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INSTRUCTIONS FOR USE

IDYLLA™ CDx MSI TEST

Biocartis NV
Generaal De Wittelaan 11B
2800 Mechelen, Belgium
www.biocartis.com

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REF A0220/6

IVD **For *in vitro* diagnostic use**

Rx only **For Prescription Use Only**

Version 1 08/2025

BIOCARTIS

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1 Name

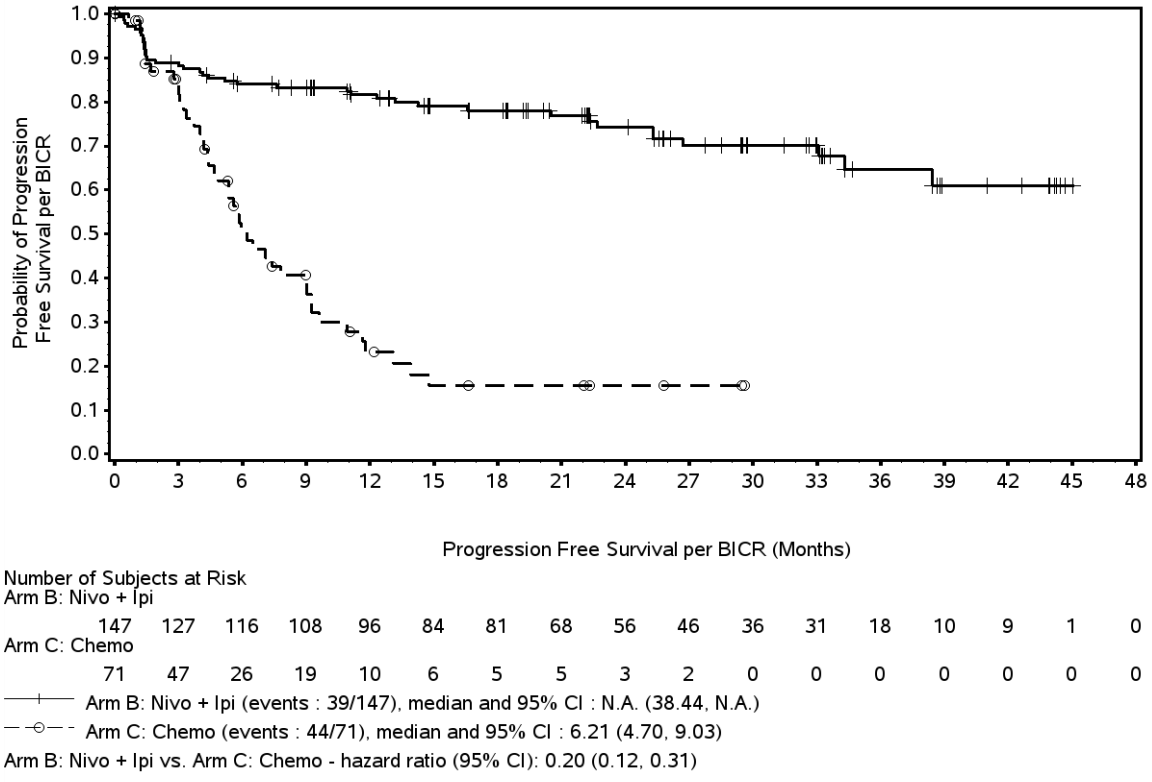
Name	Idylla ¡ CDx MSI Test
Short name	MSI-CDx
Product version	MSI-CDx_IVD/3.0

2 Intended Use

For in vitro diagnostic use. For Prescription Use Only.
For use on the Biocartis Idylla System only.

Figure 2. Kaplan-Meier Curve of PFS per BICR for nivolumab + ipilimumab vs chemotherapy in first line by Idylla CDx MSI Test testing results. A: CTA+ Randomized Subjects with Centrally Confirmed MSI-H by Idylla CDx MSI Test; B: CTA+ Randomized Subjects with Centrally Confirmed MSS by Idylla CDx MSI Test Statistical model for HR: stratified Cox proportional hazard model and stratified log-rank test by tumor sidedness (left vs. right) as entered into the interactive response system. Symbols represent censored observations. Excludes data collected one month after first crossover dose date. 1L: first line treatment; BICR: blinded independent central review; chemo: chemotherapy; HR: hazard ratio; nivo + ipi: nivolumab plus ipilimumab; PFS: progression-free survival.

A.



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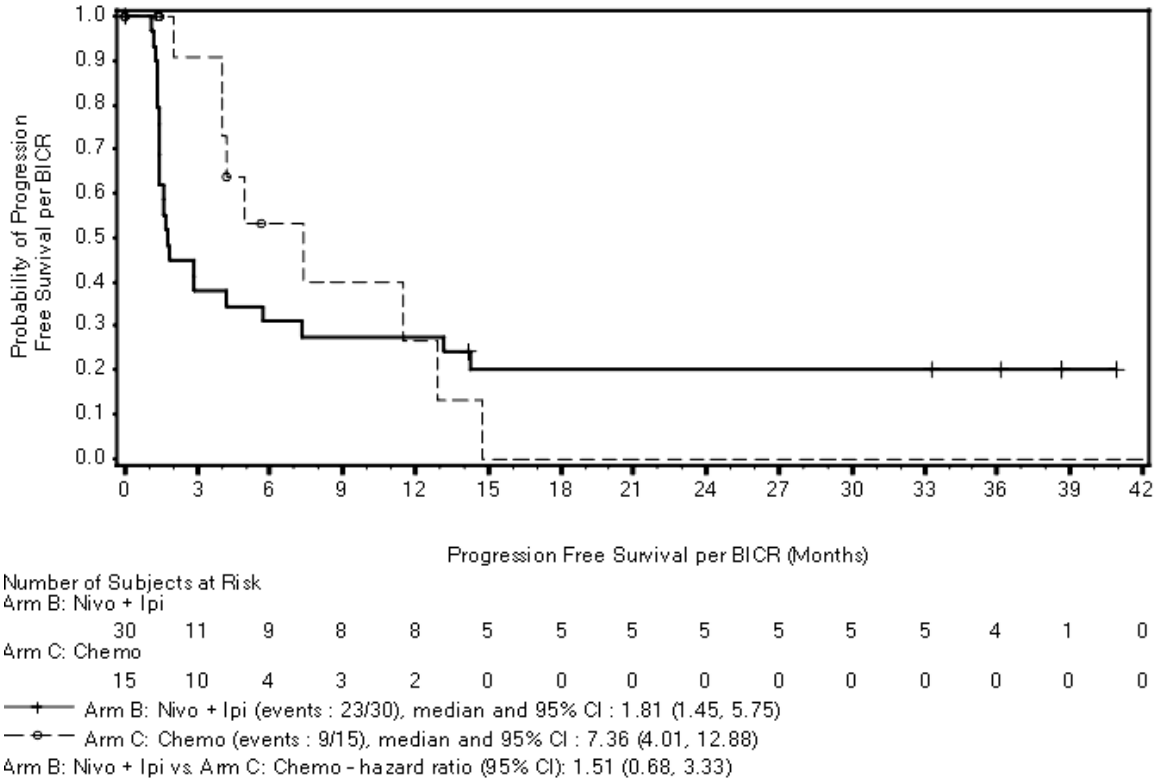
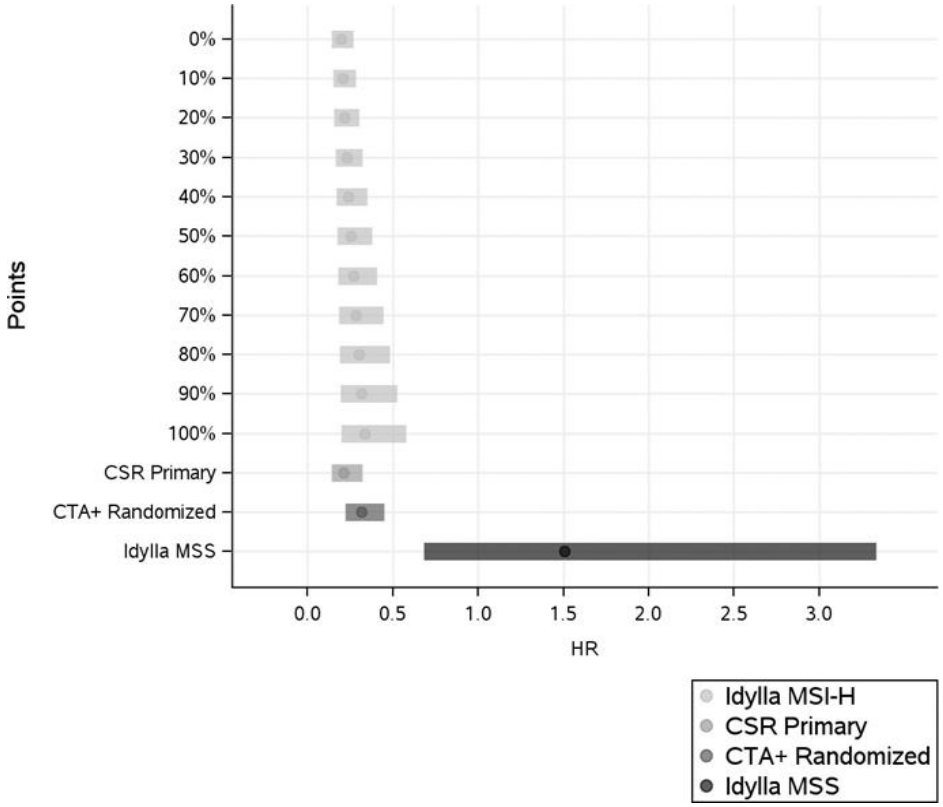


The clinical efficacy was estimated using a tipping point analysis with a simulated range for the missing HR of PFS potentially with Idylla CDx MSI Test MSI-H status and unenrolled to CA209-8HW due to their locally tested negative status (CTA-). It was assumed the best scenario to be equal to the HR in the concordant population with CTA+ and Idylla CDx MSI Test MSI-H status, i.e., HR = 0.2, and the worst scenario to be HR=1. The overall PFS HR estimated for nivolumab + ipilimumab vs chemotherapy in first line from the tipping point analysis ranges from 0.20 (95% CI, 0.14 - 0.28) to 0.34 (95% CI, 0.20 - 0.58). The results showed that, across the tipping point range, the clinical utility for the intended use of Idylla CDx MSI Test MSI-H is similar to the efficacy observed from the CTA+ population, and different with the patients with the enrolled CTA+ but Idylla CDx MSI Test MSS status. In addition, the clinical utility results for the Idylla CDx MSI Test intended use are clinically meaningful meeting the preset acceptance criteria.

Figure 3. Forest Plot of PFS per BICR of Nivolumab plus Ipilimumab vs. Chemotherapy in First Line for Idylla CDx MSI Test MSI-H of the Intended Use Estimated from Tipping Point Analysis Compared to Efficacies in CTA+ Randomized, Clinical Study Report (CSR) Primary and Idylla CDx MSI Test MSS Participants in First Line



Idylla MSI-H population is the intended use population of Idylla CDx MSI Test. CSR primary population is randomized subjects with centrally confirmed dMMR/MSI-H status. CTA+ randomized subjects are subjects who were randomized in CA209-8HW with locally tested dMMR/MSI-H status. Idylla CDx MSI Test MSS population is subjects with centrally confirmed Idylla CDx MSI Test MSS status and locally confirmed dMMR/MSI-H status. Tipping point analysis results range from the best (0%) to the worst scenario (100%), where the best scenario represents HR equal to the estimated value from the data of the concordant population with CTA+ & Idylla CDx MSI Test MSI-H and the worst scenario represents HR equal to 1.

12.7.2.2 Clinical Efficacy of the Idylla CDx MSI Test for All Lines OPDIVO (Nivolumab) and OPDIVO (Nivolumab) in Combination with YERVOY (Ipilimumab)

Of the total 705 CTA+ participants randomized to Arm B (nivolumab + ipilimumab) and Arm A (nivolumab) in all lines of mCRC, 504 were confirmed to be MSI-H by central testing with the Idylla CDx MSI Test. For patients with the centrally confirmed Idylla CDx MSI Test MSI-H status, the median ages for Arm B and Arm A were 64 years and 63 years, respectively. The sex distribution was 45.7% Male and 54.3% Female in Arm B and, 43.2% Male and 56.8% Female in Arm A. For comparison, in the CTA+ participants, the median ages for Arm B and Arm A were 63 years and 62 years, respectively, with sex distribution of 53.8% Male and 46.2% Female in Arm B and, 45% Male and 56% Female in Arm A. The distribution of demographic and other baseline disease and specimen characteristics of patients were generally balanced between the two arms and similar between the CTA+ and those centrally confirmed as MSI-H by the Idylla CDx MSI Test.

Table26. PFS per BICR of All Lines OPDIVO (Nivolumab) and OPDIVO (Nivolumab) in Combination with YERVOY (Ipilimumab) Estimated from CA209-8HW

Source	Arm B: nivolumab + ipilimumab			Arm A: nivolumab			Hazard Ratio***	
	N	Median** (months)	95% CI	N	Median** (months)	95% CI	Estimate	95% CI
All CTA+ Randomized	352	54.08	(46.62 - N.A.*)	353	18.43	(9.20 - 28.16)	0.63	(0.51 - 0.79)
Idylla CDx MSI Test MSI-H and CTA+	257	N.A.*	(53.82 - N.A.*)	247	44.85	(22.97 - N.A.*)	0.60****	(0.45 - 0.80)
Idylla CDx MSI Test MSS and CTA+	55	2.66	(1.58 - 3.58)	53	1.94	(1.45 - 2.83)	0.76	(0.50 - 1.16)

*: N.A.: Not available since the median PFS is not reached

**: Median PFS is based on Kaplan-Meier Estimates

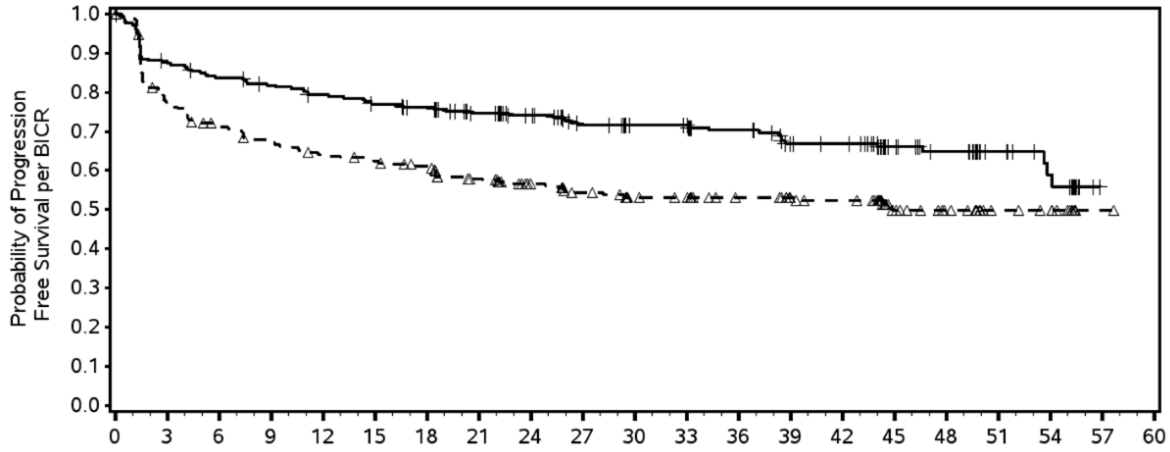
***: Hazard Ratio (HR) is Arm B over Arm A from a Cox Model stratified by tumor sidedness (left vs. right) and prior lines of therapy (0, 1, >=2) as entered into the Interactive Response Technology (IRT) system.

**** The HR is based on the Idylla CDx MSI Test MSI-H and CTA+ subjects. The difference between the HRs (0.60 in the table above vs. 0.62 in the drug labeling) for all lines PFS comparison of nivolumab plus ipilimumab versus nivolumab is due to the slightly different population since the intended use population in the drug labeling is based on at least one of the two centrally confirmed tests on the CTA+ randomized subjects (Idylla CDx MSI Test or MMR IHC Panel pharmDx).

Of the total 705 subjects with the CTA+ status from all lines randomized to receive nivolumab + ipilimumab (n = 352) or nivolumab (n = 353) therapy, nivolumab + ipilimumab demonstrated a clinically meaningful improvement in PFS per BICR over nivolumab (HR = 0.63). Of these randomized subjects with centrally confirmed MSI-H status by Idylla CDx MSI Test, the PFS benefit by nivolumab + ipilimumab (n = 257) vs. nivolumab (n = 247) was consistently observed (HR = 0.60). Median PFS per BICR was not reached for nivolumab + ipilimumab (95% CI: 53.82 t N.A. months), compared to 44.85 months for nivolumab (95% CI: 22.97 t N.A. months; see Table 26, Figure 4A). Of the CTA+ randomized subjects with centrally confirmed MSS status by Idylla CDx MSI Test, the PFS HR for nivolumab + ipilimumab vs nivolumab was 0.76. The median PFS per BICR was 2.66 months (95% CI, 1.58 - 3.58 months) for nivolumab + ipilimumab compared to 1.94 months (95% CI, 1.45 - 2.83 months) for nivolumab (see Table 26 and Figure 4B).

Figure 4. Kaplan-Meier Curve of PFS per BICR for nivolumab + ipilimumab vs nivolumab in all lines by Idylla CDx MSI Test testing results. A: CTA+ Randomized Subjects with Centrally Confirmed MSI-H by Idylla CDx MSI Test; B: CTA+ Randomized Subjects with Centrally Confirmed MSS by Idylla CDx MSI Test

A.

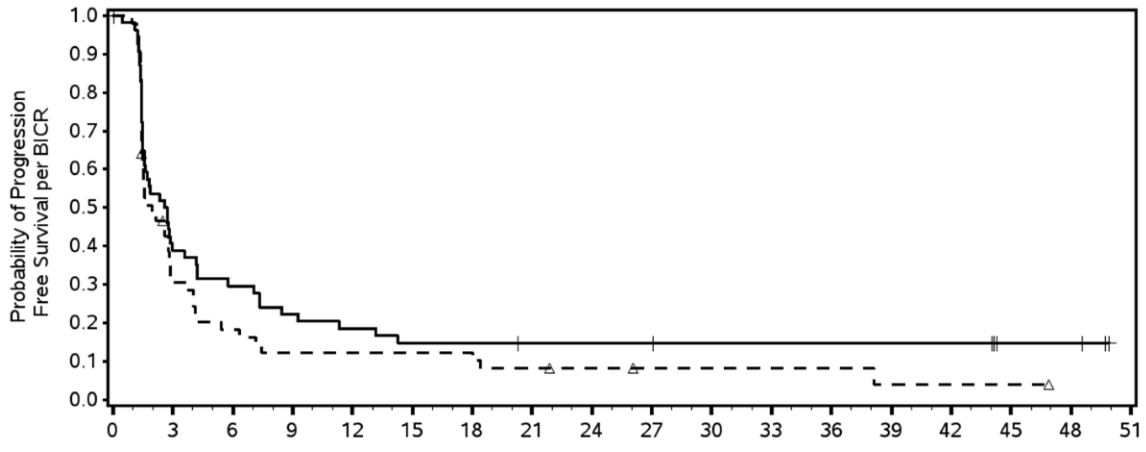


Number of Subjects at Risk

Arm A: Nivo	247	185	170	160	150	146	140	125	108	94	84	82	73	67	64	36	29	13	11	1	0
Arm B: Nivo + Ipi	257	221	210	202	195	188	181	163	148	131	121	120	108	91	89	55	48	26	20	0	0

Arm A: Nivo (events : 113/247), median and 95% CI : 44.85 (22.97, N.A.)
Arm B: Nivo + Ipi (events : 81/257), median and 95% CI : N.A. (53.82, N.A.)
Arm B: Nivo + Ipi vs. Arm A: Nivo - hazard ratio (95% CI): 0.60 (0.45, 0.80)

B.



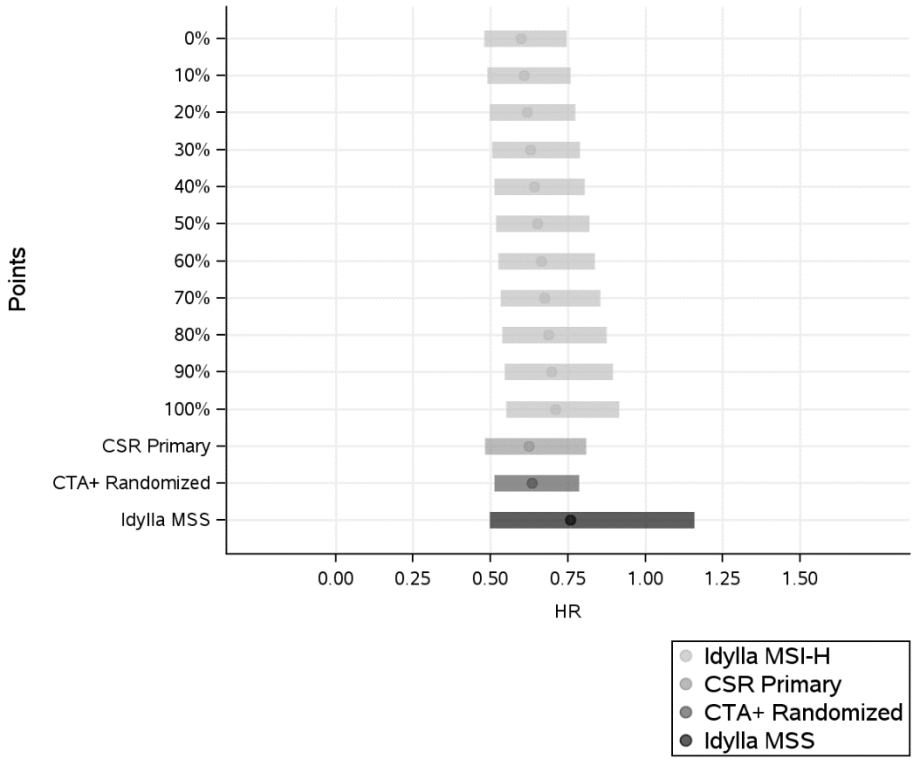
Number of Subjects at Risk

Arm A: Nivo	53	15	9	6	6	6	6	4	3	2	2	2	2	1	1	1	0	0
Arm B: Nivo + Ipi	55	21	16	12	10	8	8	7	7	7	6	6	6	6	6	3	3	0

Arm A: Nivo (events : 48/53), median and 95% CI : 1.94 (1.45, 2.83)
Arm B: Nivo + Ipi (events : 46/55), median and 95% CI : 2.66 (1.58, 3.58)
Arm B: Nivo + Ipi vs. Arm A: Nivo - hazard ratio (95% CI): 0.76 (0.50, 1.16)

The clinical utility was estimated using a tipping point analysis with a simulated range for the missing HR of PFS potentially with Idylla CDx MSI Test MSI-H status and unenrolled to CA209-8HW due to their locally tested negative status (CTA-). It was assumed the best scenario to be equal to the HR in the concordant population with CTA+ and Idylla CDx MSI Test MSI-H status, i.e., HR = 0.6, and the worst scenario to be HR=1. The overall PFS HR estimated from the tipping point analysis ranges from 0.60 (95% CI, 0.48 - 0.75) to 0.71 (95% CI, 0.55 - 0.92). The results showed that, across the tipping point range, the clinical utility for the intended use of Idylla CDx MSI Test MSI-H is similar to the CTA+ patients in all lines of therapy (depicted in Figure 5), showing clinically meaningful improvement.

Figure 5. Forest Plot of PFS per BICR of nivolumab plus ipilimumab vs. nivolumab in all lines for Idylla CDx MSI Test MSI-H of the Intended Use Population Estimated from Tipping Point Analysis Compared to Efficacies in CTA+ Randomized, CSR Primary and Idylla CDx MSI Test MSS Participants in all lines.



Idylla MSI-H population is the intended use population of Idylla CDx MSI Test. CSR primary population is randomized subjects with centrally confirmed dMMR/MSI-H status. CTA+ randomized subjects are subjects who were randomized in CA209-8HW with locally tested dMMR/MSI-H status. Idylla CDx MSI Test MSS population is subjects with centrally tested MSS status and locally confirmed dMMR/MSI-H status. Tipping point analysis results range from the best (0%) to the worst scenario (100%), where the best scenario represents HR equal to the estimated value from the data of the concordant population and the worst scenario represents HR equal to 1.

The ORR in all lines for nivolumab and nivolumab + ipilimumab is provided in Table 27. The ORR for nivolumab + ipilimumab and nivolumab alone in all lines with centrally confirmed MSI-H status by Idylla CDx MSI Test were 73.5% (95% CI: 67.7, 78.8) and 58.7% (95% CI: 52.3, 64.9), respectively. The results are consistent with the ORR observed in CTA+ patients randomized to nivolumab + ipilimumab (63.6%, 95% CI: 58.4, 68.7) and nivolumab monotherapy (49.3%, 95% CI: 44.0, 54.6) arms, respectively. In contrast, the ORR in patients with enrolled CTA+ but Idylla CDx MSI Test MSS status were 23.6% (95% CI: 13.2, 37.0) in nivolumab + ipilimumab and 11.3% (95% CI: 4.3, 23.0) nivolumab alone.

Table27. ORR per BICR of All Lines OPDIVO (Nivolumab) and OPDIVO (Nivolumab) in Combination with YERVOY (Ipilimumab) Estimated from CA209-9HW

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CRR = Complete Response Rate, PRR = Partial Response Rate, N.A = not applicable.

*ORR (CRR+PRR), confidence interval based on the Clopper and Pearson method.

**Based on Cochran-Mantel-Haenszel (CMH) test stratified by the same factors as used in the Cox proportional hazards model and not evaluated for statistical significance.

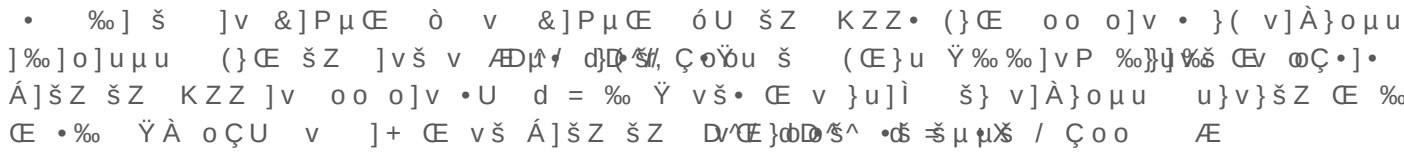

Figure 6. Forest Plot of ORR per BICR for Idylla CDx MSI Test MSI-H of the Intended Use All Lines Subjects by Nivolumab Monotherapy

Idylla MSI-H population is the intended use population of Idylla CDx MSI Test. CTA+ randomized Subjects are subjects who were randomized in CA209-8HW with locally confirmed dMMR/MSI-H status. Idylla CDx MSI Test MSS population is subjects with centrally tested MSS status and locally confirmed dMMR/MSI-H status. Tipping point analysis results range from the best (0%) to the worst scenario (100%), where the best scenario assumes the inestimable ORR in locally misclassified as pMMR/MSS status & Idylla CDx MSI Test MSI-H population equal to the estimated value from the data of the concordant population and the worst scenario assume the inestimable ORR equal to 0%.