European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

17 November 2022

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# NASOPHARYNGEAL CARCINOMA: STANDARD CLINICAL PRACTICE RECOMMENDATIONS

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Funded by the European Union's EU4Health Programme

SIOP Europe
the European Society for Paediatric Oncology

St. Anna Kinderkrebs Forschung

# COI declaration

No COI to declare

# Content

- Background Information
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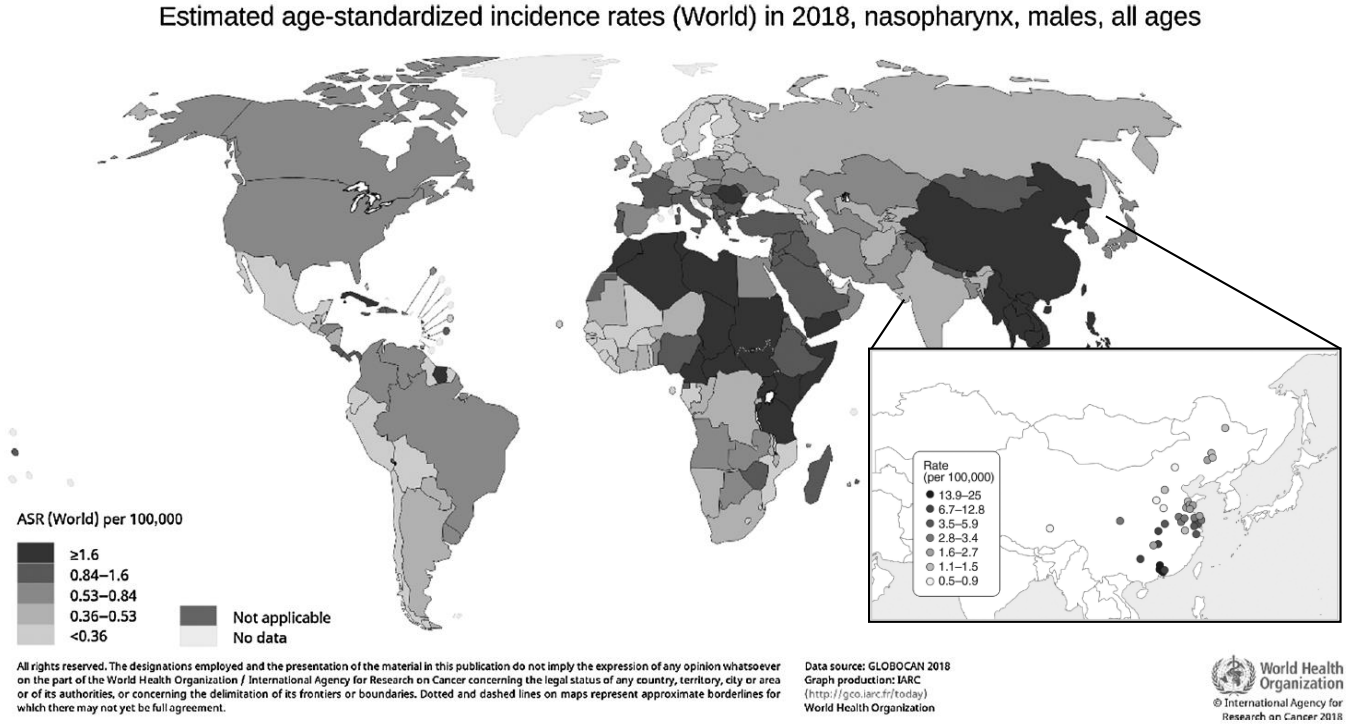
# Epidemiology

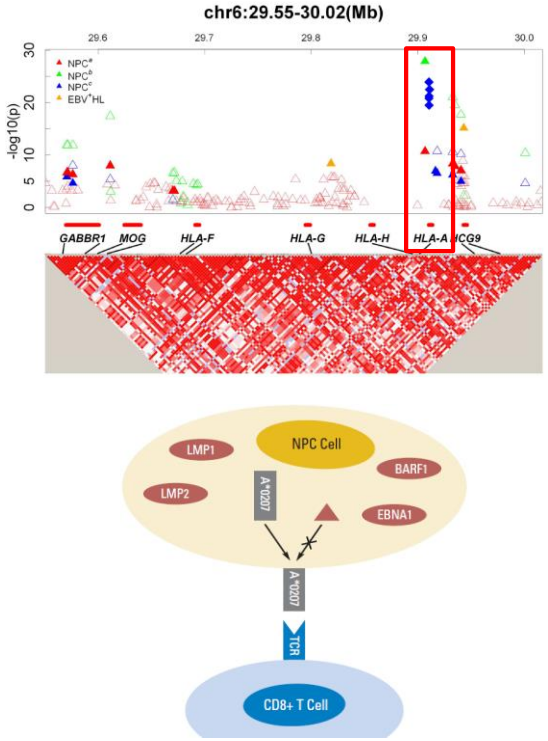



*Chang et al., Cancer Epidemiol Biomarkers Prev, 2021*

# Etiology

- Genetic predisposition
- Environmental factors
- EBV infection

⇒ Deficiency of immune response to EBV, mediated by host *and* viral factors[1,2]




[1] *Su et al., Front Oncol, 2013*

[2] *Bruce et al., J Clin Oncol, 2015*

# WHO Classification

- Type I: Keratinizing squamous cell carcinoma
- Type II: Non-keratinizing squamous cell carcinoma
- **Type III: Undifferentiated carcinoma**

*ALWAYS* EBV-positive **!**

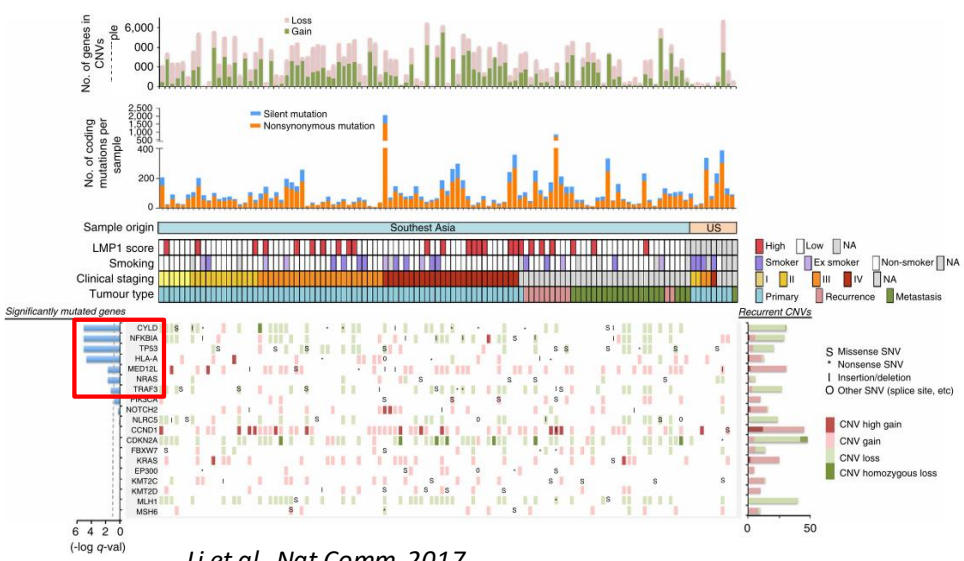
# Molecular Genetics

ARTICLE

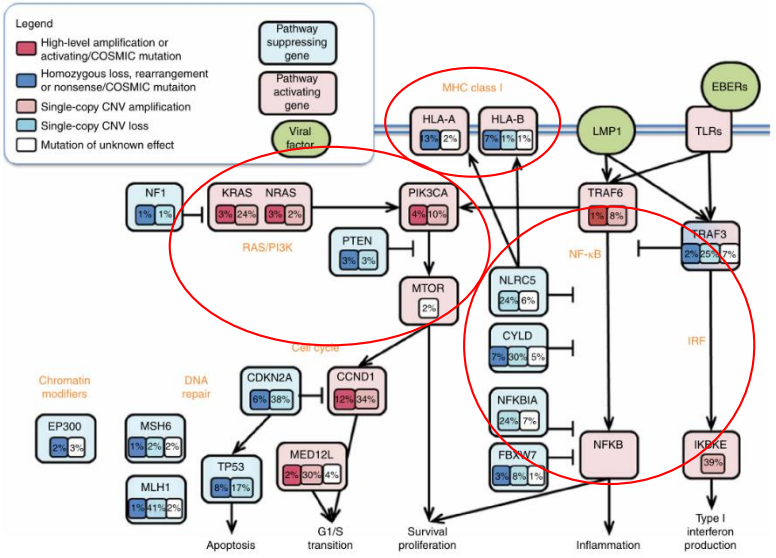
Received 18 Feb 2016 | Accepted 4 Nov 2016 | Published 18 Jan 2017

DOI: 10.1038/ncomms14121 OPEN

## Exome and genome sequencing of nasopharynx cancer identifies NF-κB pathway activating mutations




*Li et al., Nat Comm, 2017*



# Clinical Presentation

German registry (*NPC-2016*): n=32, median age 15.4y (9–20y), m:f=1.5:1

| | |
|---|---|
| • Cervical lymphadenopathy | **57%** |
| • Pain (head, neck, face) | **54%** |
| • Rhinological (nasal obstruction, epistaxis, rhinorrhea, dysosmia) | **39%** |
| • Otological (hearing loss, tympanic effusion, vertigo) | **29%** |
| • Dysphagia | 11% |
| • B-symptoms (weight loss, fatigue) | 11% |
| • Impairment of head movement and/or mouth opening (trismus) | 7% |
| • Dyspnea | 4% |

Received: 17 February 2021 | Revised: 2 March 2021 | Accepted: 3 March 2021

DOI: 10.1002/pbc.29018

Pediatric Blood & Cancer

SUPPLEMENT ARTICLE

# Nasopharyngeal carcinoma in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations

Tal Ben-Ami[1] | Udo Kontny[2] | Aurore Surun[3] | Ines B. Brecht[4] | Ricardo López Almaraz[5] | Monica Dragomir[6] | Apostolos Pourtsidis[7] | Michela Casanova[8] | Brice Fresneau[9,10] | Gianni Bisogno[11] | Dominik T. Schneider[12] | Yves Reguerre[13] | Ewa Bien[14] | Teresa Stachowicz-Stencel[14] | Gustaf Österlundh[15] | Marc Wygoda[16] | Geert O Janssens[17,18] | József Zsiros[18] | Nina Jehanno[19] | Herve J Brisse[20] | Lorenza Gandola[21] | Hans Christiansen[22] | Line Claude[23] | Andrea Ferrari[8] | Carlos Rodriguez-Galindo[24] | Daniel Orbach[3]

# EXPeRT Recommendations

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

**Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System [1])**

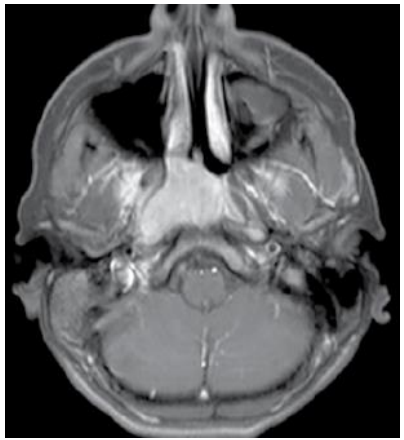
| | |
|---|---|
| **Levels of evidence** | |
| I | Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity |
| II | Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity |
| III | Prospective cohort studies |
| IV | Retrospective cohort studies or case-control studies |
| V | Studies without control group, case reports, experts' opinions |
| **Grades of recommendation** | |
| A | Strong evidence for efficacy with a substantial clinical benefit, strongly recommended |
| B | Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended |
| C | Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional |
| D | Moderate evidence against efficacy or for adverse outcome, generally not recommended |
| E | Strong evidence against efficacy or for adverse outcome, never recommended |

# Histologic Diagnosis

- Biopsy of primary tumor during nasopharyngeal endoscopy by ENT doctor [Level V; Grade A]
- Biopsy of involved cervical lymph node also acceptable [Level V; Grade B]
- Immunohistochemistry mandatory for exclusion of differential diagnoses
- Detection of EBV by immunohistochemistry (EBNA1, LMP1/2) and EBER in situ hybridization [Level IV; Grade B]
- Revision of histological slides by reference pathologist [Level IV, Grade B]
- Asservation of frozen tumor tissue for potential molecular studies [Level IV; Grade C]

# Imaging & Staging

- MRI (or CT) head/neck, incl. supraclavicular fossa [Level V; Grade A]
- 18F-FDG-PET/CT (or MRI), if not available: technetium bone scintigraphy [Level V; Grade C]
- CT chest & abdomen [Level IV; Grade A]



# Staging (AJCC 8th ed.) [Level IV; Grade A]

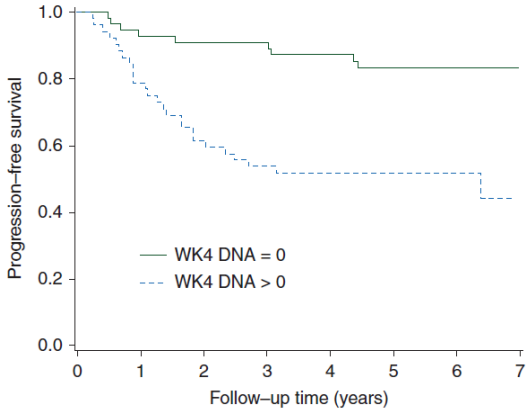
| American Joint Committee on Cancer staging system | |
|---|---|
| | **Primary tumor** |
| T1 | Tumor confined to the nasopharynx or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension |
| T2 | Tumor with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles |
| T3 | Tumor invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses |
| T4 | Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or infiltration beyond the lateral surface of the lateral pterygoid muscle |
| | **Nodes** |
| N1 | Unilateral metastasis, in cervical lymph node(s) above the caudal border of cricoid cartilage, and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less |
| N2 | Bilateral metastasis in cervical lymph node(s), 6 cm or less above the caudal border of cricoid cartilage |
| N3 | Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage |
| | **Distant metastases** |
| MX | Distant metastases cannot be assessed |
| M0 | No distant metastases |
| M1 | Distant metastases |
| | **Stage** |
| I | T1 N0 M0 |
| II | T1–2 N1 M0 or T2 N0 M0 |
| III | T3 N0–1 M0 or T1–3 N2 M0 |
| IVA | T1–4 N3 M0 or T4 N0–2 M0 |
| IVB | Any T N M1 |

# Monitoring of Plasma EBV DNA

## [Level IV; Grade C]

- Initial EBV DNA level associated with tumor stage and relapse risk[1,2,3,4,5]
- Clearance of EBV DNA during treatment of prognostic relevance[1,6,7]
- Useful for early detection of relapse/PD (``MRD marker´´)[1,2]
- Further biomarkers under investigation:

  microRNAs (BARTs), CTCs[8]




[1]Ferrari et al., BMC Cancer, 2012

[2]Wei et al., Oncol Res Treat, 2014

[3]Shen et al., Med (Balt), 2015

[4]Zhang et al., Oncotarget, 2016

[5]Peng et al., Cancer Med, 2018

[6]Wang et al., Cancer, 2013

[7]Leung et al., Ann Oncol, 2014

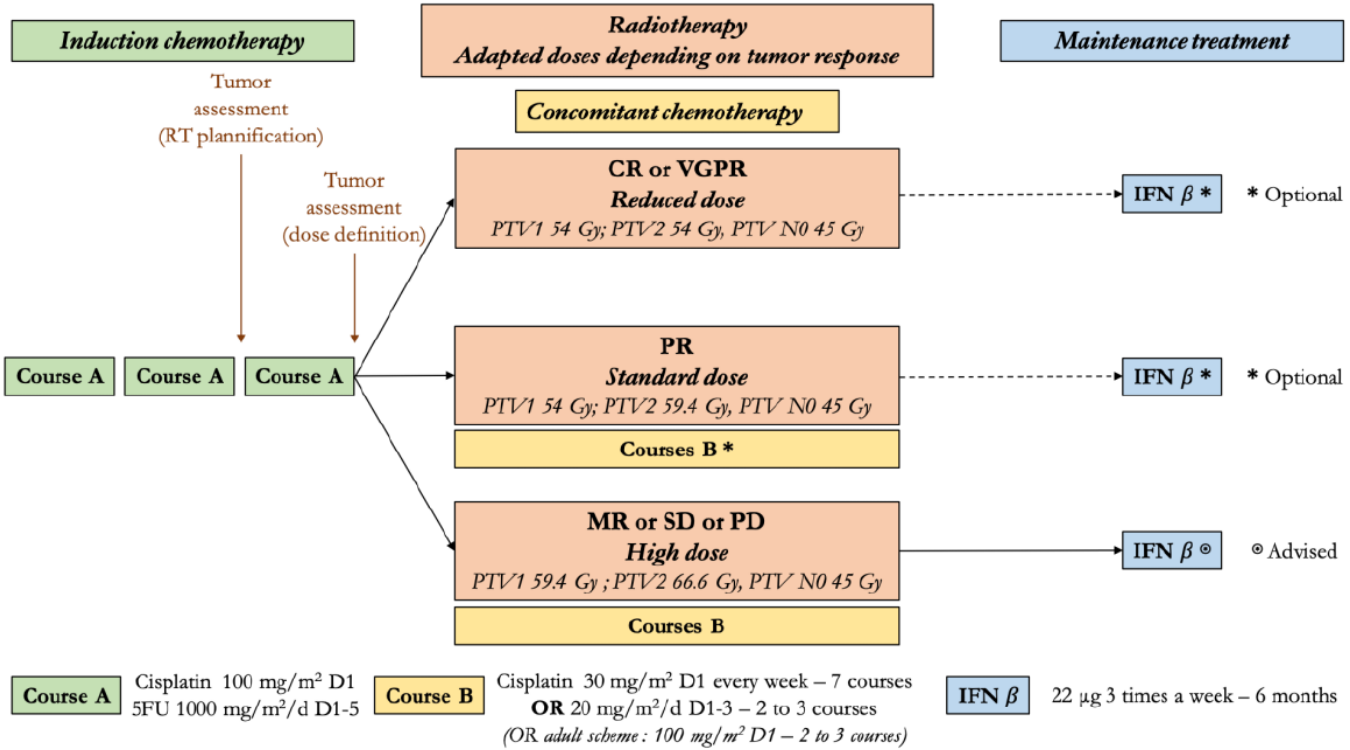
[8]Tan et al., Cancer Comm, 2020

# Additional Assessments

- Oral and dental evaluation, nutritional assessment [Level IV; Grade A]
- Audiometric evaluation [Level IV; Grade A]
- DPD deficiency testing before treatment with 5-FU [Level III; Grade A];

  if not available, reduce initial 5-FU dose for first course to test tolerability [Level V; Grade C]
- Fertility preservation [Level V; Grade A]
- Molecular biology studies for research purposes [Level V; Grade C]

# Treatment Recommendations



# Induction Chemotherapy (IC)

- Standard of care for locoregionally advanced disease (≥st.II, N1) [Level III; Grade A]
- High response rates to Cis/5-FU in children and AYA[1,2,3] [Level III; Grade B]
- Proven benefit of different regimens on survival in adults[4,5,6,7,8]
- Greatest benefit on distant tumor control (=avoidance of metastatic dissemination)[9,10]
- Good response enables de-escalation of RT → reduction of RT-related toxicities[11]

[1]*Buehrlen et al., Cancer, 2012*
[2]*Casanova et al., Cancer, 2012*
[3]*Rodriguez-Galindo et al., J Clin Oncol, 2019*
[4]*Sun et al., Lancet Oncol, 2016*
[5]*Frikha et al., Ann Oncol, 2018*
[6]*Yang et al., Eur J Cancer, 2019*
[7]*Zhang et al., NEJM, 2019*
[8]*Wang et al., Med (Balt), 2020*
[9]*Ribassin-Majed et al., J Clin Oncol, 2017*
[10]*Chen et al., Clin Cancer Res, 2018*
[11]*Ou et al., Oral Oncol, 2016*

# Response Evaluation

- MRI or CT after 2nd & 3rd IC course → Response definition according to WHO criteria or RECIST 1.1 criteria [Level IV; Grade B]
- Very good response group: CR + VGPR (>80% reduction of tumor mass)
- Partial response group: PR (>50–80% reduction of tumor mass)
- Poor response group: MR (>25–50% reduction of tumor mass), SD (tumor mass ±25%), PD (increase in tumor mass >25% and/or new distant metastase or lymphadenopathy)
- Metabolic response evaluation by PET/CT optional, prognostic significance not yet confirmed

# Radiotherapy (RT)

- Radiation doses of 66.0–70.2Gy to PT/involved LN standard of care in adults[1]
- Reduction of radiation dose safe in children and AYA with GR to IC[2,3,4] [Level III; Grade B]
- Total dose to PT/involved LN 54–67Gy depending on response to IC, with 1.8Gy daily fractions [Level III; Grade B]
- IMRT as preferred technique → better survival & fewer toxicities[5,6,7,8] [Level II; Grade A]


[1] *Colevas et al., J Natl Compr Canc Netw, 2018*

[2] *Jouin et al., Strahlenther Onkol, 2019*

[3] *Rodriguez-Galindo et al., J Clin Oncol, 2019*

[4] *Römer et al., Cancers, 2022*

[5] *Peng et al., Radiother Oncol, 2012*

[6] *Zhang et al., Eur J Cancer, 2015*

[7] *Qiu et al., J Cancer Res Clin Oncol, 2017*

[8] *Bisof et al., Radiol Med, 2018*

# Radiotherapy (RT)

Radiotherapy doses scheduled for patients with NPC according to response after induction

| *Cavum = T*<br>*Lymph nodes = N* | ***PTV2***<br>***Residual tumor following induction chemotherapy*** | ***PTV1***<br>***Macroscopic tumor and involved nodes prior to induction chemotherapy*** | ***PTV N0***<br>***Uninvolved nodal areas*** |
|---|---|---|---|
| ***Reduced dose:***<br>***CR or VGPR***<br>***> 80% (T and N)*** | PTV T2 = 54.0 Gy (no boost)<br>PTV N2 = 54.0 Gy (no boost) | PTV T1 = 54.0 Gy<br>PTV N1 = 54.0 Gy | 45.0 Gy |
| ***Standard dose:***<br>***PR***<br>***[50-80%] (T or N)*** | PTV T2 = 59.4 Gy (boost 5.4 Gy)<br>PTV N2 = 59.4 Gy (boost 5.4 Gy) | PTV T1 = 54.0 Gy<br>PTV N1 = 54.0 Gy | 45.0 Gy |
| ***High dose:***<br>***MR (< 50%)***<br>***or SD or PD*** | PTV T2 = 66.6 Gy (boost 7.2 Gy)<br>PTV N2 = 66.6 Gy (boost 12.6 Gy) | PTV T1 = 59.4 Gy<br>PTV N1 = 54.0 Gy | 45.0 Gy |

*Abbreviations*: PTV, Planned tumor volume; Gy, grays.

# Concomitant Chemo-Radiotherapy (CCRT)

- Proven survival benefit in adults with locoregionally advanced disease[1]
- Different Cis-based regimens also in children and AYA, but *no* randomized data[2,3,4,5]
- COG: Trend for improved 5y-EFS with three vs. two cycles of Cis-CCRT 100mg/m$^2$ every 21d, but additional toxicity with potential treatment delay[5]
- Recommended regimens: Cis 30mg/m$^2$ once weekly x7 *OR* 20mg/m$^2$/d x3d x2–3 *OR* 100mg/m$^2$ x2–3 every 21d [Level III; Grade B]

[1] *Lee et al., J Clin Oncol, 2015*
[2] *Bührlen et al., Cancer, 2012*
[3] *Casanova et al., Cancer, 2012*
[4] *Jouin et al., Strahlenther Onkol, 2019*
[5] *Rodriguez-Galindo et al., J Clin Oncol, 2019*

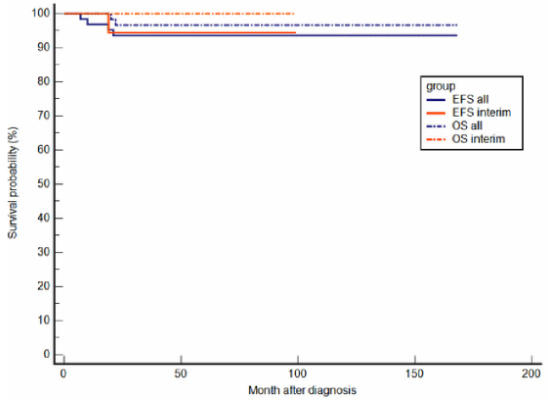
# Interferon Maintenance [Level III; Grade B/C]

cancers

MDPI

*Article*

**Multimodal Treatment of Nasopharyngeal Carcinoma in Children, Adolescents and Young Adults-Extended Follow-Up of the NPC-2003-GPOH Study Cohort and Patients of the Interim Cohort**




*Römer et al., Cancers, 2022*

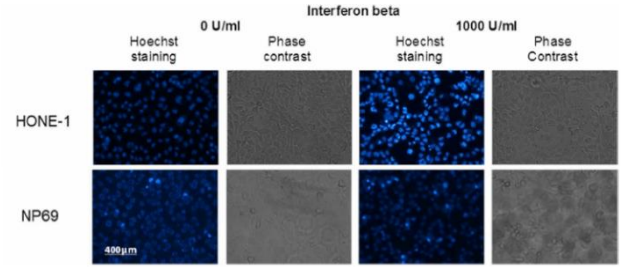
- n=66 pat. <25y
- n=45 NPC-2003 study:
  MFU 85mo. → EFS 93%, OS 95% (3 rel., 1 suicide, 1 SM)
- n=21 Interim pat.:
  MFU 40mo. → EFS 94%, OS 100% (1 rel.)

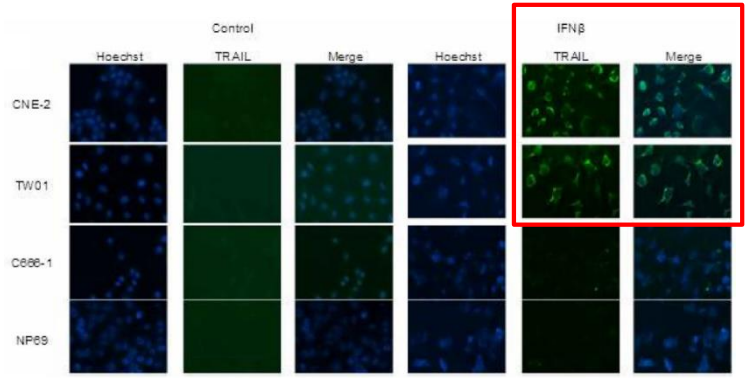
⇒ **MFU 6y: EFS 94%**
**OS 97%**

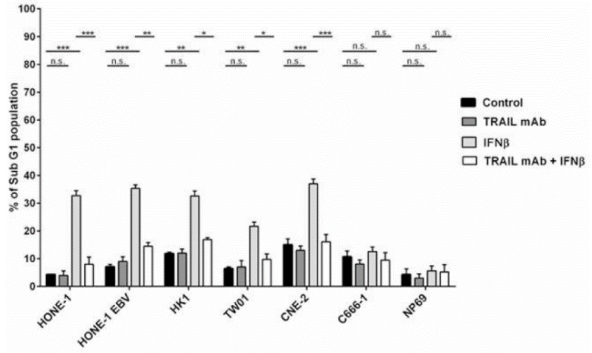
**RT 54Gy in 7 pat. with CR after IC**
**→ *no* relapses after MFU 7y**

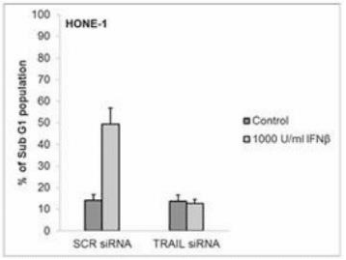
# Interferon Maintenance [Level III; Grade B/C]

IFN-β induces apoptosis in NPC cells via autocrine TRAIL signaling:



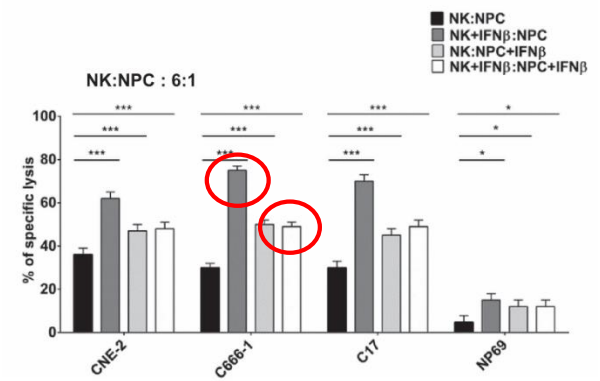



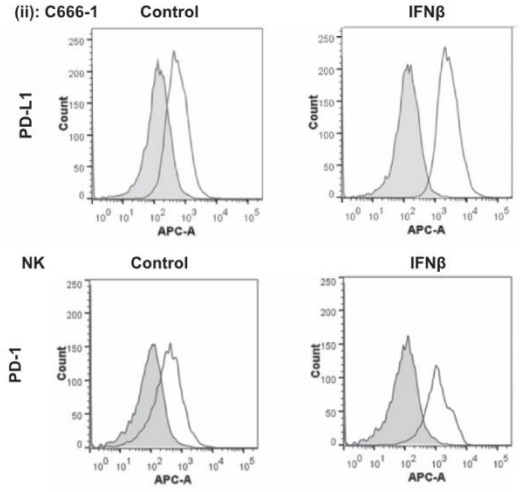




*Makowska et al., Oncotarget, 2018*

# Interferon Maintenance [Level III; Grade B/C]

Treatment of NK cells with IFN-β increases killing of NPC cells via TRAIL signaling, but additional treatment of NPC cells with IFN-β reduces NK-cell-mediated killing by enhanced PD-1/PD-L1 interaction:

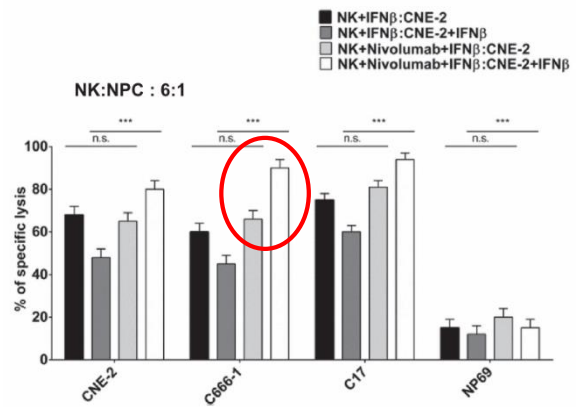


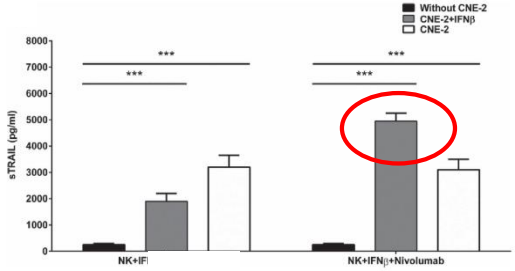



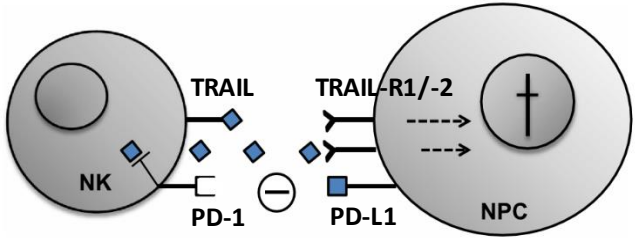

*Makowska et al., Transl Oncol, 2019*

# Interferon Maintenance [Level III; Grade B/C]

Treatment of IFN-β-activated NK cells with Nivolumab increases killing of IFN-β-treated vs. untreated NPC cells, which is mediated by release of cytoplasmatic TRAIL from NK cells:




*Makowska et al., Transl Oncol, 2019*

# Interferon Maintenance [Level III; Grade B/C]

IFN-β

1. induces apoptosis in NPC cells via the extrinsic pathway

2. increases NK-cell-mediated killing of NPC cells, which can be enhanced by ICI treatment

# Relapsed/Refractory & Metastatic NPC

- Most relapses within two years after initial diagnosis and as distant metastases
- Distant metastases at diagnosis in <10%, associated with poor survival
- Multiple chemotherapy agents with activity in recurrent or metastatic NPC[1,2,3,4,5]
- Survival benefit with Gem/Cis compared to Cis/5-FU IC in adults[6]
- Local treatment options for locoregional relapse and oligometastases (RT, surgery, thermal ablation)[7,8,9] [Level IV; Grade C]

[1] Ngeow et al., Ann Oncol, 2011
[2] Chen et al., Oral Oncol, 2012
[3] Yau et al., Oral Oncol, 2012
[4] Jin et al., J Cancer Res Clin Oncol, 2012
[5] Chen et al., Cancer Chemother Pharmacol, 2013
[6] Zhang et al., Lancet, 2016
[7] Hu et al., Sci Rep, 2017
[8] Liang et al., Oral Oncol, 2019
[9] You et al., JAMA Oncol, 2020

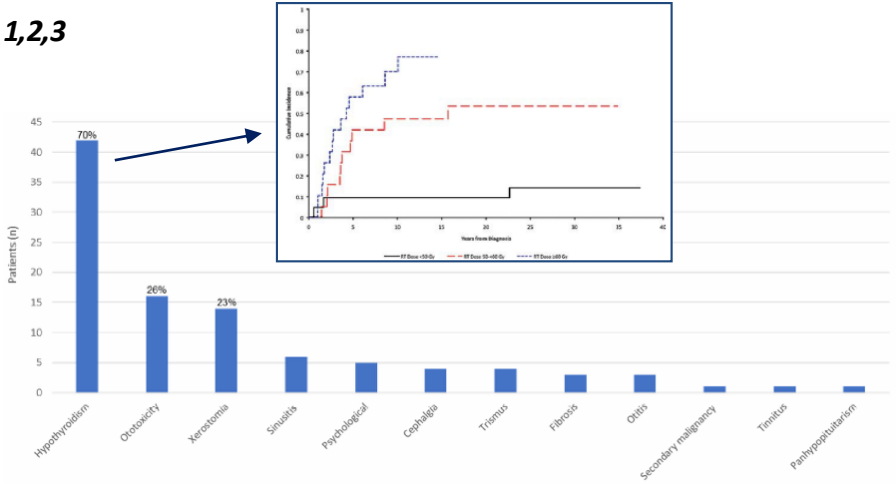
# Relapsed/Refractory & Metastatic NPC

- Proven efficacy of ICIs in adults (pembrolizumab, nivolumab, camrelizumab, toripalimab), as monotherapy or in combination with chemotherapy[1,2,3,4,5] [Level III; Grade C]
- EBV-specific T cells (EBV-CTLs) with some anti-tumor activity in heavily pretreated adults, but lack of methodological standardization, expensive and time-consuming[6,7,8,9,10,11] [Level III; Grade C]


[1]Hsu et al., J Clin Oncol, 2017
[2]Burtness et al., Lancet, 2019
[3]Ma et al., J Clin Oncol, 2018
[4]Yang et al., Lancet Oncol, 2021
[5]Mai et al., Nat Med, 2021
[6]Louis et al., J Immunother, 2010
[7]Chia et al., Mol Ther, 2014
[8]Huang et al., Cancer, 2017
[9]Smith et al., Cancer Res, 2012
[10]Smith et al., Oncoimmunol, 2017
[11]Smith et al., NPJ Precis Oncol, 2021

# Follow-up

- High rate of long-term morbidities (>80%)[1,2,3]
- Regular examinations incl. audiometry and assessment of endocrine functions mandatory [Level IV; Grade A]
- Lifelong awareness of radiation-induced secondary cancers




[1]Cheuk et al., Cancer, 2011

[2]Ben-Ami et al., PBC, 2020

[3]Römer et al., Cancers, 2022

# Conclusions

- IC–CCRT(–IFN-β) standard of care in children and AYA with locoregionally advanced NPC with excellent primary cure rates
- High burden of treatment-related toxicities → response-adapted RT dosing, lifelong follow-up
- ICIs efficious in relapsed/refractory and metastatic disease, potential role also in front-line treatment

# Thanks for your attention !

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

EXPeRT

Partner

SIOP Europe
the European Society for Paediatric Oncology