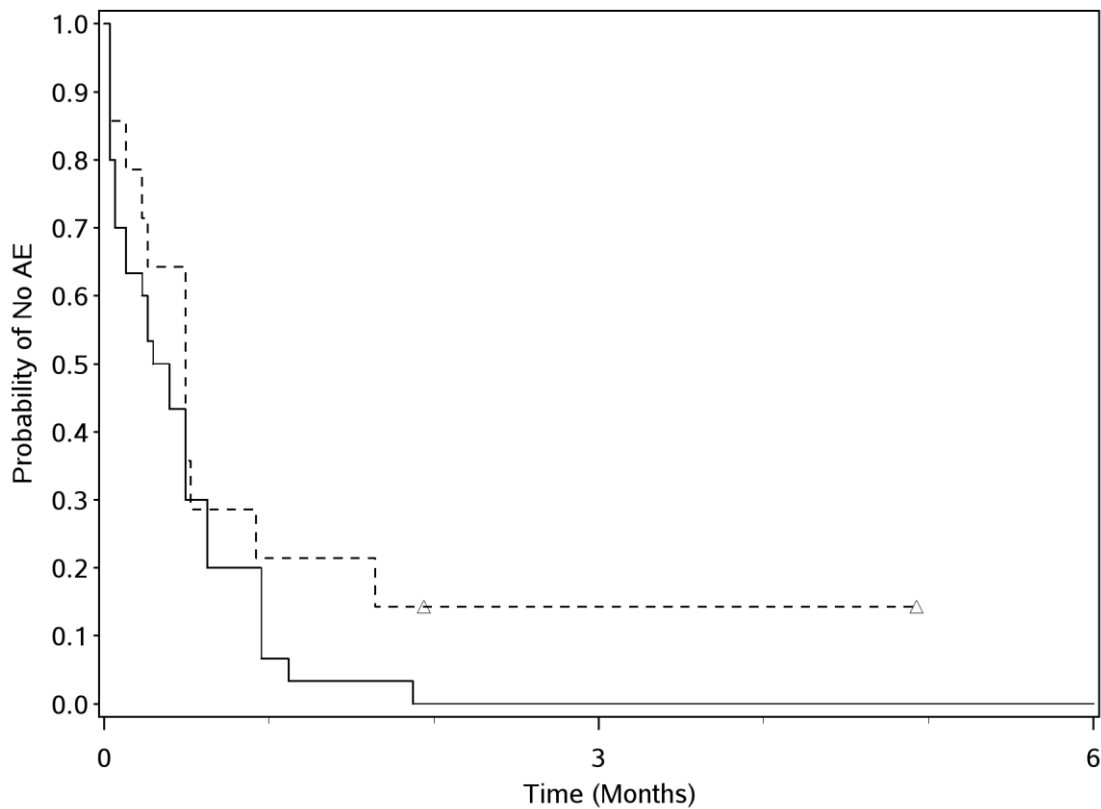
Methotrexate

29	0	0	0
----	---	---	---

—△— Nivolumab 3 mg/kg (events : 77/80), median and 95% CI : 0.26 (0.16, 0.39)

--○-- Methotrexate (events : 28/29), median and 95% CI : 0.10 (0.03, 0.20)

Subgruppe  $\geq 65$  -  $< 75$  Jahre



Number of Subjects at Risk

Nivolumab 3 mg/kg

30

0

0

Methotrexate

14

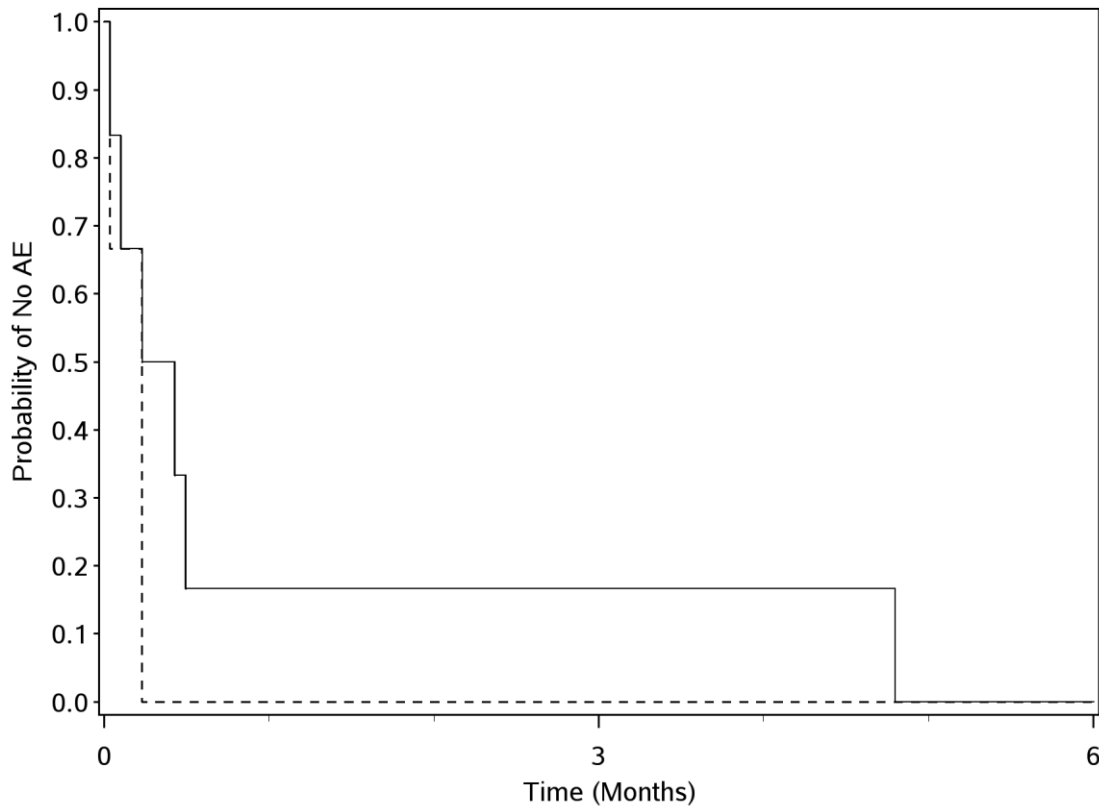
1

0

—△— Nivolumab 3 mg/kg (events : 30/30), median and 95% CI : 0.34 (0.13, 0.49)

--○-- Methotrexate (events : 12/14), median and 95% CI : 0.49 (0.13, 0.92)

Subgruppe  $\geq 75$  Jahre



Number of Subjects at Risk

Nivolumab 3 mg/kg

6	1	0
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Methotrexate

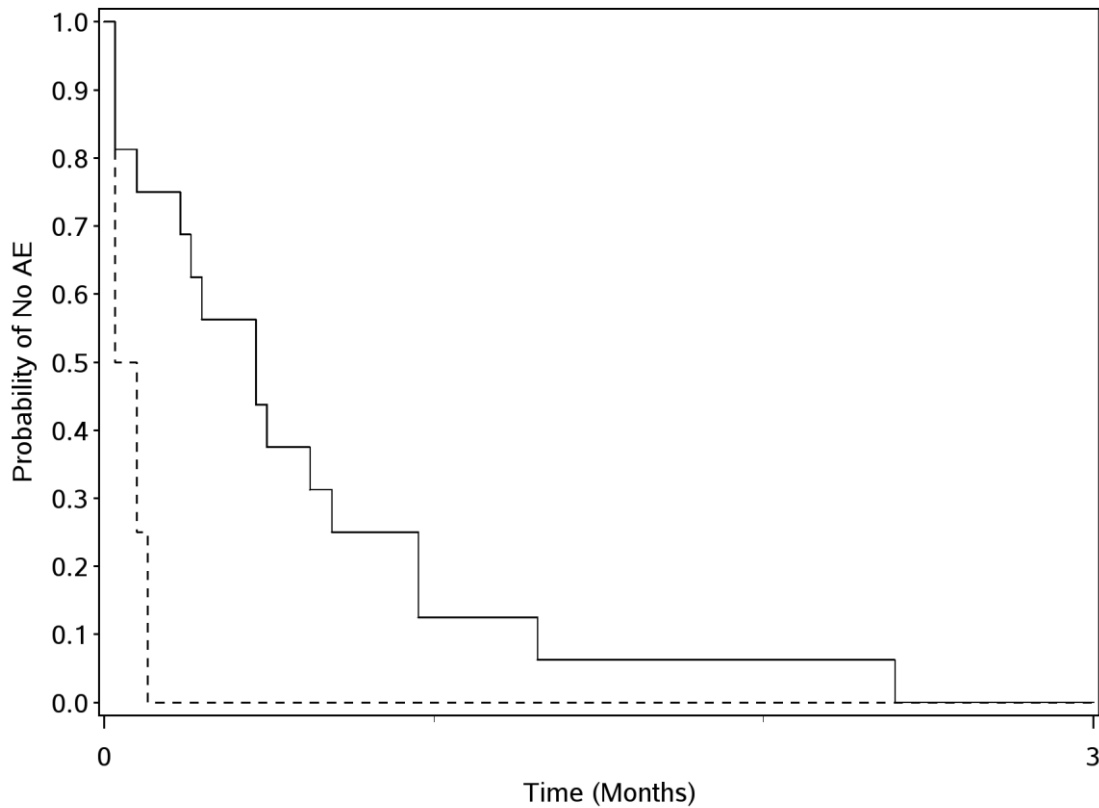
3	0	0
---	---	---

—△— Nivolumab 3 mg/kg (events : 6/6), median and 95% CI : 0.33 (0.03, 4.80)

--○-- Methotrexate (events : 3/3), median and 95% CI : 0.23 (0.03, 0.23)

Subgruppenmerkmal: Krankheitsstadium

Subgruppe III



Number of Subjects at Risk

Nivolumab 3 mg/kg

16

0

Methotrexate

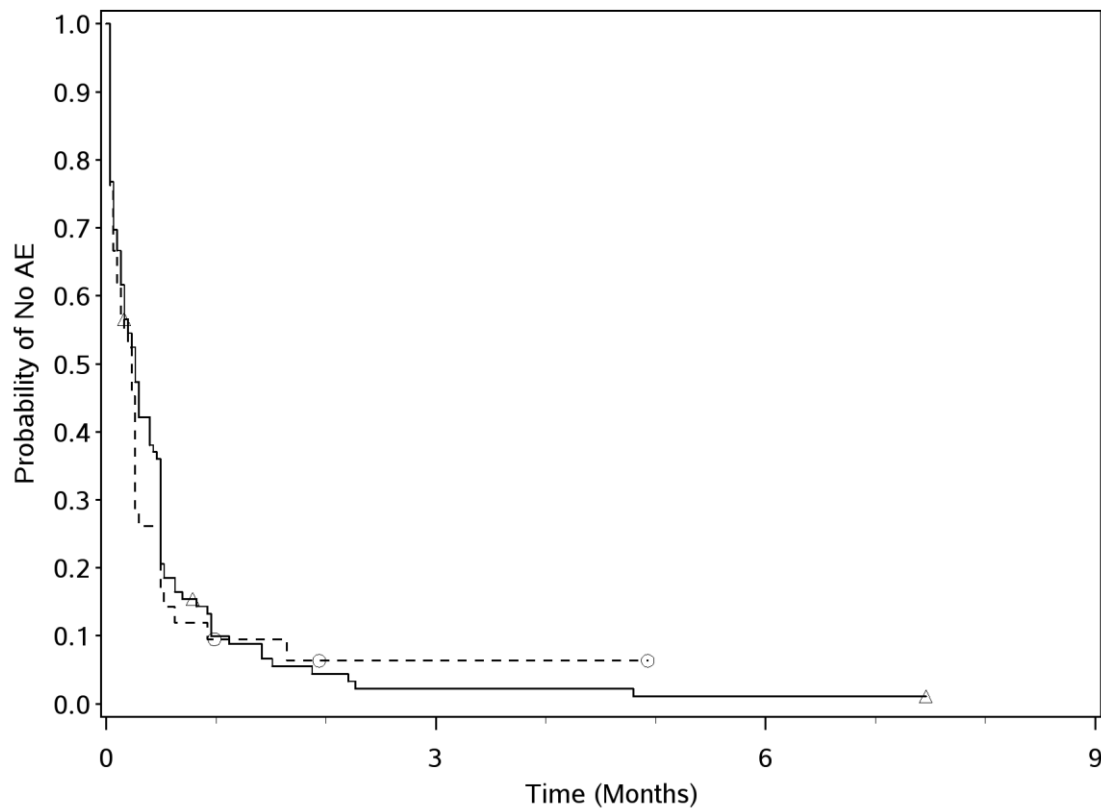
4

0

—△— Nivolumab 3 mg/kg (events : 16/16), median and 95% CI : 0.46 (0.10, 0.69)

--○-- Methotrexate (events : 4/4), median and 95% CI : 0.07 (0.03, 0.13)

Subgruppe IV



Number of Subjects at Risk

Nivolumab 3 mg/kg	99	2	1	0
Methotrexate	42	1	0	0

—△— Nivolumab 3 mg/kg (events : 96/99), median and 95% CI : 0.26 (0.16, 0.39)

--○-- Methotrexate (events : 39/42), median and 95% CI : 0.23 (0.10, 0.26)

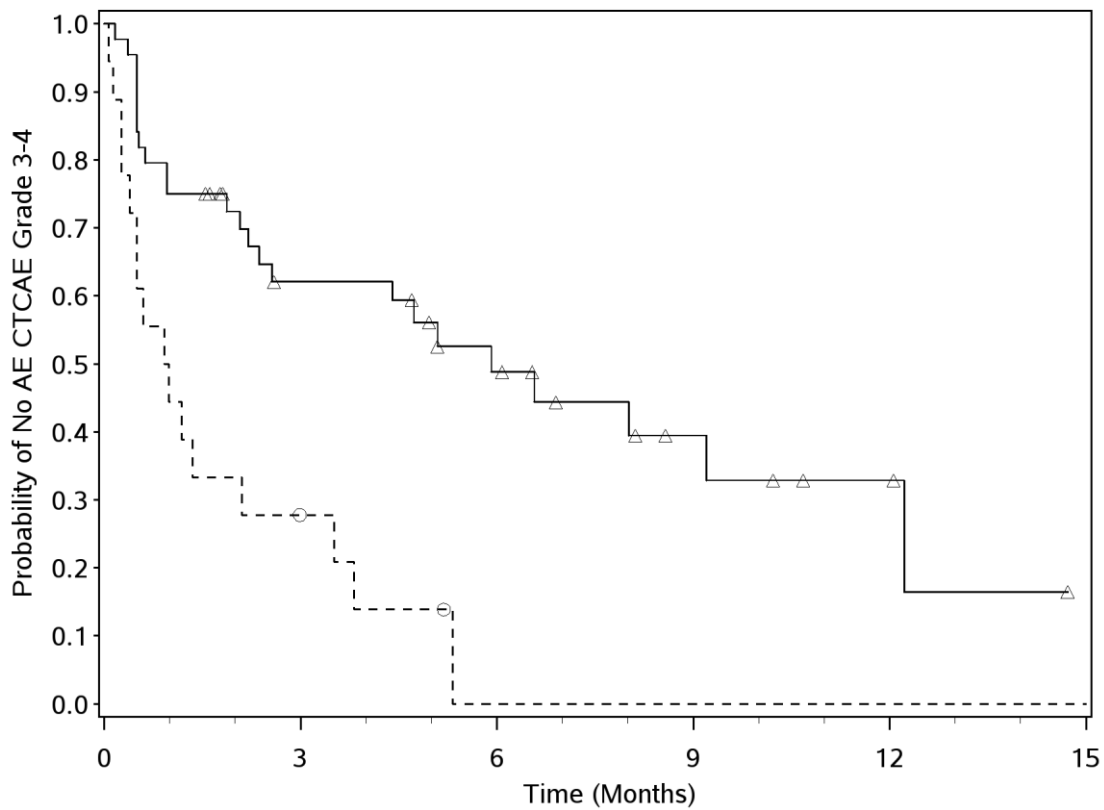
Abbildung 29: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt jegliches UE aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

Ergänzung der Kaplan-Meier-Kurven für UE Grad 3-4

**Gesamtpopulation**

*Subgruppenmerkmal: Ansprechen auf zuletzt erhaltene Therapie*

Subgruppe Responder



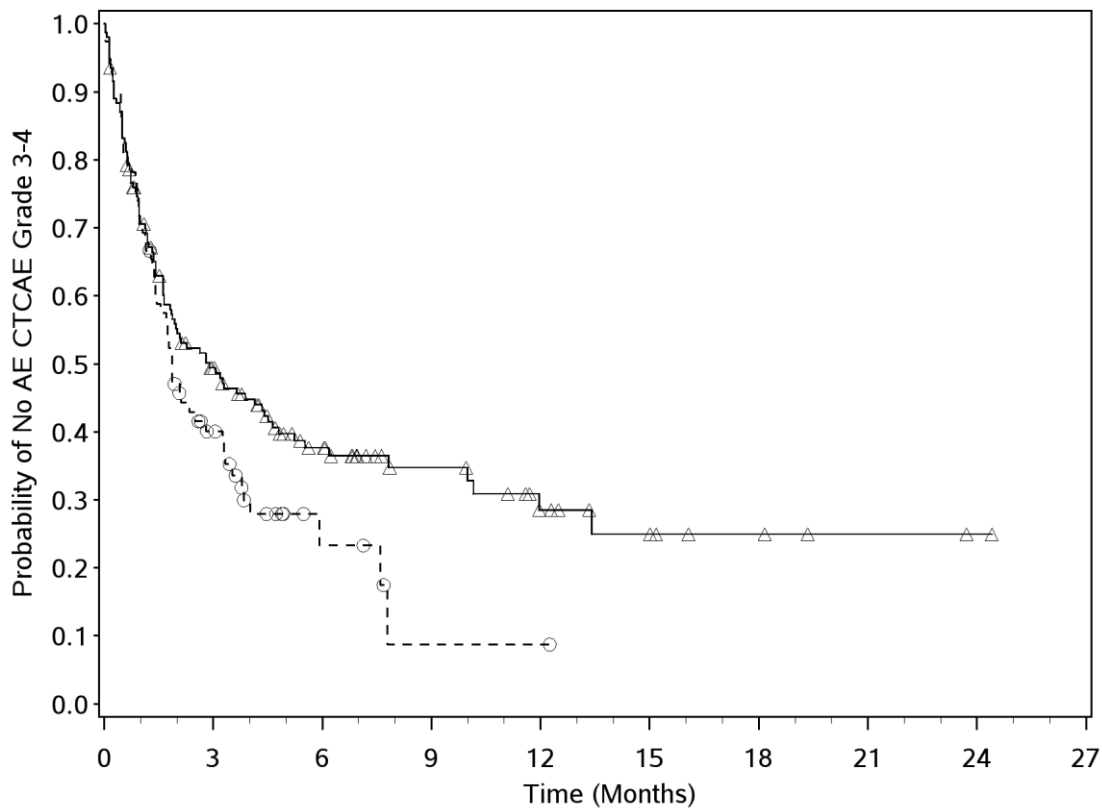
Number of Subjects at Risk

Nivolumab 3 mg/kg	44	23	13	6	3	0
Investigator's Choice	18	4	0	0	0	0

—△ Nivolumab 3 mg/kg (events : 24/44), median and 95% CI : 5.91 (2.37, 12.22)

--○-- Investigator's Choice (events : 16/18), median and 95% CI : 0.95 (0.39, 2.10)

Subgruppe Nicht-Responder



Number of Subjects at Risk

Nivolumab 3 mg/kg	155	66	35	19	11	7	4	2	1	0
Investigator's Choice	78	26	5	1	1	0	0	0	0	0

—△— Nivolumab 3 mg/kg (events : 95/155), median and 95% CI : 2.89 (1.81, 4.50)

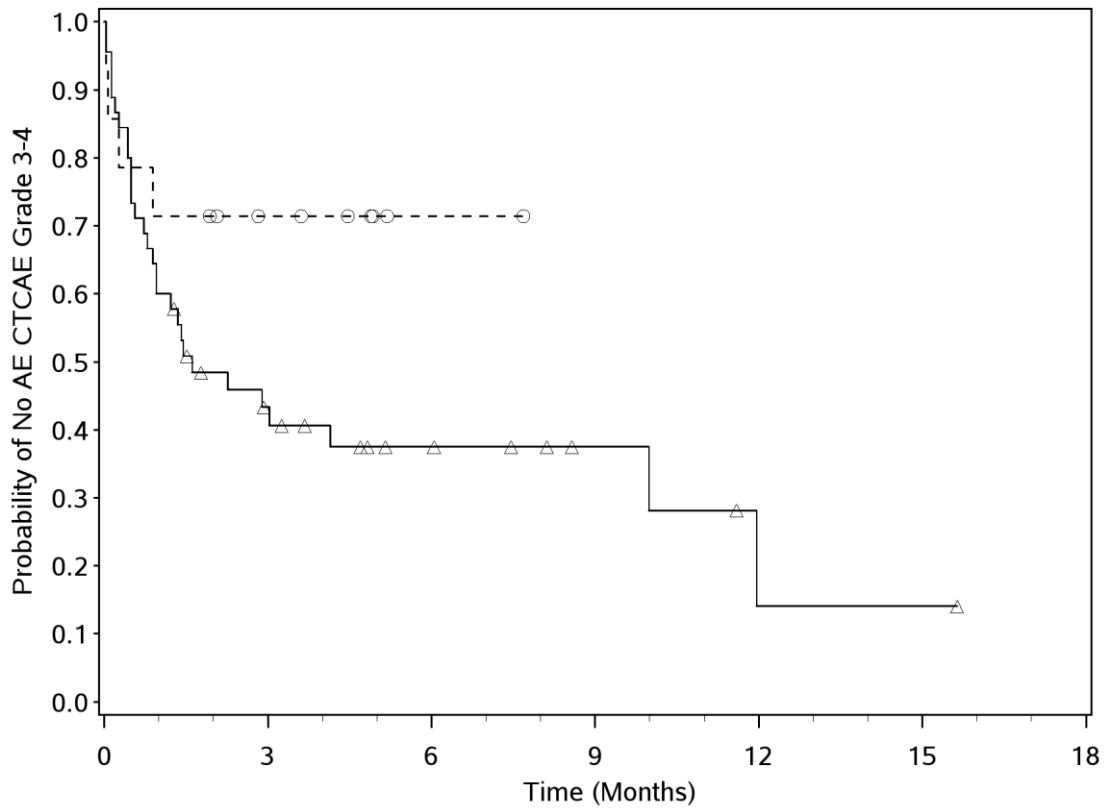
--○-- Investigator's Choice (events : 56/78), median and 95% CI : 1.87 (1.41, 3.25)

Abbildung 30: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt UE Grad 3-4 aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

**MTX-Teilpopulation**

Subgruppenmerkmal: Region

Subgruppe Nordamerika



Number of Subjects at Risk

Nivolumab 3 mg/kg

45	16	8	4	1	1	0
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Methotrexate

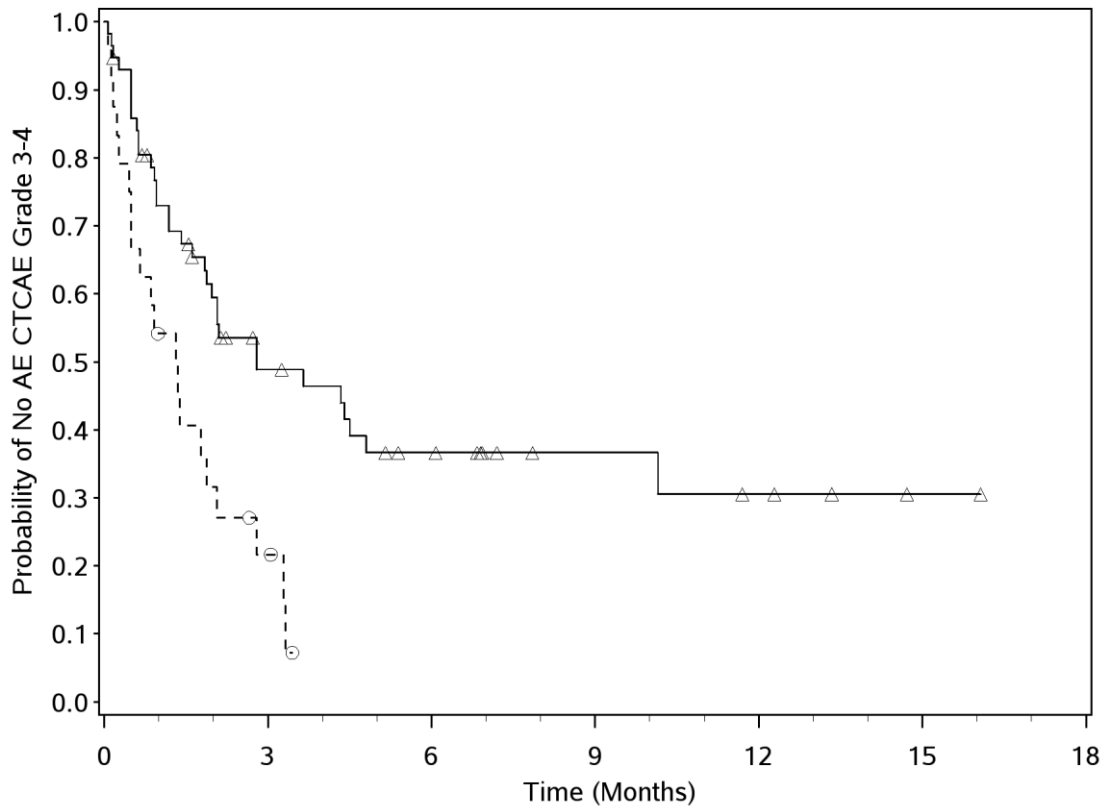
14	7	1	0	0	0	0
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—△— Nivolumab 3 mg/kg (events : 29/45), median and 95% CI : 1.61 (0.89, 9.99)

--○-- Methotrexate (events : 4/14), median and 95% CI : N.A. (0.26, N.A.)



Subgruppe Europa



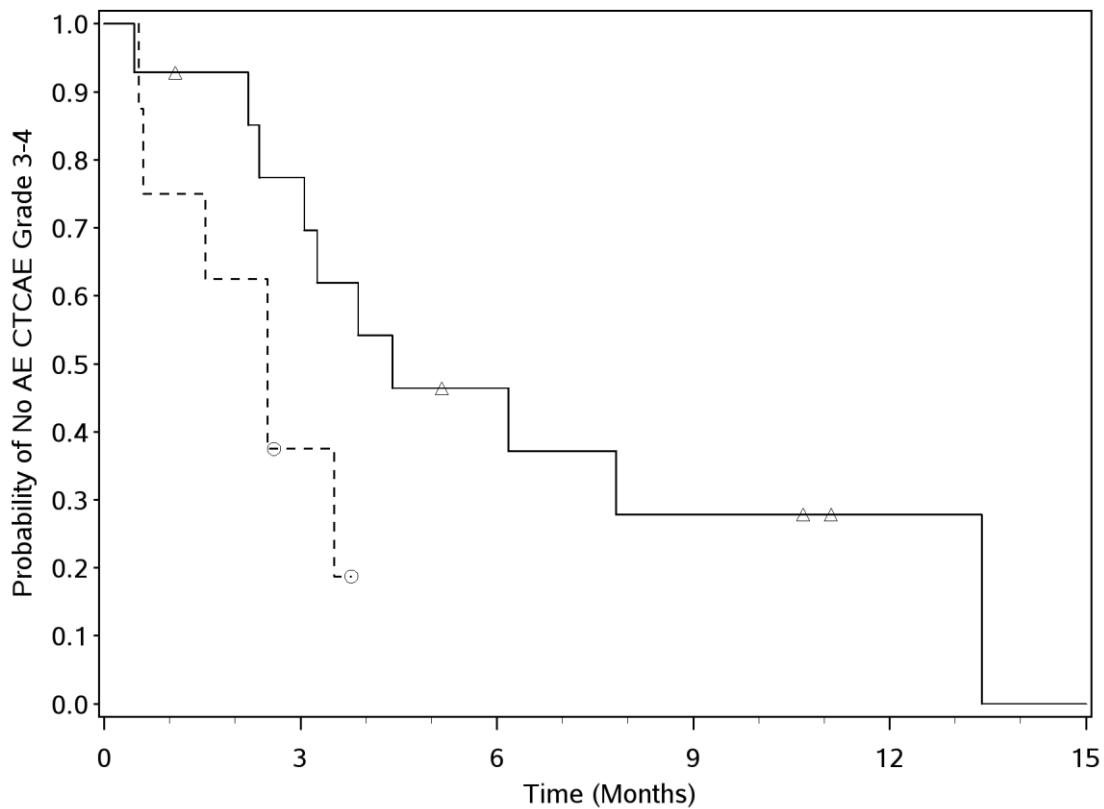
Number of Subjects at Risk

Time (Months)	0	1.5	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5
Nivolumab 3 mg/kg	57	21	13	6	4	1	0					
Methotrexate	24	4	0	0	0	0	0					

—△— Nivolumab 3 mg/kg (events : 33/57), median and 95% CI : 2.79 (1.84, 10.15)

--○-- Methotrexate (events : 20/24), median and 95% CI : 1.31 (0.49, 2.07)

Subgruppe Rest der Welt



Number of Subjects at Risk

Nivolumab 3 mg/kg	14	10	5	3	1	0
Methotrexate	8	2	0	0	0	0

—△— Nivolumab 3 mg/kg (events : 10/14), median and 95% CI : 4.40 (2.37, 13.40)

--○-- Methotrexate (events : 6/8), median and 95% CI : 2.50 (0.53, N.A.)

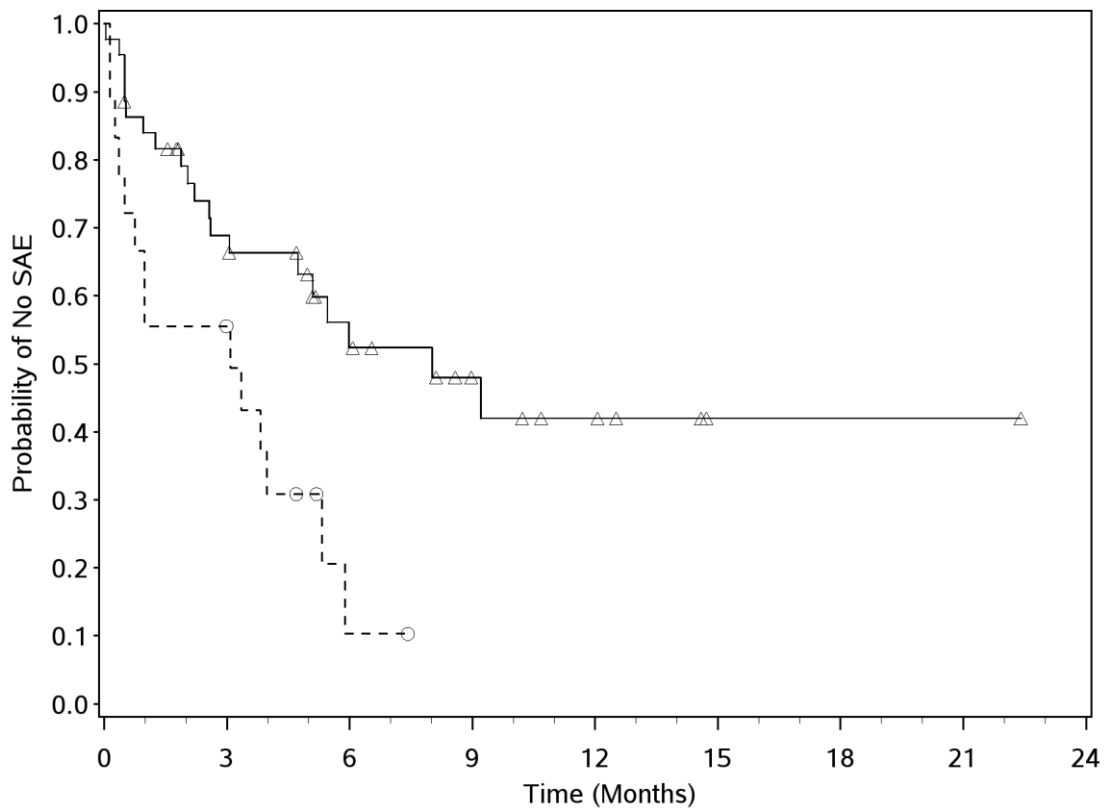
Abbildung 31: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt UE Grad 3-4 aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

Ergänzung der Kaplan-Meier-Kurven für SUE

**Gesamtpopulation**

*Subgruppenmerkmal: Ansprechen auf zuletzt erhaltene Therapie*

Subgruppe Responder



Number of Subjects at Risk

Nivolumab 3 mg/kg

44    27    14    8    5    1    1    1    0

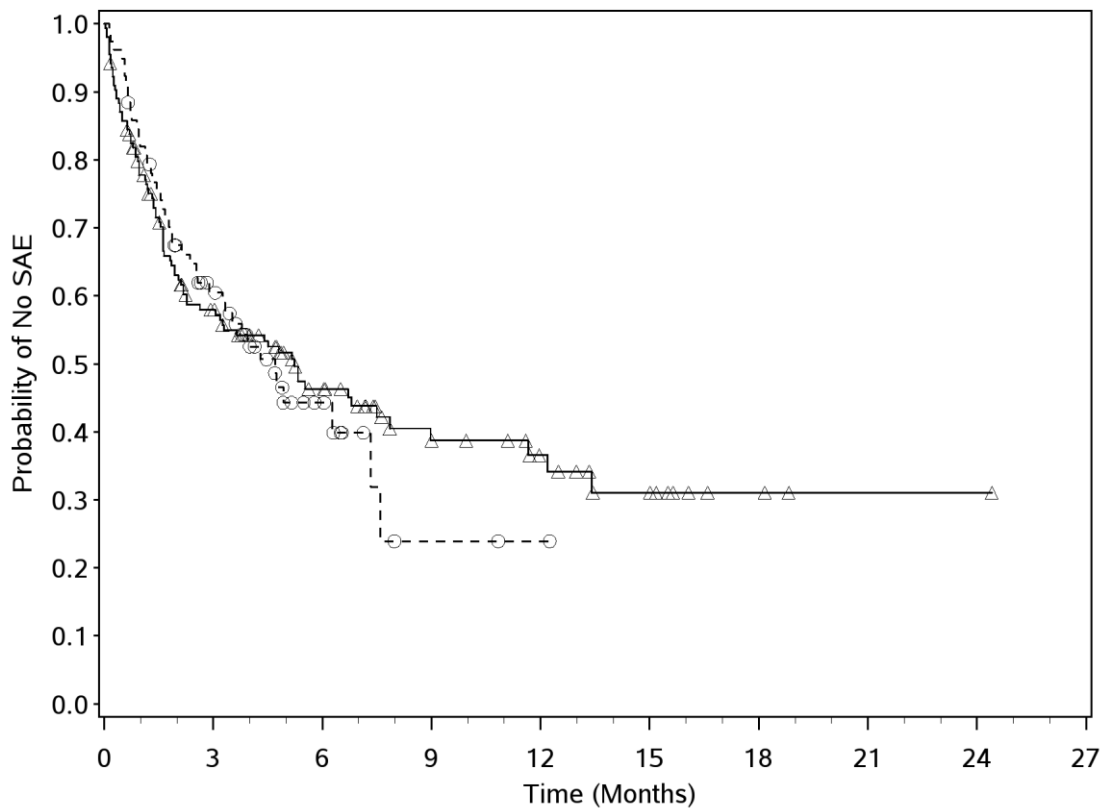
Investigator's Choice

18    9    1    0    0    0    0    0    0

—△— Nivolumab 3 mg/kg (events : 20/44), median and 95% CI : 8.02 (3.06, N.A.)

--○-- Investigator's Choice (events : 14/18), median and 95% CI : 3.09 (0.49, 5.32)

Subgruppe Nicht-Responder



Number of Subjects at Risk

Nivolumab 3 mg/kg	155	78	41	22	15	9	3	1	1	0
Investigator's Choice	78	41	11	2	1	0	0	0	0	0

—△— Nivolumab 3 mg/kg (events : 83/155), median and 95% CI : 5.22 (2.63, 7.85)

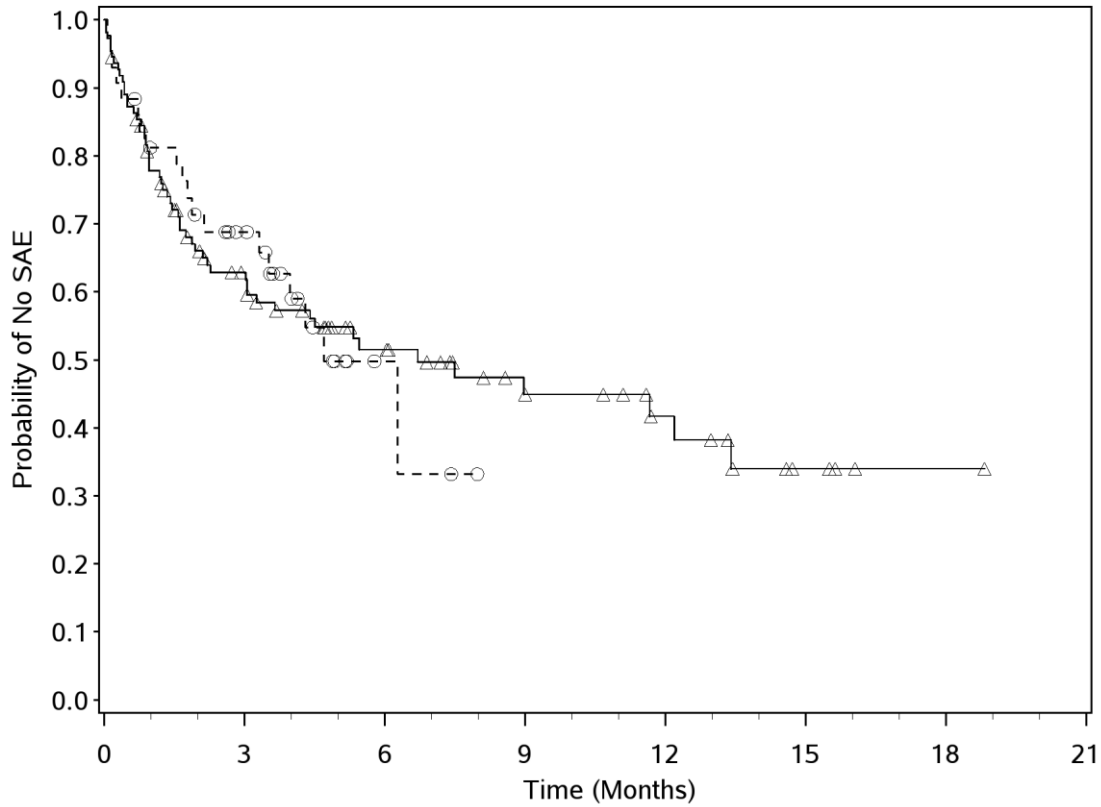
--○-- Investigator's Choice (events : 42/78), median and 95% CI : 4.70 (2.89, 7.33)

Abbildung 32: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt SUE aus CA209-141 (Gesamtpopulation; 2. Datenschnitt vom 20.09.2016)

**MTX-Teilpopulation**

*Subgruppenmerkmal: Altersgruppe II*

Subgruppe < 75 Jahre



Number of Subjects at Risk

Nivolumab 3 mg/kg

110      57      31      18      12      5      1      0

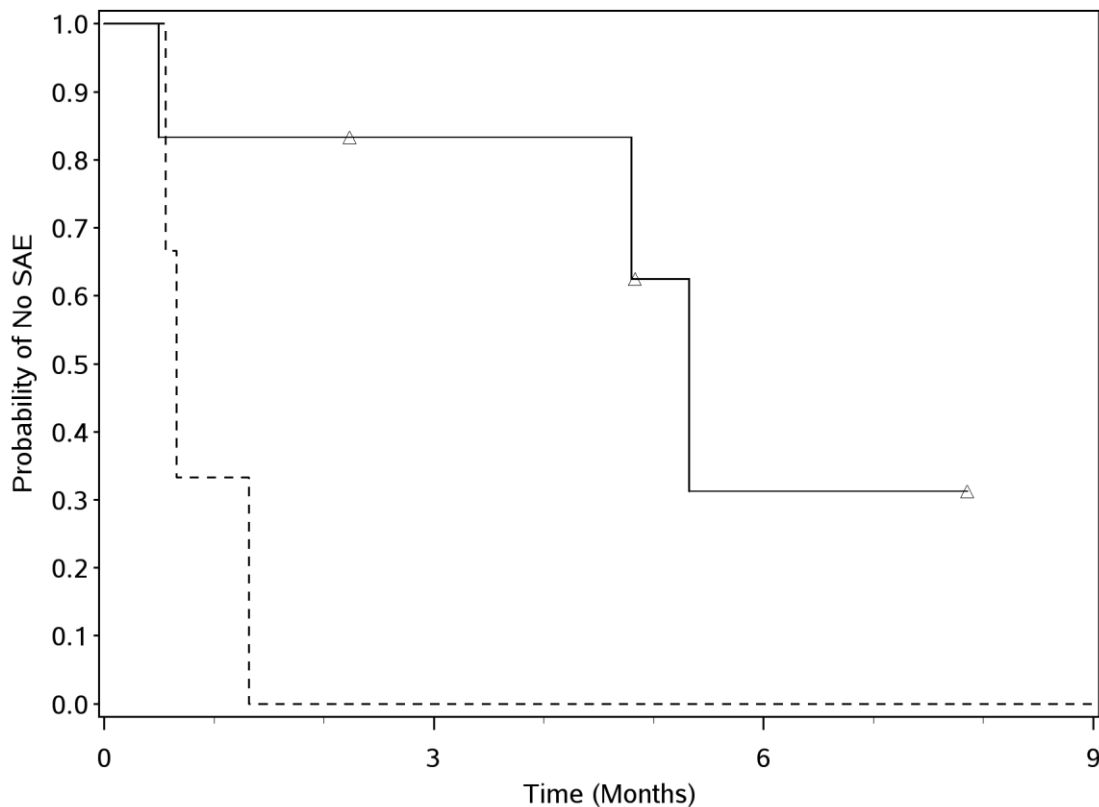
Methotrexate

43      24      3      0      0      0      0      0

—△— Nivolumab 3 mg/kg (events : 54/110), median and 95% CI : 6.70 (3.06, 13.40)

--○-- Methotrexate (events : 19/43), median and 95% CI : 4.70 (3.32, N.A.)

Subgruppe  $\geq 75$  Jahre



Number of Subjects at Risk

Nivolumab 3 mg/kg

6	4	1	0
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Methotrexate

3	0	0	0
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—△— Nivolumab 3 mg/kg (events : 3/6), median and 95% CI : 5.32 (0.49, N.A.)

--○-- Methotrexate (events : 3/3), median and 95% CI : 0.66 (0.56, 1.31)

Abbildung 33: Kaplan-Meier-Kurven der Subgruppenanalysen für den Endpunkt SUE aus CA209-141 (MTX-Teilpopulation; 2. Datenschnitt vom 20.09.2016)

Ergänzung der Kaplan-Meier-Kurven für Therapieabbruch wegen UE

**Gesamtpopulation**

Keine Subgruppen mit Beleg auf Interaktion

**MTX-Teilpopulation**

Keine Subgruppen mit Beleg auf Interaktion