



UCCH Pathway

UCCH Guideline

Cancer of unknown Primary in the Head and Neck Area

2.03.01 Anlage 27

Version Oct/2021

Guideline Cancer of unknown Primary in the Head and Neck Area

Version 08, Oct/2021

according to TNM classification 8th edition

Cancer of unknown Primary in the Head and Neck area board members

M. Freytag, M. Gosau (CMF)

J. Müller (Psychooncology)

A. Böttcher, C. Betz (ENT)

P. Schafhausen (Med. Oncology)

C. Petersen (Radiooncology)

U. Göbel (patient representative UCCH)

W. Wilczak (Pathology)

J. Salamon (Radiology)

Responsible author

A. Böttcher (ENT)

Implemented

Apr/2008

Revised

Dec/2010, Dec/2011, May/2015, May/2016, Jun/2017, Apr/2019, Oct/2021

Next planned review

Oct/2023

Legend of Colours



= Therapeutic procedure



= Clinical or diagnostical condition



= Diagnostic procedure



= Clinical trial



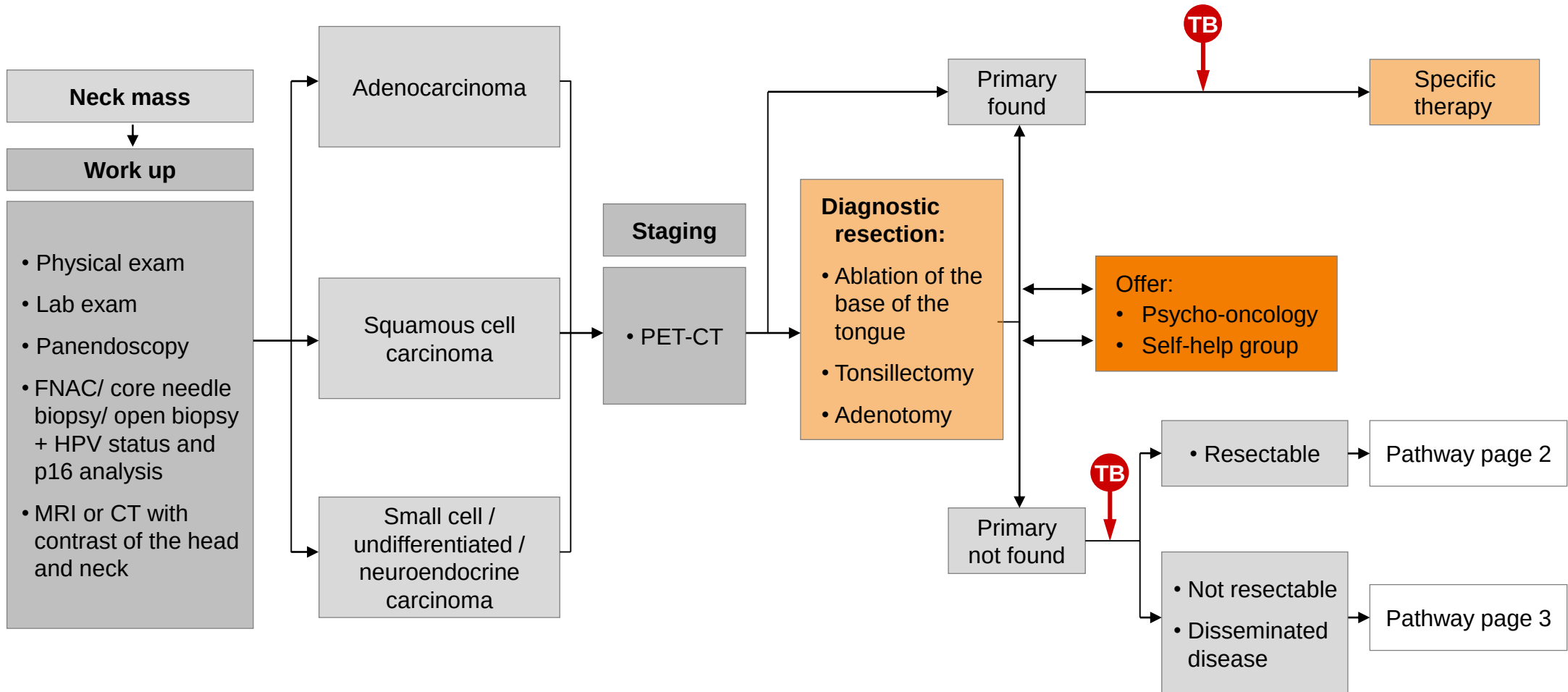
= Supportive measure



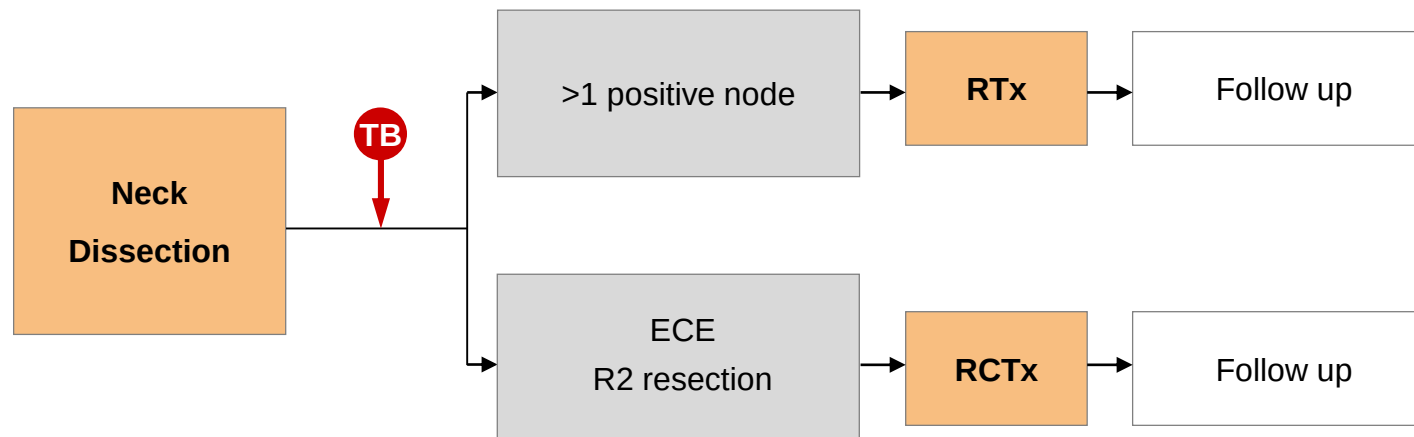
= Referral



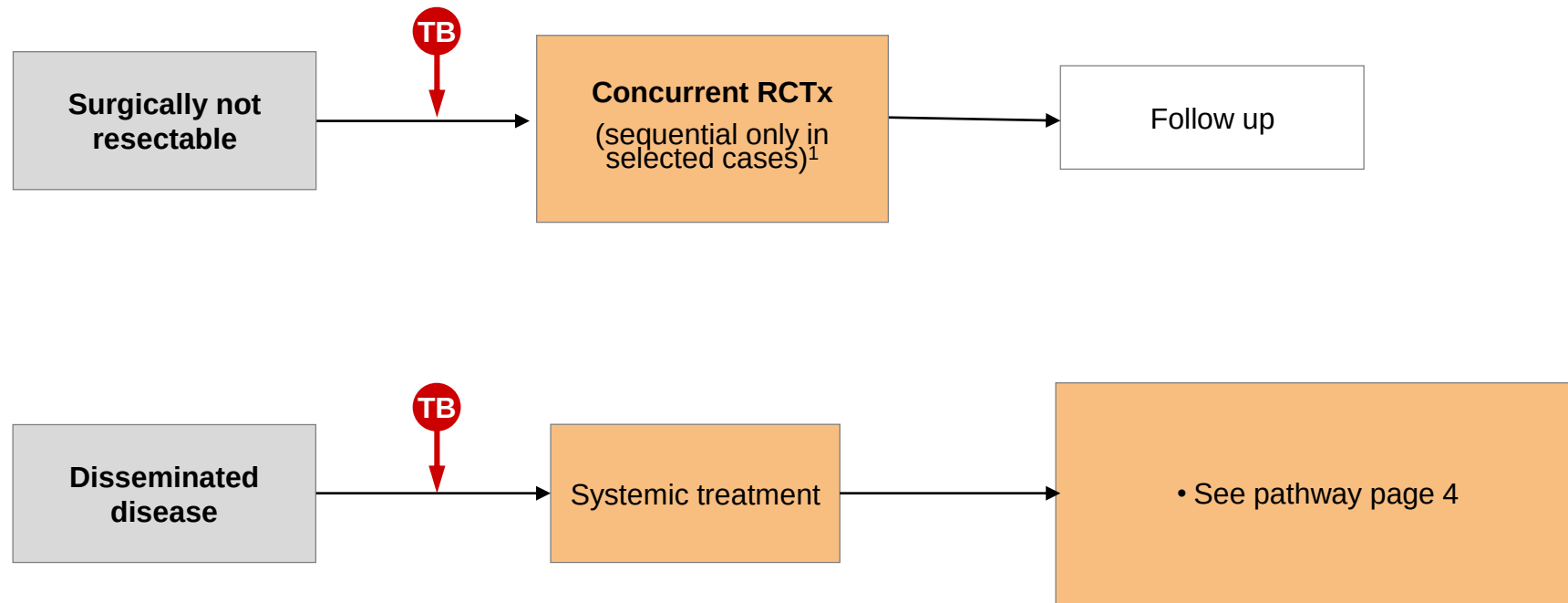
= Tumorboard
(including post
tumorboard interaction
with patient that follows
the principles of shared
decision-making)



Pathway page 2: Surgical resection (histology SCC, NOS, undifferentiated)



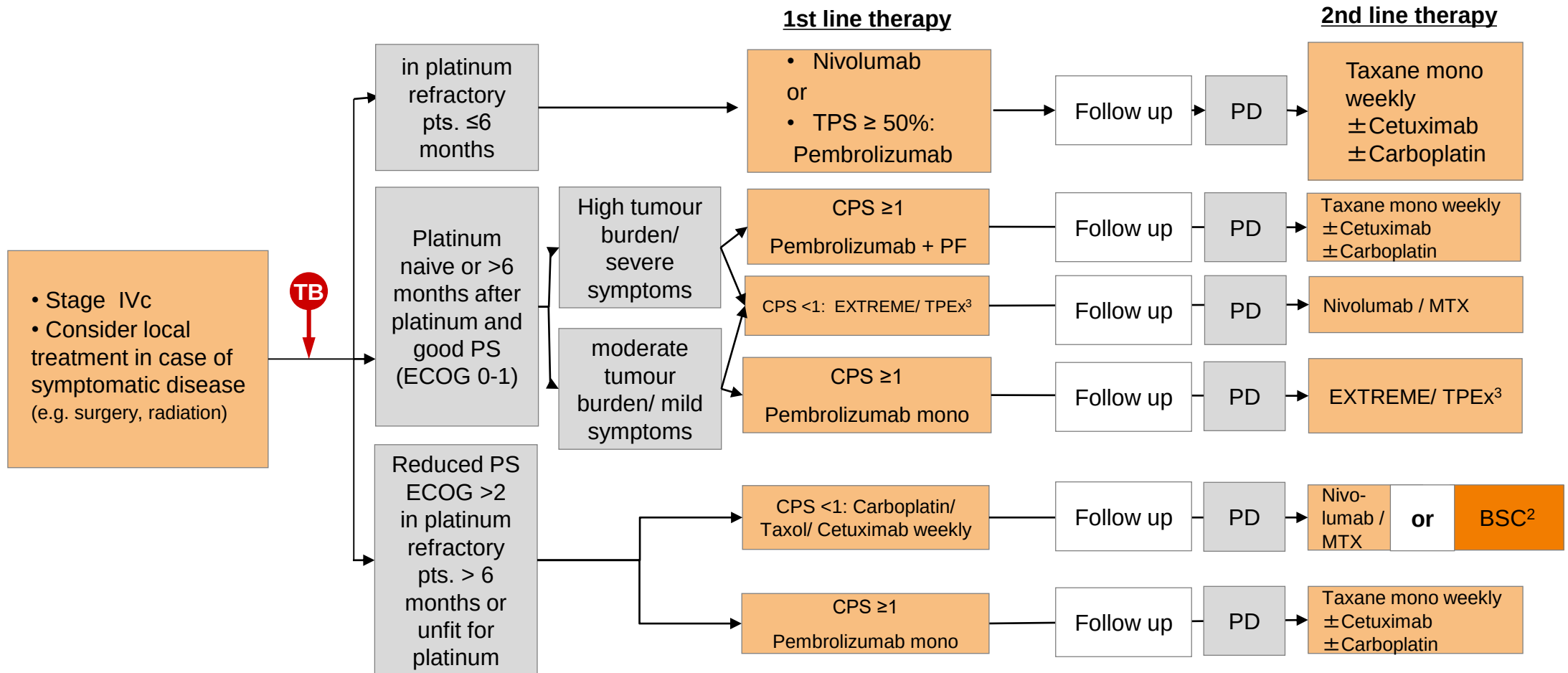
Pathway page 3: CUP not resectable or disseminated disease



RCTx Radiochemotherapy, RTx Radiotherapy

¹ See preconditions for Protocol Sequential Therapy on page 16-18

Pathway page 4: Metastatic disease (systemic treatment)



PS Performance Status, ECOG The Eastern Cooperative Oncology Group, BSC Best supportive care, PD Progressive Disease, CPS combined proportion score

² See palliative care screening tool on page 8

³ See therapy protocols SCCHN on pages 10-12

Pathway Page 5: Restaging

6 weeks after completion of therapy

- Clinical examination
- Ultrasound neck
- Examination (endoscopy) under anesthesia
- MRI neck (including primary lesion), if contraindication CT neck
- In case of unclear or suspicious lesion in thorax or abdomen: CT chest, CT/ultrasound abdomen

Palliative setting

- CT imaging after 6-8/9 weeks, depending on clinical outcome. No imaging in clinically measurable manifestation.

Pathway Page 6: Follow up

Every 3 months up to 30 months, afterwards every 6 months (5-year follow up)
Offer contact to self help group and psychooncological support whenever necessary

- Clinical examination
- Ultrasound of the neck
- Thyroid function 1, 2 and 5 years after irradiation of the neck
- UICC I/ II:
 - Chest x-ray every 12 months and in case of suspicion of recurrence
 - MRI of the neck every 12 months and in case of suspicion of recurrence
- UICC III/ IV:
 - MRI of the neck and CT of the thorax every 12 months and in case of suspicion of recurrence
 - Abdominal ultrasound

Pathway Page 7: Best supportive care

Best supportive care / palliative treatment

Consider nutritional counseling, psychological counseling, offering contact to self-help group

Upper airway obstruction:

PEG tube

Tracheostomy

Tumor associated pain:

analgetics (WHO)

palliative (chemo)radiation

Pathway page 8: Palliative care screening tool

Screening items		Points
1.	• Presence of metastatic or locally advanced cancer	2
2.	• ECOG score (functional status score, performance status)	0-4
3.	• Presence of one or more serious complications of advanced cancer usually associated with a prognosis of < 12 months (e.g. brain metastases, hypercalcemia, delirium, spinal cord compression, cachexia)	1
4.	• Presence of one or more serious comorbid diseases also associated with poor prognosis (e.g. moderate-severe COPD or CHF, dementia, AIDS, end stage renal failure end stage liver cirrhosis)	1
5.	• Presence of palliative care problems	1
	a. • Symptoms uncontrolled by standard approaches	1
	b. • Moderate to severe distress in patient or family, related to cancer diagnosis or therapy (personal targets and expectations, educational and informational requirements, cultural factors)	1
	c. • Patient/family requests palliative care consult	1
	d. • Team needs assistance with complex decision making or determining goals of care (benefit/side effects of treatment)	1
	e. • Instable or deficient network especially for emergency situation or 24-h care	1

A total of > 5 points signalizes need for supportive palliative care

According to Glare et al. (2011); NCCN Clinical Practice guidelines in Oncology 2015

Therapy Protocols RTx/ RCTx

Definitive Radiotherapy (definitive RTx)⁴:

high risk:

- $\geq 70-72$ Gy (2.0 Gy/day) or equivalent or moderately accelerated in an integrated dose concept
- External-beam RT ≥ 50 Gy +/- brachytherapy

Medium risk:

- ≥ 60 Gy (2,0/die) or equivalent or moderately accelerated in an integrated dose concept

Low risk:

- ≥ 50 Gy (2,0/die) or equivalent or moderately accelerated in an integrated dose concept

Postoperative (adjuvant) Radiotherapy (RTx)⁴:

Primary:

- ≥ 60 Gy (2.0 Gy/die) or equivalent or moderately accelerated in an integrated dose concept

Neck:

- Involved nodal stations: 60 Gy (2 Gy/day) or equivalent or moderately accelerated in an integrated dose concept
- Uninvolved nodal stations: 50 GY (2 Gy/day) or equivalent or moderately accelerated in an integrated dose concept

Palliative Radiotherapy (RTx)⁴:

- Moderate Hyperfraction or moderately accelerated in an integrated dose concept

Radio-chemotherapy (RCTx)⁴:

- Definitive or high risk adjuvant 70-72 Gy, 2 Gy/die or equivalent or moderately accelerated in an integrated dose concept
- Adjuvant 66 Gy or equivalent or moderately accelerated in an integrated dose concept
- Cisplatin 40 mg/m² every week (max. 7 cycles)

or

- Mitomycin 10 mg/m² day 5 and day 36 and
- 5-FU 600 mg/m² during 120 h infusion day 1-5

⁴ SIB (simultane integrated boost possible)

Therapy protocols SCCHN (1)

TPEx

- Cisplatin 75 mg/m² every 3 weeks
- Docetaxel 75 mg/m² every 3 weeks
- Cetuximab 250 mg/m² weekly (400 mg/m² loading dose)
- + G-CSF after each cycle
- Maintenance after 4 cycles TPEx: Cetuximab 500 mg/m² biweekly

EXTREME

- Cisplatin 100 mg/m² every 3 weeks (max. 6 cycles)
- 5-FU 4000 mg/m² during 96h infusion every 3 weeks (max. 6 cycles)
- Cetuximab 250 mg/m² weekly (400 mg/m² loading dose)
- + G-CSF after each cycle
- Maintenance after 4-6 cycles EXTREME: Cetuximab 500 mg/m² biweekly

Therapy protocols SCCHN (2)

Carboplatin/Paclitaxel/Cetuximab weekly (R/M-SCCHN)

- Paclitaxel 80 mg/m² weekly
- Carboplatin AUC2 weekly
- Cetuximab 250 mg/m² weekly (400 mg loading dose)
- Maintenance after 18 weeks: Cetuximab 500 mg/m² biweekly

TPF (Induction) (max. 3 cycles)

- Cisplatin 80-100 mg/m² every 3 weeks
- 5-FU 4000 mg/m² during 96h infusion every 3 weeks
- Docetaxel 75 mg/m² every 3 weeks
- + G-CSF after each cycle

Therapy protocols SCCHN (3)

Nivolumab Mono

- Nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks

Pembrolizumab Mono

- Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks

Pembrolizumab + PF

- Pembrolizumab 200 mg every 3 weeks
- Cisplatin 100 mg/m² every 3 weeks (max. 6 cycles)
- 5-FU 4000 mg/m² during 96h infusion every 3 weeks (max. 6 cycles)
- After PF-cycles Pembrolizumab Mono maintenance

Protocol Sequential Therapy - page 1

Staging: ENT-clinic

- Physical exam
- Ultrasound neck
- Biopsy (including HPV p16 analysis)
- MRI for primary and neck (CT with contrast if contraindications against MRI)
- Chest x-ray and ultrasound abdomen **or**
- CT chest and abdomen (UICC stage III or IV and recurrent disease)
- Panendoscopy under anesthesia
- Preanesthesia studies
- Dental evaluation and panoramic view as indicated
- Voice, speech, swallowing and breathing evaluation as indicated
- Multidisciplinary consultation as indicated
- Portacath (Department of radiology, registration in angiographie phone: 54022)
- Creatinine clearance
- Audiometry
- PEG tube



Protocol Sequential Therapy - page 2

Induction chemotherapy: Medical Oncology

- 3 cycles TPF on d1, d22 and d43 (Precondition:
 - ECOG 0-1
 - Adequate bone marrow function: leucocytes $> 3.0 \times 10^9/L$, neutrophils $> 1 \times 10^9/L$, platelets $> 80 \times 10^9/L$, hemoglobin $> 9.0 \text{ g/dL}$
 - Adequate liver function: Bilirubin $< 2.0 \text{ g/dL}$, SGOT, SGPT, AP, G-GT $< 3 \times \text{ULN}$
 - Adequate renal function: serum creatinine $< 1.5 \text{ mg/dL}$, or if creatinin between 1.5 mg/dL and 1.8 mg/dL, creatinine clearance $> 60 \text{ ml}$
 - No serious co-morbidity, e.g. arterosclerosis + apoplexy, recent MI, high-grade carotic stenoses, unstable cardiac disease despite treatment, congestive heart failure NYHA grade 3/4, Insulin-dependent diabetes mellitus, uncontrolled hypertension, liver cirrhosis (Quick $< 75\%$, total protein $< 3.0 \text{ g/dl}$, bilirubine $> 2 \text{ mg/ml}$) or kidney insufficiency)
- Docetaxel 75 mg/m² d1, Cisplatin 100 mg/m² d1, 5-FU 1000 mg/m² d1-4 (In case of dip in hearing sensitivity Cisplatin may be splitted into 50 mg/m² on d1+2)
- Supportive therapie: GCSF (e.g. Neulasta) d6, Ciprobay 500 mg 1-0-1 in case of neutropenia $< 1000/\mu\text{l}$



Protocol Sequential Therapy - page 3

Restaging after 3 cycles TPF has to be organized by Medical Oncology within 3 weeks after 3. cycle TPF so that radiation can start on d 64-71!!

- Panendoscopie (ENT-clinic)
- MRI-neck (or CT if contraindications against MRI)
- Audiometry and Creatinine Clearance if necessary
- In case of CR/PR: combined radiochemotherapy beginning d63 (=>PEG-tube necessary)
- In case of SD/PD: salvage-resection with adjuvant radiation



**Radiotherapy:
Department for radiotherapy**

- Radiatio: 70Gy, 2 Gy/d (five fractions per week until week seven)



Follow up: Interdisciplinary tumor consultation