Synopsis

Item	Description
Study Title	Nivolumab in combination with cisplatin and 5-fluorouracil as induction therapy in children and adults with EBV-positive nasopharyngeal carcinoma
Study Short Name	Nivolumab in children and adults with nasopharyngeal carcinoma
EudraCT-Number **EUCT Number**	2021-006477-32 2022-500676-59-00
Phase	II
Protocol version	V1.2, 18.07.2022
Sponsor	German Society for Pediatric Oncology and Hematology (GPOH) gGmbH Univ.-Prof. Dr. med. Dirk Reinhardt
Coordinating Investigator	Univ.-Prof. Dr. med. Udo Kontny Head of Div. Pediatric Hematology, Oncology and Stem Cell Transplantation Department of Pediatrics and Adolescent Medicine – Uniklinik RWTH Aachen
Financing	This is an investigator-initiated trial. Bristol-Myers Squibb provides support for this study by providing Nivolumab. Bristol-Myers Squibb bears no responsibility for the study design or the content of the protocol, nor for the conduct of the study, nor for final report and publications based upon the results of this study. Bristol-Myers Squibb supports this study in accordance with paragraph 3.2.2 collaboration of undertakings and research organisations of the COMMUNITY FRAMEWORK FOR STATE AID FOR RESEARCH AND DEVELOPMENT AND INNOVATION (2006/C 323/01).
Risk Benefit Assessment	Addition of Nivolumab to induction chemotherapy may increase the probability of reaching a complete remission (CR) of the primary tumor after induction chemotherapy. The reduction of the radiation dosage to the primary tumor in patients with CR after induction chemotherapy has been previously shown to be safe in children, adolescents and young adults ≤ 25 years. As the rate and severity of late effects after radiotherapy correlate with the radiation dosage, a lower radiation

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	dosage in patients with CR after induction chemotherapy reduces the probability of late effects. The addition of Nivolumab to platinum-containing induction chemotherapy has been shown to be safe in a previous study. Patients will be monitored closely for the occurrence of adverse reactions towards Nivolumab and chemotherapy. Exclusion criteria and dose modification rules are defined to minimize the risk for adverse reactions to induction therapy.
Key Words	Nasopharyngeal carcinoma, Nivolumab, children, adolescents, young adults (AYA)
Study Drug INN	Nivolumab Dose: 4.5 mg/kg (max. 360 mg) every 3 weeks, 3-7 doses Mode of administration: intravenously
Comparator Drug(s) INN if applicable	Not applicable
Indication	Nasopharyngeal carcinoma (NPC)
Medical Study Rationale	About 90% of patients with nasopharyngeal carcinoma (NPC) have locoregional disease. Survival probabilities are around 70 - 80% for adults and > 90% for children, adolescents and young adults ≤ 25 years undergoing combination treatment with induction chemotherapy, followed by radiochemotherapy and subsequent maintenance treatment with interferon-ß. Standard radiation dosages used range between 60 Gy and 70 Gy and are associated with severe late sequelae like endocrine disturbances, hearing impairment and secondary neoplasms. As the probability of such complications correlates with the dose of radiation, lowering the radiation dose could be a means to decrease the incidence and severity of late effects. In a previous study lowering the radiation dosage from 59.4 Gy to 54 Gy has shown to be safe in children, adolescents and young adults ≤ 25 years with NPC who had a complete response of the primary tumor on MRI and PET-CT to induction chemotherapy (12% of patients). Combination of a PD-1 checkpoint-inhibitor with induction chemotherapy has been shown to be safe and to increase the overall response rate in patients with non-small cell lung cancer. As PD-1 checkpoint inhibition has proved to be safe and to demonstrate activity in patients with NPC, the addition of Nivolumab to standard induction chemotherapy in patients with NPC is hypothesized to increase the rate of complete tumor responses, allowing the reduction of the

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	radiation dose in children, adolescents and young adults ≤ 25 years, thereby potentially reducing the risk of late effects. In adults > 25 years of age, reduction of the radiation dose following a complete response after induction therapy has not yet been studied and will be investigated in a subsequent trial. As the probability of survival for patients with metastatic NPC is below 20% and the combination of radiochemotherapy plus PD-1 checkpoint-inhibition has shown to be safe in other head and neck tumors, treatment with Nivolumab is extended for the whole period of radiation therapy in these patients as well as in patients not responding to induction chemotherapy which has been considered to be a risk factor for therapy failure. In adult patients with metastatic disease the combination of gemcitabine and cisplatin has proved to slightly prolong progression-free survival compared to 5-fluorouracil and cisplatin. Therefore, in these patients, approximately 8% of expected patients, Nivolumab will be added to gemcitabine/cisplatin during induction therapy and then given throughout radiochemotherapy.
Primary Objectives	To increase the percentage of NPC patients with complete response (CR) on magnetic resonance imaging (MRI) and PET-(CT or MRI) after induction chemotherapy, thereby allowing to reduce the dosage of radiotherapy from 59.4 Gy to 54 Gy in in children, adolescents and young adults ≤ 25 years with locoregional disease
Secondary Objectives	To investigate the safety of Nivolumab in combination with standard induction chemotherapy in children and adults with nasopharyngeal carcinoma To investigate the safety of Nivolumab in combination with radiochemotherapy in children and adults with nasopharyngeal carcinoma not responding to induction therapy or with metastases Event-free and overall survival of patients
Explorative Objectives	To assess the patient-reported outcomes about own health, quality of life and functional status associated with the treatment received
Evaluation Criteria	<u>Primary endpoint:</u> Complete remission rate (CRR): defined as the proportion of subjects achieving a complete response on MRI and PET-(CT or MRI) after

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	induction chemotherapy with 5-fluorouracil and cisplatin in combination with Nivolumab according to RECIST 1.1 criteria <u>Secondary endpoints:</u> Event-free survival (EFS) and overall survival (OS) Safety and tolerability: adverse events (AEs), serious adverse events (SAEs) Efficacy based on PD-L1 expression in tumor tissue
Study Design	This is a multicentre, prospective, single-arm, phase II, interventional study for patients with untreated nasopharyngeal carcinoma, stage II or higher. All patients ≤ 25 years and patients > 25 years without metastases will receive Nivolumab (4.5 mg/kg BW (max. 360 mg) q 3 weeks) added to standard induction chemotherapy (3 blocks of cisplatin/5-fluorouracil). In patients not responding to induction chemotherapy, the application of Nivolumab will be extended throughout the period of radiochemotherapy. Patients > 25 years with metastatic disease will receive Nivolumab (4.5 mg/kg BW (max. 360 mg) q 3 weeks) added to induction chemotherapy with 3 blocks of cisplatin/gemcitabine. All patients with metastatic disease will continue to receive Nivolumab during radiochemotherapy. The dose and treatment schedules are as follows: All patients ≤ 25 years and patients > 25 years without metastases: Nivolumab 4.5 mg/kg IV (max. 360 mg) every 3 weeks + cisplatin (100 mg/m^2) on day 1 and 5-fluorouracil (1 000 mg/m^2 per day for 5 days) every 3 weeks for 3 cycles. In patients with non-metastatic disease not responding to induction chemotherapy after three cycles of chemotherapy, Nivolumab (4.5 mg/kg IV (max. 360 mg) every 3 weeks) is continued during radiochemotherapy. In adults > 25 years and metastatic disease: Nivolumab 4.5 mg/kg IV (max. 360 mg) every 3 weeks + cisplatin (80 mg/m^2) on day 1 and gemcitabine (1 000 mg/m^2 per day on day 1 and day 8) every 3 weeks for 3 cycles. In all patients with metastatic disease responding to chemotherapy a 4th cycle can be added. Nivolumab (4.5 mg/kg IV (max. 360 mg) every 3 weeks) is continued during radiochemotherapy.

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	Treatment with study medication will continue until unacceptable toxicity, a maximum of 3 dosages of Nivolumab for non-metastatic patients responding to induction chemotherapy, 6 dosages for non-metastatic patients not responding to induction chemotherapy, 7 dosages for patients with metastases, or withdrawal of consent. Tumor progression or response endpoints will be assessed by investigator by MRI and PET-(CT or MRI) using RECIST 1.1 criteria after the 3rd cycle of induction chemotherapy. In addition to investigator assessment of response and progression, there will be an independent central review (ICR) of tumor scans and study sites will need to submit tumor scans for central radiology review. A DMC will be established and meet regularly during the study to ensure that subject safety is carefully monitored and to provide oversight regarding safety and efficacy considerations in this protocol.
Study Duration	• Total trial duration: 5 years • Duration of the clinical phase: 2 years • Accrual: 3 years • First patient first visit (FPFV): late 2022 • Last patient first visit (LPFV): late 2025 • Trial Report completed: 2028
Patients Number	In total 57 patients Screening is expected to be necessary in 65 patients.
Inclusion Criteria	1. Histologically confirmed new diagnosis of nasopharyngeal carcinoma according to the current WHO classification in children and adolescents, aged between 3 years and 17 years, OR histologically confirmed new diagnosis of EBV-positive nasopharyngeal carcinoma, WHO stage II or III, in subjects ≥ 18 years 2. Stage II or higher in patients ≤ 25 years of age, stage III and IV in patients > 25 years of age (AJCC, 8th edition) 3. Measurable disease by MRI per RECIST 1.1 criteria 4. Sufficient tumor tissue to be sent for central review, including PD-L1 staining, either as 2 full blocks or a minimum of 25

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	slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen 5. Written informed consent by legal guardians (if patient not ≥ 18 years) and patient prior to study participation
Exclusion Criteria	1. Newly diagnosed nasopharyngeal carcinoma, Stage I in all patients, Stage II in patients > 25 years of age 2. Recurrent nasopharyngeal carcinoma 3. Nasopharyngeal carcinoma diagnosed as second malignancy and preceding chemotherapy and/or radiotherapy 4. Prior chemotherapy and/or radiotherapy 5. Other active malignancy 6. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways. 7. The subject received an investigational drug within 30 days prior to inclusion into this study 8. Subjects who are enrolled in another clinical trial 9. Subjects with prior organ allograft or allogenic bone marrow transplantation 10. Subjects with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enrol. 11. Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days before start of therapy. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. 12. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection 13. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

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	14. Inadequate hematologic, renal or hepatic function defined by any of the following screening laboratory values: a. WBC < 2 000/µl b. Neutrophils < 1 500/µl c. Platelets < 100 x 10^3/µL d. Hemoglobin < 9.0 g/dL e. Creatinine >1.5 x ULN or creatinine clearance < 50 mL/min (using the Cockcroft Gault formula or Schwartz formula in patients < 18 years) f. AST/ALT > 3 x ULN (> 5 x ULN if liver metastases) g. Total Bilirubin > 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level ≥ 3.0 x ULN) 15. Hearing loss > 20 dB loss at 3 kHz 16. History of allergy or hypersensitivity to platinum-containing compounds or other study drug components 17. Clinically significant, uncontrolled heart disease (including history of any cardiac arrhythmias, e.g., ventricular, supraventricular, nodal arrhythmias, or conduction abnormality within 12 months of screening). 18. Vaccinated with live attenuated vaccines within 4 weeks of the first dose of the study drug. 19. Adequate performance status (Karnofsky score ≥ 60 for patients (age ≥ 16), Lansky score ≥ 60 (age < 16). 20. The subject has a history of any other illness, which, in the opinion of the Investigator, might pose an unacceptable risk by administering study medication. 21. The subject has any current or past medical condition and/or required medication to treat a condition that could affect the evaluation of the study. 22. Pregnant females as determined by positive [serum or urine] hCG test at Screening or prior to dosing. Participants of child-bearing age should use adequate contraception as defined in the study protocol. (Please refer to section 4.4) 23. Lactating females 24. Subjects, who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities

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	25. The subject is unwilling or unable to follow the procedures outlined in the protocol 26. The subject is mentally or legally incapacitated.
Treatment and Visits	All participants receive Nivolumab (4.5 mg/kg (max. 360 mg) every three weeks) during induction chemotherapy for a total of 3 doses, starting on day 1 of cycle 1 of induction standard chemotherapy with cisplatin 100 mg/ on day 1, plus 5-fluorouracil 1 000 mg/m^2/d from day 1-5, or cisplatin 80 mg/m^2 on day 1, plus gemcitabine 1 000 mg/m^2/d on day 1 and day 8, respectively. To reduce 5-fluorouracil toxicity leucovorin 25 mg/m^2/dose is given for 6 dosages in 6 hours intervals starting 30 min before the start of the 5-fluorouracil infusion. Each chemotherapy cycle lasts 21 days. Patients with metastases responding to induction therapy may have a fourth cycle of induction therapy, including a fourth dose of Nivolumab. For patients with metastatic disease or patients with locoregional disease without objective response after induction chemotherapy, Nivolumab (4.5 mg/kg (max. 360 mg) every three weeks) will be continued during radiochemotherapy, adding a total of 3 further doses of Nivolumab. There will be a screening visit before study enrolment in which patients and legal guardians will be informed on the trial. There will be 4 visits on study for patients included in the trial; patients with metastatic disease at diagnosis or patients with non-metastatic disease with no tumor response at visit 5 will continue to receive Nivolumab during radiotherapy and will have an additional visit on treatment after the end of radiotherapy (visit 5add). All study participants will have an off treatment visit, 10 weeks (+/- 3 days) after the last dose of Nivolumab. Patients are then followed up every 3 months until 2 years from inclusion into the study. Laboratory testing will be performed (CBC w/differential, (albumin if clinically indicated), LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, amylase, lipase, cholesterol, triglycerides, uric acid, TSH, Free T4, Free T3) at all visits. Cholesterol, triglycerides uric acid, TSH, Free T4, Free T3 are not required at visits 2-4 if within normal limits at baseline.
Sample size and Statistics	The safety and efficacy of Nivolumab in combination with cisplatin and 5-fluorouracil will be assessed in relation to prior published historical

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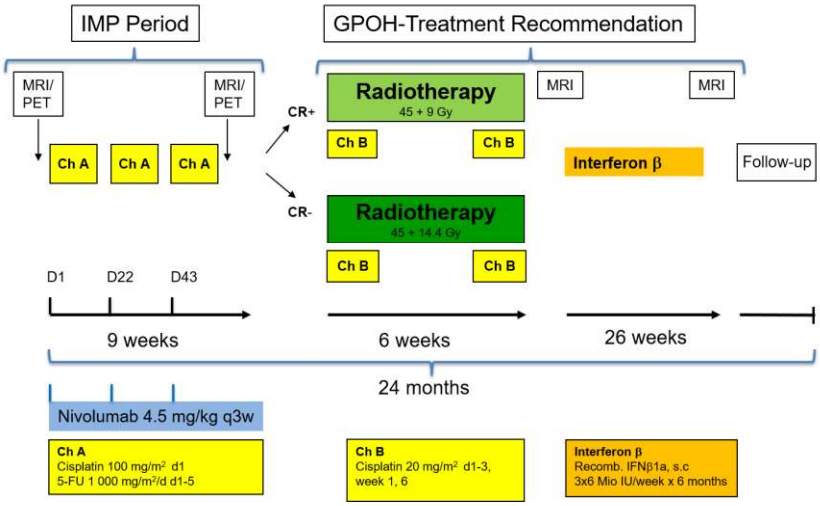
	control group data, since the rarity of the patient population does not allow for fully powered randomized comparison. The primary efficacy endpoint is the tumor response on MRI and PET-(CT or MRI) according to RECIST 1.1 criteria after 3 cycles of induction immunochemotherapy with Nivolumab, 5-fluorouracil and cisplatin. A phase-II optimum Simon design with alpha=0.1 and beta=0.2 will be used. With a response rate p0 of 12% for the historical control and an expected better response rate p1 of 25%, 18 patients have to be treated in the first phase (upper limit for rejection: less than 3 responders). 48 patients have to be treated overall in phase I and II when the second stage will be reached (upper limit for rejection: less than 9 responders). A second cohort of 4 adult patients with metastatic disease > 25 year will only be analysed for secondary endpoints as they receive with gemcitabine/cisplatin a different induction regimen. A dropout rate of 5 patients who will enter the trial but will not be available for response evaluation due to i.e. violation of the treatment protocol or insufficient imaging studies is estimated on the base of the previous GPOH-NPC-2003 trial. All patients with evaluable response after 5-fluorouracil and cisplatin which received at least one dose of Nivolumab will be analysed for the primary endpoint. As secondary endpoint, survival rates will be analysed in all patients with suitable descriptive methods (Kaplan-Meyer estimates with confidence intervals) and compared with historical data using descriptive log-rank tests. Almost all events occur within 2 years after diagnosis. A follow-up phase of 2 years is therefore sufficient. Another secondary endpoint will be the efficacy based on PD-L1 expressions. All patients who received at least one dose of Nivolumab will be analysed for safety with descriptive methods (frequency tables, rates of AE's and SAE's with 95% confidence intervals).

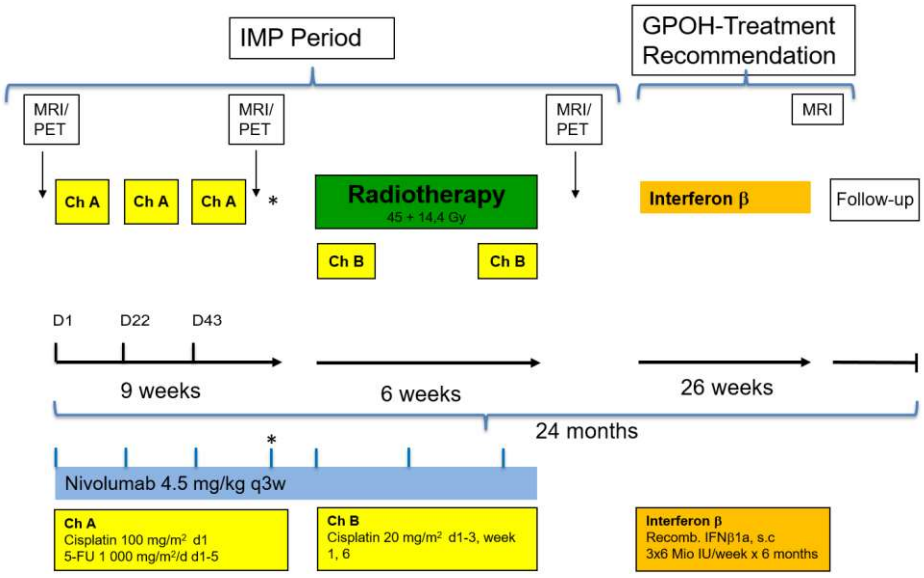
Study Flow Chart

1. Children, adolescents and young adults (AYAs) ≤ 25 years

1.1 Patients with non-metastatic disease with CR or PR after induction chemotherapy



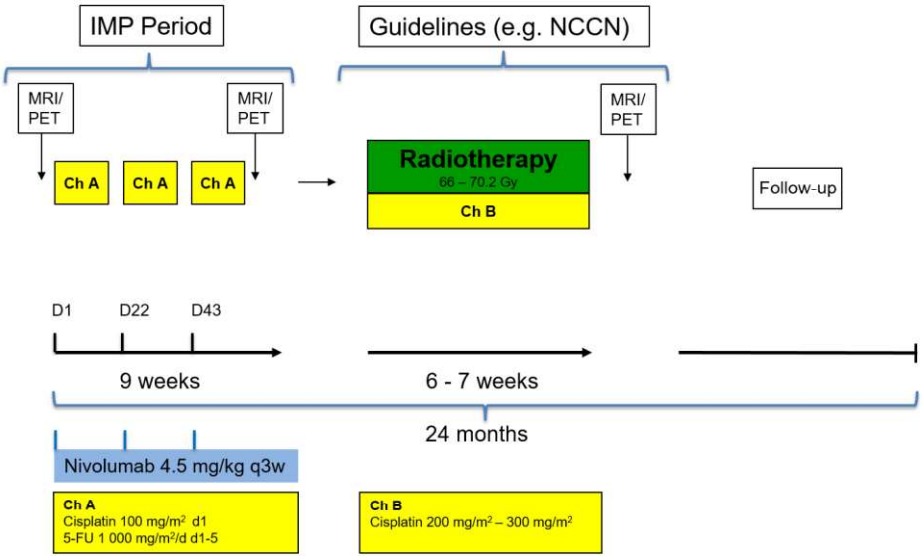
1.2 Patients with non-metastatic disease with SD or Progression after induction chemotherapy or patients with metastatic disease at diagnosis



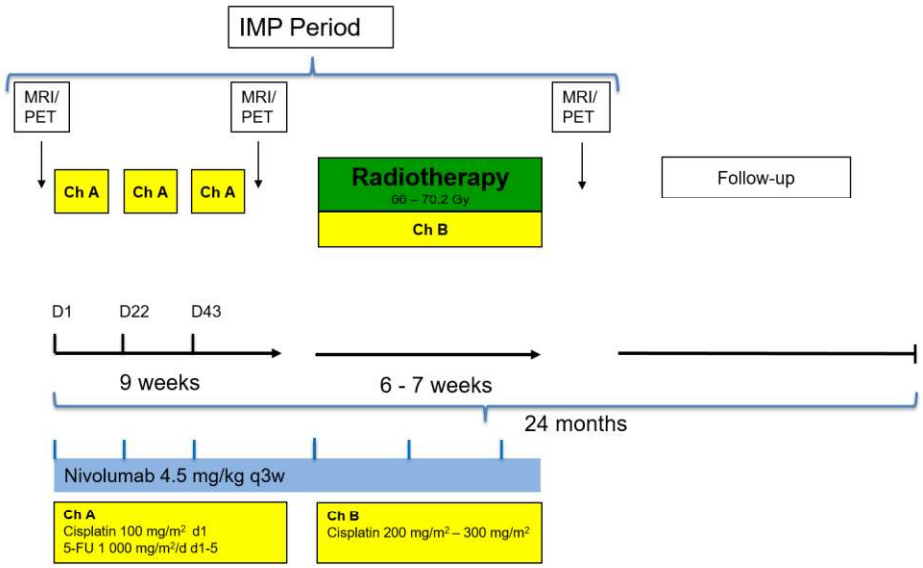
* Patients with metastatic disease responding to induction therapy are eligible for a fourth cycle of chemotherapy

2. Adults > 25 years

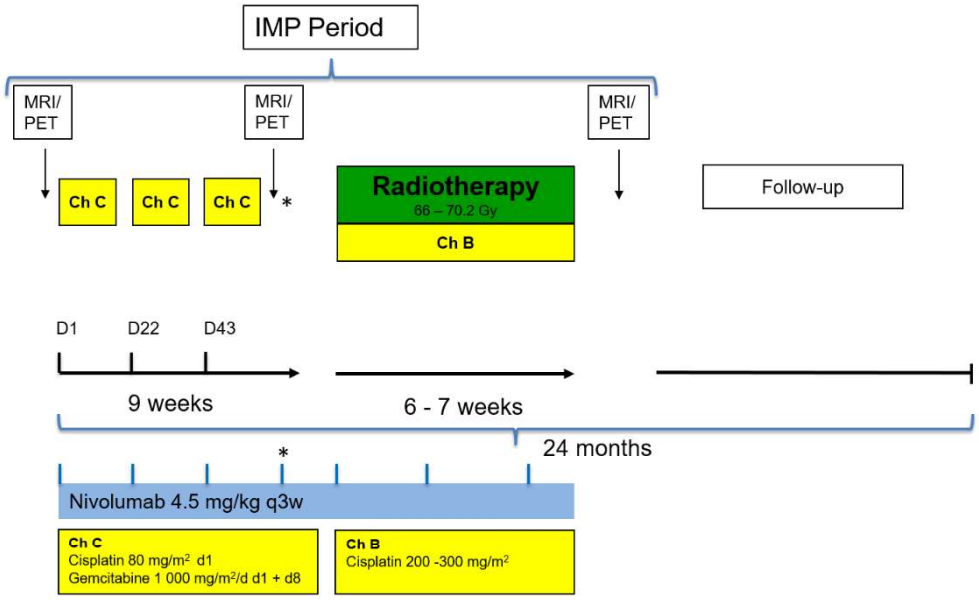
2.1 Patients with non-metastatic disease with CR or PR after induction chemotherapy



2.2 Patients with non-metastatic disease with SD or Progression after induction chemotherapy



2.3 Patients with metastatic disease at diagnosis who will receive local therapy in a curative intent



* Patients responding to induction therapy are eligible for a fourth cycle of chemotherapy

Table 1 Visit Schedule

Phase	Pre-Study	Treatment					Off Treatment	Follow-Up
Study Period	Screening	Chemo Cycle 1	Chemo Cycle 2	Chemo Cycle 3		Radiotherapy[1]		
Visit No	1	2	3	4	5	5add[1]	6	
Activity		Baseline			Response Evaluation	Response Evaluation[1]		Disease Status
Visit window +/- calendar days	Day -14 - -1	Day 1	Day 0 - 1	Day 0 -1	Day 20 - 25	12 weeks after last dose of radiotherapy[1]	100 days +/-3 days after last dose of Nivolumab	Every 3 months until 2 years from enrolment
Written informed consent	X							

[1] Only for patients with metastatic disease at diagnosis or non-metastatic disease with SD/PD at Visit5; this visit can be combined with Visit 6, if calculated time points for Visits 5add and 6 are not > 1 week apart.

[2] Tumor tissue to be sent for central review, including PD-L1 staining is mandatory. Sufficient tumor tissue should be submitted either 2 full block or a minimum of 25 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen. Contact the Study Director if sufficient tissue is not available.

[3] **Vital signs** will include temperature, resting systolic and diastolic blood pressure and pulse including respiratory rates at a supine position after at least 5 minutes of resting.

[4] **Performance status** will be measured using Karnofsky or Lansky scales (Appendix I).

[5] Part of clinical routine, see Kontny et al. 2016, Colevas et al. 2018

[6] Serum or urine within 24 hours prior to start of chemotherapy

[7] CBC w/differential, (albumin if clinically indicated), LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, LDH, phosphate, glucose, amylase, lipase, cholesterol, triglycerides, uric acid, TSH, Free T4, Free T3. Cholesterol, triglycerides uric acid, TSH, Free T4, Free T3 are not required at visits 2-4 if within normal limits at base line.

[8] Hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA)

[9] Centrally done at Institute of Human Genetics via Laboratory of Pediatric Hematology/Oncology, Uniklinik RWTH Aachen, only for patients receiving 5-fluorouracil

[10] Centrally done at Institute of Virology, MH Hannover

[11] Centrally stored at Uniklinik RWTH Aachen via Laboratory of Pediatric Hematology/Oncology

[12] **MRI** of the head and neck without AND with Gadolinium contrast (Appendix II)

[13] (^{14}F)-FDG-PET, including diagnostic CT-thorax for detection of pulmonary metastases as part of routine staging

[14] **MRI abdomen** for detection of liver metastases as part or routine staging

[15] **AEs** may be volunteered spontaneously by the patient, or discovered as a result of general non-directed questioning by the study personnel or by physical examination. All AEs will be followed until the event resolves or stabilizes at a level acceptable to the investigator.

[16] Only at 2 years after enrolment

Phase	**Pre-Study**	**Treatment**					**Off Treatment**	**Follow-Up**
Study Period	**Screening**	**Chemo Cycle 1**	**Chemo Cycle 2**	**Chemo Cycle 3**		**Radiotherapy[1]**		
Visit No	**1**	**2**	**3**	**4**	**5**	**5add[1]**	**6**	
Activity		**Baseline**			**Response Evaluation**	**Response Evaluation[1]**		**Disease Status**
Visit window +/- calendar days	**Day -14 - -1**	**Day 1**	**Day 0 - 1**	**Day 0 -1**	**Day 20 - 25**	**12 weeks after last dose of radiotherapy[1]**	**100 days +/-3 days after last dose of Nivolumab**	**Every 3 months until 2 years from enrolment**
Inclusion/exclusion criteria	X	X						
Tumor tissue sample[2]	X							
Demographics & medical history	X							
Concomitant medication	X	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	
Vital signs[3]	X	X	X	X	X	X	X	
Height (cm)	X						X	
Weight (kg)	X	X	X	X	X	X	X	
Performance Status[4]	X	X	X	X	X	X	X	
12-lead ECG[5]	X						X	
Echocardiography[5]	X						X	
Creatinine-clearance[5]	X		X	X			X	
Audiometry[5]	X		X	X			X	
Dental Exam[5]	X						X	
Opthalmological Exam[5]	X						X	
Pregnancy Test[5,6] (WOCBP only)	X	X	X	X			X	
Laboratory Tests[5,7]	X	X	X	X	X	X	X	
Hepatitis-Screening[5,8]	X						X	
HIV-testing[5]	X						X	

Phase	**Pre-Study**	**Treatment**					**Off Treatment**	**Follow-Up**
Study Period	**Screening**	**Chemo Cycle 1**	**Chemo Cycle 2**	**Chemo Cycle 3**		**Radiotherapy[1]**		
Visit No	**1**	**2**	**3**	**4**	**5**	**5add[1]**	**6**	
Activity		**Baseline**			**Response Evaluation**	**Response Evaluation[1]**		**Disease Status**
Visit window +/- calendar days	**Day -14 - -1**	**Day 1**	**Day 0 - 1**	**Day 0 -1**	**Day 20 - 25**	**12 weeks after last dose of radiotherapy[1]**	**100 days +/-3 days after last dose of Nivolumab**	**Every 3 months until 2 years from enrolment**
DPD-Genetics[5,9]	X							
EBV-PCR[5,10]		X			X	X	X	X
Biomarkers (Blood)[11]		X	X	X	X	X	X	
Biomarkers (Saliva)[11]		X			X	X	X	
MRI-head/neck[5,12]	X				X	X		X
PET-CT or PET-MRI[5,13]	X				X	X		
MRI abdomen[5,14]	X							
Study drug administration		X	X	X				
AE evaluation[15]		X	X	X	X	X	X	
Disease and event status								X
PROs-Assessment	X				X		X	X[16]