TITLE PAGE

Study Title	A randomized phase II study on the OPTimization of IMmunotherapy in squamous carcinoma of the head and neck
Study Title German	Eine randomisierte Phase-II-Studie zur Optimierung der Immuntherapie bei Plattenepithelkarzinomen im Kopf-Hals-Bereich
Short Title	OPTIM
Sponsor's clinical trial code	AIO-KHT-0117
EudraCT No.	2017-003349-14
Test drug/product	Nivolumab, Ipilimumab
Comparator	Docetaxel
Dosage	• Nivolumab monotherapy: 240 mg fixed dose Q2W • Nivolumab/ipilimumab combination treatment: Nivolumab 3 mg/kg Q2W, ipilimumab 1 mg/kg Q6W • Docetaxel: 75 mg/m^2 Q3W
Indication	Second-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck (R/M-SCCHN)
Design	Open label, randomized, multicenter
Development phase	Phase II
Sponsor	AIO-Studien-gGmbH, Kuno-Fischer-Str. 8, 14057 Berlin
Sponsor representative	Dr. Mischo Kursar
Coordinating investigator	Professor Dr. med. Viktor Grünwald Address until 31-Dec-2018: Medical School Hannover (MHH) Dept. of Hematology, Hemostasis, Oncology, and Stem Cell Transplantation Carl-Neuberg-Str. 1 30625 Hannover Address since 01-Jan-2019: Universitätsklinikum Essen, Innere Klinik (Tumorforschung) und Klinik für Urologie Hufelandstraße 55 45147 Essen
Study initiation date	Authorized by competent authority 16-Apr-2018 First Patient In 19-Jul-2018
Date of early study termination	Recruitment halted 01-Mar-2020 Competent authority informed 04-Mar-2020
Version / date of report	V1.0 / 16-Jun-2022
The study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.	

SYNOPSIS

Name of Sponsor: AIO-Studien-gGmbH	
Name of Finished Product/Active Ingredient: Opdivo®/Nivolumab, Yervoy®/Ipilimumab **Name of Marketing Authorization Holder**: Bristol-Myers Squibb	
Title of Study: A randomized phase II study on the OPTimization of IMmunotherapy in squamous carcinoma of the head and neck)	
Coordinating Investigator: Prof. Dr. med. Viktor Grünwald, University Hospital Essen	
Study centers: 19 sites throughout Germany were initiated. 10 of these enrolled patients.	
Publication: n/a	
Studied period First Patient In: 19-Jul-2018 Recruitment halted: 01-Mar-2020	**Phase of development**: II
Primary Objective: The primary objective is to test whether dual checkpoint blockade is superior to docetaxel chemotherapy as early salvage therapy in R/M-SCCHN **Secondary Objective:** Secondary objectives of this trial are the assessment of additional efficacy parameters as well as the feasibility and safety of an intensified immunotherapy regimen.	
Methodology: Open label, randomized, multicenter phase II trial	
Number of patients (planned and analysed): **Planned**: N=280 enrolled to receive nivolumab monotherapy, N=154 randomized **Analyzed**: N=49 enrolled to receive nivolumab monotherapy, N=31 randomized (N=14 to arm A, N=17 to arm B)	
Diagnosis: Patients with R/M SCCHN progressing after prior platinum-based therapy (radiochemotherapy or systemic chemotherapy) Main criteria for inclusion: • Adult patients (≥ 18 years of age) • Histological or cytological confirmed recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) or nasal sinus not amenable to local therapies • Availability of tumor tissue from biopsy for determination of PD-L1 and HPV status • Progression or recurrence during or after platinum-based palliative chemotherapy for relapsed or metastatic disease OR progression within 6 months after completion of definitive platinum-containing radiochemotherapy for locally advanced disease • Eastern Cooperative Oncology Group (ECOG) performance status 0-1	
Test product, dose and mode of administration, batch numbers: Experimental treatment was nivolumab/ipilimumab combination, consisting of i.v. infusions of nivolumab 3 mg/kg Q2W and ipilimumab 1 mg/kg Q6W Batch numbers supplied were 072018/AAV7017 for nivolumab and 072018/AAV9534, 072019/AAX6418 and 022020/ABE3010 for ipilimumab.	
Duration of treatment: Study treatment was defined as up to one year of nivolumab monotherapy or up to one year of randomized treatment, or until occurrence of an adverse event that, in the opinion of the investigator or the sponsor, contraindicated further dosing, confirmation of PD (after more than 6 months of nivolumab monotherapy or second PD after randomization), investigator determination that the subject no longer benefitted from study treatment, or death. In the safety set of 49 patients who received nivolumab monotherapy, the median number of cycles administered was 4, the range was 2-27 cycles.	

For randomized treatment in arm A, a median number of 3.5 administered cycles of nivolumab treatment was reported (range 0-13), and a median number of 1.5 cycles for ipilimumab (range 0-5). Median number of administered cycles of docetaxel was 5, the range was 0-14.

Reference therapy, dose and mode of administration, batch number:
Patients in treatment arm B received docetaxel at a dose of 75 mg/m^2 Q3W. The comparator was sourced locally as prescription drug; therefore no batch numbers are available

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ENDPOINTS
Efficacy:
Primary endpoint: Objective response rate in all randomized subjects
Secondary endpoints:

- OS (measured from beginning of NIVO monotherapy and from randomization; including sub-group analysis for HPV status; PD-L1 expression and tumor localization (i.e., oropharynx carcinoma))
- PFS (measured from beginning of NIVO monotherapy and from randomization; including sub-group analysis for HPV status; PD-L1 expression and tumor localization (i.e., oropharynx carcinoma))
- BOR, DOR (during NIVO monotherapy and after randomization)
- QoL (EORTC QLQC30; EORTC QLQ HN35; EQ-5D)

Safety:

- AEs, SAEs and treatment emergent adverse events according to CTCAE 4.03

Statistical methods:

The primary endpoint ORR (based on investigator assessments) was defined as the number of subjects with a best overall response of CR or PR divided by the number of all randomized subjects per arm. It was to be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using the Clopper-Pearson method. Hypothesis testing was to be performed with a chi-squared test using a one-side significance level of α=0.05. The analysis of the primary endpoint ORR was to be performed on the ITT and PP population, where analysis on the ITT population was defined as the primary analysis.

Overall survival was to be calculated from date of first treatment or date of randomization (depending on type of analysis) until death from any cause. A subject who had not died was to be censored at last known date alive.

Progression-free survival was to be calculated from date of randomization until progression for the ITT population.

Duration of response was defined as the time from first confirmed response (CR or PR) to the date of the documented progressive disease as determined using RECIST 1.1 criteria or death due to any cause, whichever occurred first. Best overall response was defined as the best response designation, as determined by investigator, recorded between the date of randomization and the date of progressive disease per RECIST v1.1 or the date of death or subsequent therapy, whichever occurred first.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

Of the 14 patients randomized to NIVO/IPI treatment (arm A), none experienced a tumor response (0% response rate, 95% CI: 0-23.2%). Of the 17 patients randomized to docetaxel (arm B), a tumor response was reported for 3 patients (17.6%, 95% CI: 3.8-43.4%). Results for the per protocol set differ only marginally.

Median overall survival was 121 days (95% CI: 50-566 d) in the NIVO/IPI treatment arm, and 364 days (95% CI: 56-642 d) in the docetaxel arm (p = 0.36).

Median progression-free survival from randomization was 60 days (95% CI: 38-72 d) with NIVO/IPI treatment, and 111.5 days (95% CI: 56-174 d) with docetaxel (p = 0.036).

The best overall response achieved with randomized treatment was stable disease (SD) with NIVO/IPI (pertaining to 3 of the 14 patients in this treatment arm) and partial response (PR) with docetaxel (observed in 3 of the 17 treated patients in this arm).

The pre-planned statistical analysis of duration of response was omitted as a response was only reported for three patients in arm B. Detailed analysis of quality-of-life data was also omitted as only limited amount of data were accrued, and results are of low relevance due to lacking meaningful efficacy results.

SAFETY RESULTS:

Safety results indicate a lower incidence of treatment-related and of severe adverse events with nivolumab/ipilimumab combination treatment than with docetaxel. The experimental treatment therefore appears to be more favorable in terms of toxicity than the standard salvage treatment with docetaxel.

The following table summarizes incidence of adverse events for all tree treatment groups.

	Treatment at Onset								
	Nivolumab N = 49			Nivo/Ipi (Arm A) N = 13			Docetaxel (Arm B) N = 16		
	Events	Pat.	%	Events	Pat.	%	Events	Pat.	%
TEAEs	198	39	79.6%	60	11	84.6%	89	13	81.3%
Not related TEAEs	161	36	73.5%	47	10	76.9%	47	11	68.8%
Related TEAEs	37	17	34.7%	13	5	38.5%	42	11	68.8%
CTCAE grade 1	77	27	55.1%	14	6	46.2%	38	11	68.8%
CTCAE grade 2	57	20	40.8%	29	10	76.9%	30	11	68.8%
CTCAE grade 3	57	19	38.8%	15	5	38.5%	18	8	50.0%
CTCAE grade 4	5	3	6.1%	1	1	7.7%	2	2	12.5%
CTCAE grade 5	2	2	4.1%	1	1	7.7%	1	1	6.3%
CTCAE grade ≥ 3	64	22	44.9%	17	5	38.5%	21	11	68.8%
CTCAE grade ≥ 3 and not related	61	20	40.8%	13	5	38.5%	12	7	43.8%
CTCAE grade ≥ 3 and related	3	3	6.1%	4	2	15.4%	9	6	37.5%
TESAEs	20	12	24.5%	7	5	38.5%	10	7	43.8%
Related TESAEs	2	2	4.1%	1	1	7.7%	5	4	25.0%
Leading to discontinuation of study drug (non-fatal only)	1	1	2.0%	0	0	0.0%	4	3	18.8%
Leading to interruption of study drug	24	8	16.3%	18	2	15.4%	8	5	31.3%
Leading to death	2	2	4.1%	1	1	7.7%	1	1	6.3%
Related and leading to death	1	1	2.0%	0	0	0.0%	1	1	6.3%

The following table displays treatment-emergent adverse events reported for randomized treatment by intensity. Definition of intensity: CTCAE grade 1 = Mild; CTCAE grade 2 = Moderate; CTCAE grades 3-5 = Severe.

System organ class - Preferred term	Nivolumab/ipilimumab N = 13						Docetaxel N = 16					
	Mild		Moderate		Severe		Mild		Moderate		Severe	
Any event	6	46.2%	10	46.2%	5	38.5%	11	68.8%	11	68.8%	11	68.8%
Blood and lymphatic system disorders	**1**	**7.7%**	**0**	**0.0%**	**2**	**15.4%**	**1**	**6.3%**	**1**	**6.3%**	**2**	**12.5%**
- Anaemia	1	7.7%	0	0.0%	2	15.4%	1	6.3%	1	6.3%	0	0.0%
- Leukocytosis	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- Neutropenia	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	1	6.3%
Endocrine disorders	**1**	**7.7%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**
- Hypothyroidism	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Eye disorders	**0**	**0.0%**	**1**	**7.7%**	**0**	**0.0%**	**1**	**6.3%**	**0**	**0.0%**	**0**	**0.0%**
- Lacrimation increased	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Vision blurred	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Gastrointestinal disorders	**2**	**15.4%**	**1**	**7.7%**	**1**	**7.7%**	**3**	**18.8%**	**3**	**18.8%**	**1**	**6.3%**
- Abdominal pain	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- Cheilitis	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Colitis	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- Constipation	2	15.4%	1	7.7%	0	0.0%	1	6.3%	1	6.3%	0	0.0%
- Diarrhoea	0	0.0%	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%
- Dry mouth	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Dysphagia	0	0.0%	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%
- Nausea	1	7.7%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Stomatitis	0	0.0%	0	0.0%	0	0.0%	1	6.3%	1	6.3%	0	0.0%
General disorders and administration site conditions	**1**	**7.7%**	**3**	**23.1%**	**0**	**0.0%**	**5**	**31.3%**	**1**	**6.3%**	**1**	**6.3%**
- Asthenia	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- Face oedema	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Fatigue	0	0.0%	2	15.4%	0	0.0%	2	12.5%	1	6.3%	0	0.0%

- Mucosal inflammation	0	0.0%	0	0.0%	0	0.0%	1	6.3%	1	6.3%	0	0.0%
- Oedema	1	7.7%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Pain	0	0.0%	0	0.0%	0	0.0%	2	12.5%	0	0.0%	0	0.0%
- Pyrexia	0	0.0%	0	0.0%	0	0.0%	2	12.5%	0	0.0%	0	0.0%
Infections and infestations	**0**	**0.0%**	**3**	**23.1%**	**3**	**23.1%**	**3**	**18.8%**	**2**	**12.5%**	**3**	**18.8%**
- Bronchitis	0	0.0%	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%
- Conjunctivitis	0	0.0%	0	0.0%	0	0.0%	1	6.3%	1	6.3%	0	0.0%
- Device related infection	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Folliculitis	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Infection	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Medical device site infection	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Parotitis	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- Periodontitis	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Pharyngitis	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Pneumonia	0	0.0%	2	15.4%	2	15.4%	0	0.0%	0	0.0%	1	6.3%
- Rhinitis	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Sepsis	0	0.0%	0	0.0%	1	7.7%	0	0.0%	0	0.0%	1	6.3%
- Skin infection	0	0.0%	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%
Injury, poisoning and procedural complications	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**1**	**6.3%**	**0**	**0.0%**	**1**	**6.3%**
- Spinal fracture	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- Tooth fracture	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
Investigations	**0**	**0.0%**	**1**	**7.7%**	**1**	**7.7%**	**0**	**0.0%**	**3**	**18.8%**	**3**	**18.8%**
- Blood alkaline phosphatase increased	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- C-reactive protein increased	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	1	6.3%
- Gamma-glutamyltransferase increased	0	0.0%	0	0.0%	1	7.7%	0	0.0%	1	6.3%	0	0.0%
- Lymphocyte count decreased	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- Procalcitonin increased	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- White blood cell count decreased	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	1	6.3%
Metabolism and nutrition disorders	**0**	**0.0%**	**3**	**23.1%**	**1**	**7.7%**	**1**	**6.3%**	**3**	**18.8%**	**0**	**0.0%**
- Decreased appetite	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Dehydration	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Hypercalcaemia	0	0.0%	1	7.7%	1	7.7%	0	0.0%	0	0.0%	0	0.0%
- Hypoalbuminaemia	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Hypocalcaemia	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Hypokalaemia	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Hypomagnesaemia	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Hyponatraemia	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
Musculoskeletal and connective tissue disorders	**0**	**0.0%**	**2**	**15.4%**	**1**	**7.7%**	**2**	**12.5%**	**2**	**12.5%**	**1**	**6.3%**
- Arthralgia	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Back pain	0	0.0%	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%
- Intervertebral disc protrusion	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Muscular weakness	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Musculoskeletal chest pain	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Myalgia	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Osteoporosis	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Pain in jaw	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Trismus	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**0.0%**	**2**	**15.4%**	**3**	**23.1%**	**0**	**0.0%**	**0**	**0.0%**	**2**	**12.5%**
- Acute myeloid leukaemia	0	0.0%	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%
- Metastases to soft tissue	0	0.0%	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%
- Squamous cell carcinoma of skin	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- Tumour haemorrhage	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
- Tumour pain	0	0.0%	1	7.7%	1	7.7%	0	0.0%	0	0.0%	0	0.0%
- Tumour ulceration	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Nervous system disorders	**2**	**15.4%**	**2**	**15.4%**	**0**	**0.0%**	**5**	**31.3%**	**3**	**18.8%**	**1**	**6.3%**

- Balance disorder	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Dizziness	1	7.7%	0	0.0%	0	0.0%	0	0.0%	2	12.5%	0	0.0%
- Headache	0	0.0%	1	7.7%	0	0.0%	1	6.3%	1	6.3%	0	0.0%
- Myoclonus	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Neuropathy peripheral	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Paraesthesia	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Peripheral sensory neuropathy	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Polyneuropathy	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Somnolence	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Syncope	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
Product issues	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**1**	**6.3%**
- Device leakage	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%
Psychiatric disorders	**0**	**0.0%**	**2**	**15.4%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**
- Agitation	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Insomnia	0	0.0%	2	15.4%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Renal and urinary disorders	**2**	**15.4%**	**0**	**0.0%**	**0**	**0.0%**	**1**	**6.3%**	**0**	**0.0%**	**0**	**0.0%**
- Acute kidney injury	1	7.7%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Nephritis	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Respiratory, thoracic and mediastinal disorders	**2**	**15.4%**	**3**	**23.1%**	**0**	**0.0%**	**2**	**12.5%**	**1**	**6.3%**	**0**	**0.0%**
- Cough	1	7.7%	0	0.0%	0	0.0%	1	6.3%	1	6.3%	0	0.0%
- Dyspnoea	0	0.0%	2	15.4%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
- Haemoptysis	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Pleural effusion	0	0.0%	2	15.4%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Pleurisy	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Skin and subcutaneous tissue disorders	**2**	**15.4%**	**1**	**7.7%**	**0**	**0.0%**	**5**	**31.3%**	**5**	**31.3%**	**0**	**0.0%**
- Alopecia	0	0.0%	0	0.0%	0	0.0%	1	6.3%	5	31.3%	0	0.0%
- Blister	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Dermatitis acneiform	0	0.0%	1	7.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
- Dry skin	1	7.7%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Erythema	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Onycholysis	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Pruritus	1	7.7%	0	0.0%	0	0.0%	1	6.3%	0	0.0%	0	0.0%
- Skin fissures	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%	0	0.0%
Surgical and medical procedures	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**	**1**	**6.3%**
- Intervertebral disc operation	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	6.3%

CONCLUSION:
Nivolumab-refractory patients did not respond to escalated immunotherapy using the nivolumab/ipilimumab combination. Instead, 17.6% of patients in the docetaxel arm responded to treatment. While this difference does not reach statistical significance, it still supports the use of docetaxel after failure of platinum and nivolumab treatments. This observation is confirmed by the result for PFS, where a statistically significant difference between the two treatment strategies was observed.

Protocol versions and amendments

Protocol version	Version date	Approval by competent authority	Appoval by ethics committee
2.0	29-Mar-2018	16-Apr-2018	14-May-2018

Protocol version	Version date	Approval by competent authority	Appoval by ethics committee
3.0	04-Sep-2018	29-Sep-2018	18-Oct-2018
Main change			
Dosing of nivolumab monotherapy changed from 3 mg/kg to fixed dose of 240 mg in order to harmonize with marketing authorization for the study indication			

Protocol version	Version date	Approval by competent authority	Appoval by ethics committee
4.0	14-Dec-2018	07-Feb-2019	21-Feb-2019

Main changes

- Change of address of coordinating investigator (transfer from Hannover to Essen)
- Change of inclusion criterion no. 5: cetuximab pre-treatment no longer mandatory in order to harmonize with marketing authorization
- Change of inclusion criterion for randomization no. 2: tumor biopsy at disease progression no longer mandatory, since had been proven not to be feasible in all patients

This report is based on protocol version V4.0 dated 14-Dec-2018.

Date of the report: 16-Jun-2022