XXII Congreso Nacional

SEOR 2024

Hacia un horizonte +INtegrador Interactivo Inteligente

25 - 27 SEPTIEMBRE | OVIEDO

PALACIO DE EXPOSICIONES Y CONGRESOS

Increasing radiation response in head and neck cancer via the use of nanoparticles

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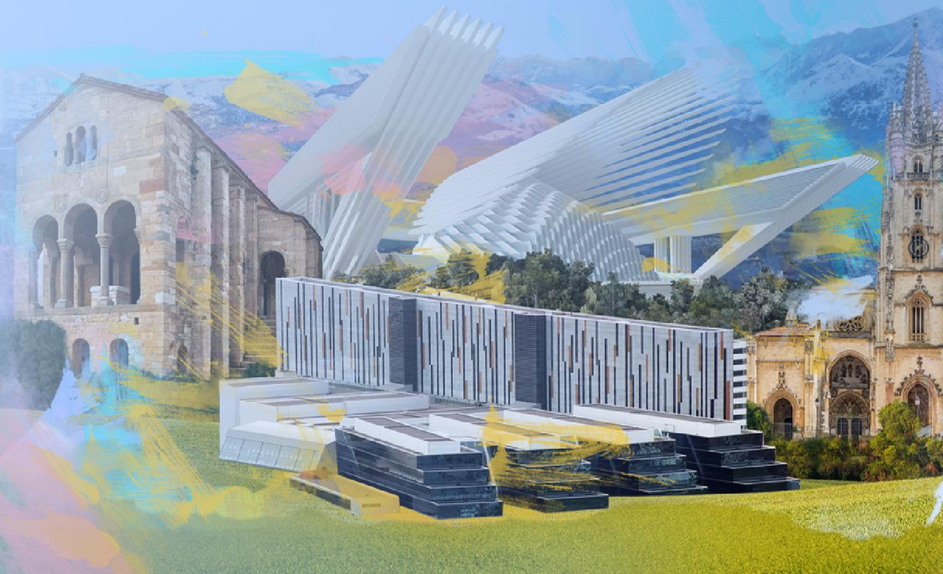


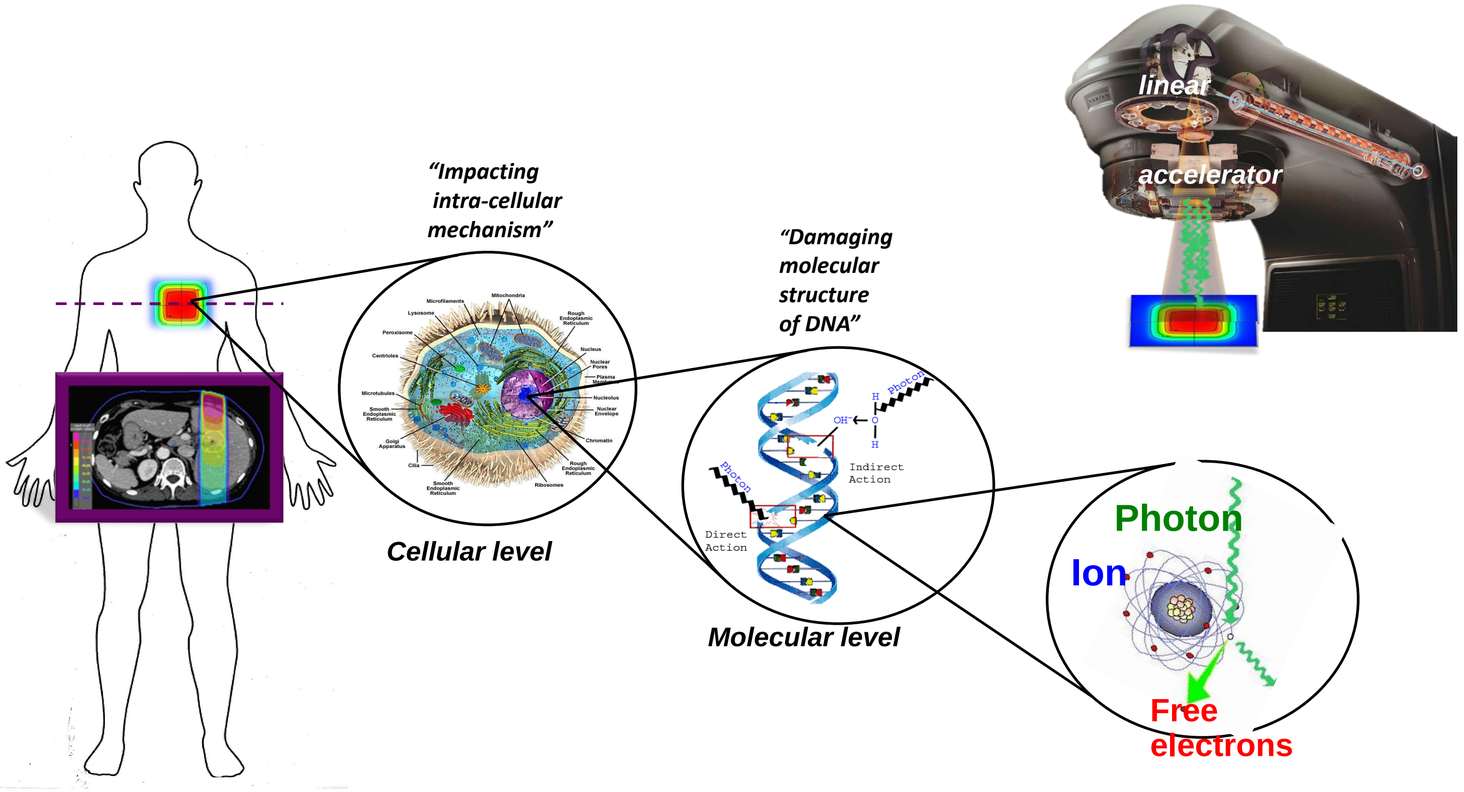
ORGANIZA:

SEOR SOCIEDAD ESPAÑOLA DE ONCOLOGÍA RADIOTERÁPICA

Increasing radiation response in head and neck cancer via the use of nanoparticles

Outline

- Clinical needs to improve radiation response in HNC
- Principles NP’s
- NBTXR3
    - Results clinical trials
        - phase 1
        - Nanoray-312
        - combination immunotherapy



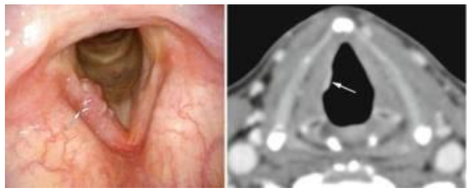
– About 80% of HNC patients are treated with RT

– By 2025: HNC will be the 4th largest cancer group requiring RT (ESTRO-HERO analyses Radiother Oncol 2016)

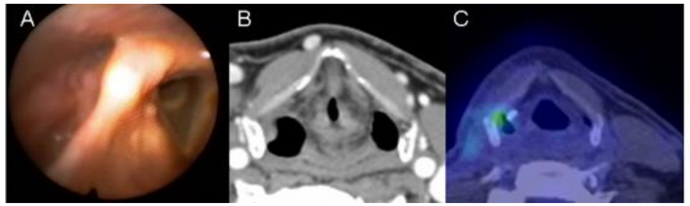
Current standard treatment for HNC

Early HNC: single modality

- Surgery (organ sparing)
- Radiotherapy alone



T1 vocal cord



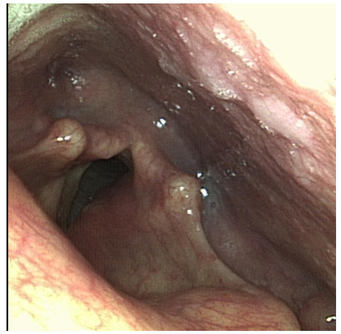
T1 piriform sinus

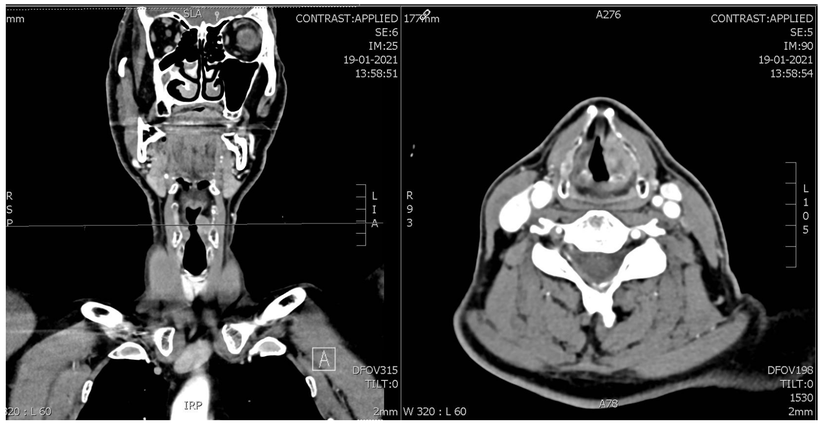
Locally advanced HNC:

– Inoperabel LAHNC: CRT

– Operabel LAHNC

- CRT: Organ and function preservation
- Surgery + postoperative (C)RT





T3N2b Supraglottic SCC

Clinical needs HNC

Up to 50% **locoregional relapse**

often due to radioresistance

Normal tissue toxicity (xerostomia, dysphagia)

Cisplatin ineligibility: Approximately 1/3 of patients are ineligible for cisplatin

Comorbidities in LA-HNSCC assessed by Age-adjusted Charlson Comorbidity Index (ACCI)

ACCI: Age and 19 comorbidities (diabetes, cardiovascular, liver, pulmonary disease, etc.)

ACCI ≥ 4: correlated with lower OS in LA-HNSCC[1]; ~20-30% of patients with LA-HNSCC[2]

Elderly patient concerns:

~30% of HNSCC patients > 70 years old

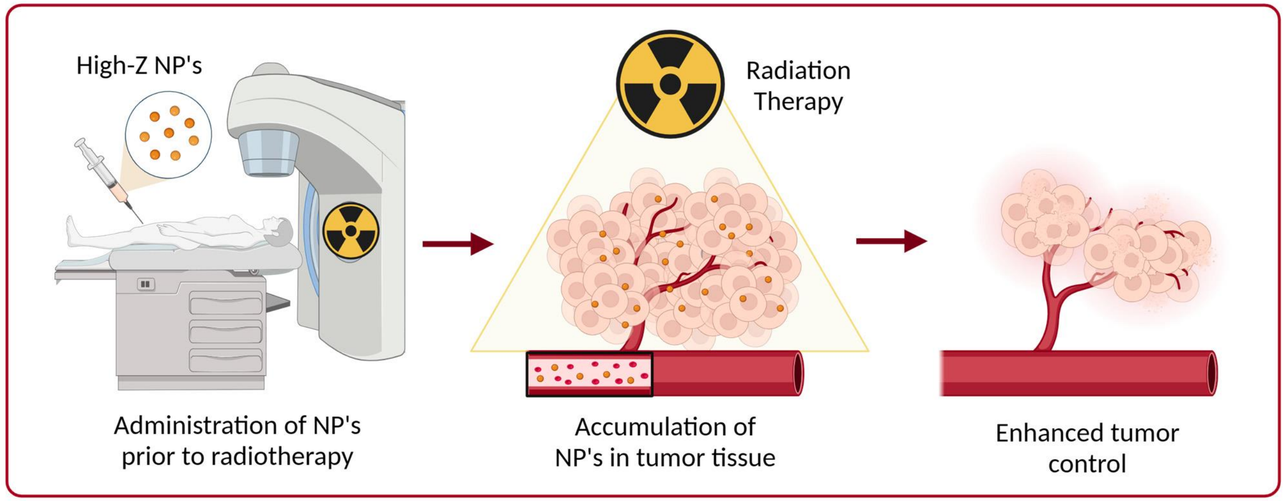
Poor outcomes (PFS ~9 months[3]; OS ~12 months[3,4,5])

→ **New treatment options needed**

[1]*Zumsteg et al. Cancer (2017);* [2]*Göllnitz et al. Cancer Medicine (2016);* [3]*Moye et al., Oncologist (2015);* [4]*Amini A, et al. Cancer (2016);* [5]*Shia et al. Cancers (2020)*

Nanoparticles as ‘radiosensitizers’

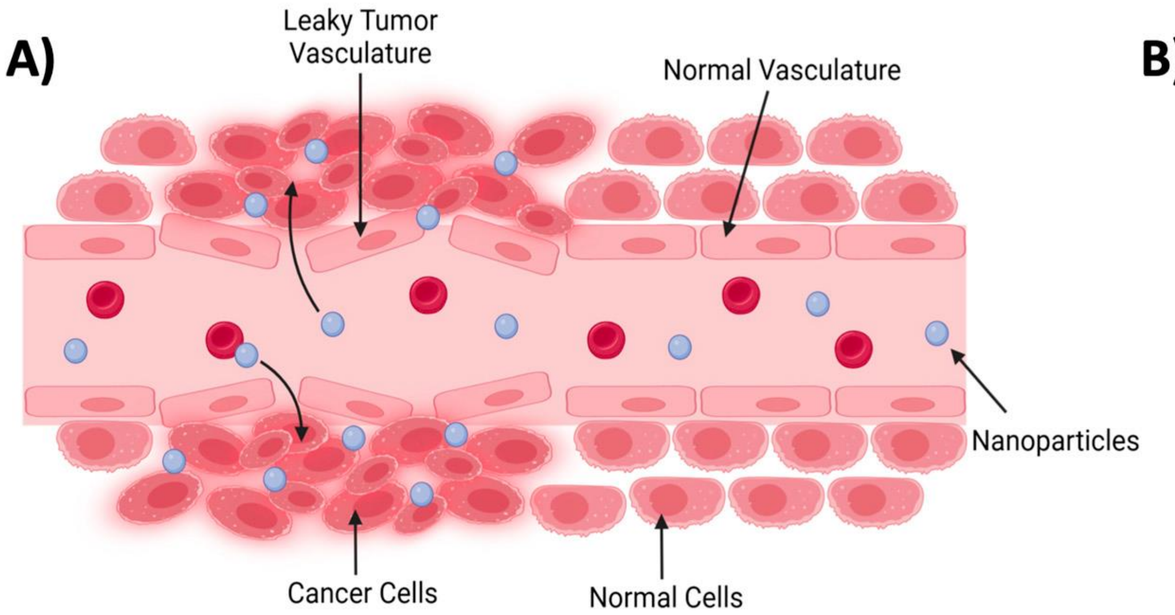
- typically ranging from 1 to 100 nanometres
- unique physical and chemical properties at the nanoscale that allow them to be engineered and tailored for specific applications
- Various high-atomic-number (Z) NPs have shown promising radiosensitizing effects and can be functionalized in ways such that they preferentially target tumor cells in comparison with normal tissue
- high-Z NPs being investigated for this purpose are, but not limited to, gold (Z = 79), silver (Z = 47), bismuth (Z = 83), gadolinium (Z = 64), and hafnium (Z = 72).

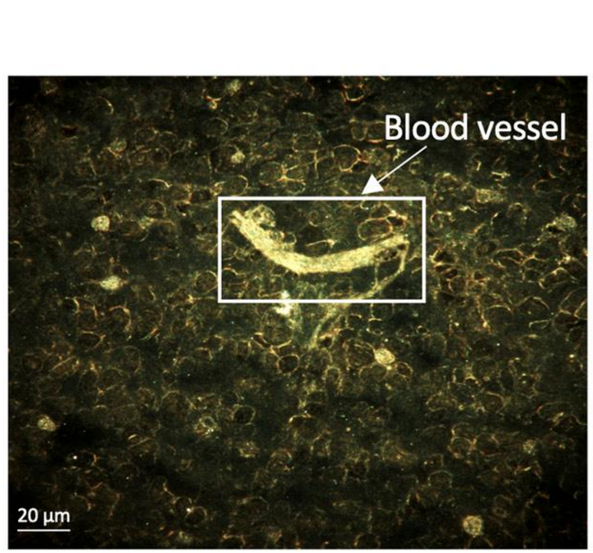


Tumor targeting of Nanoparticles

- Passive

- NP’s can preferentially accumulate in tumor tissue via the enhanced permeability and retention (EPR) effect (due to leaky neovasculature and poor lymphatic drainage and slow venous return)

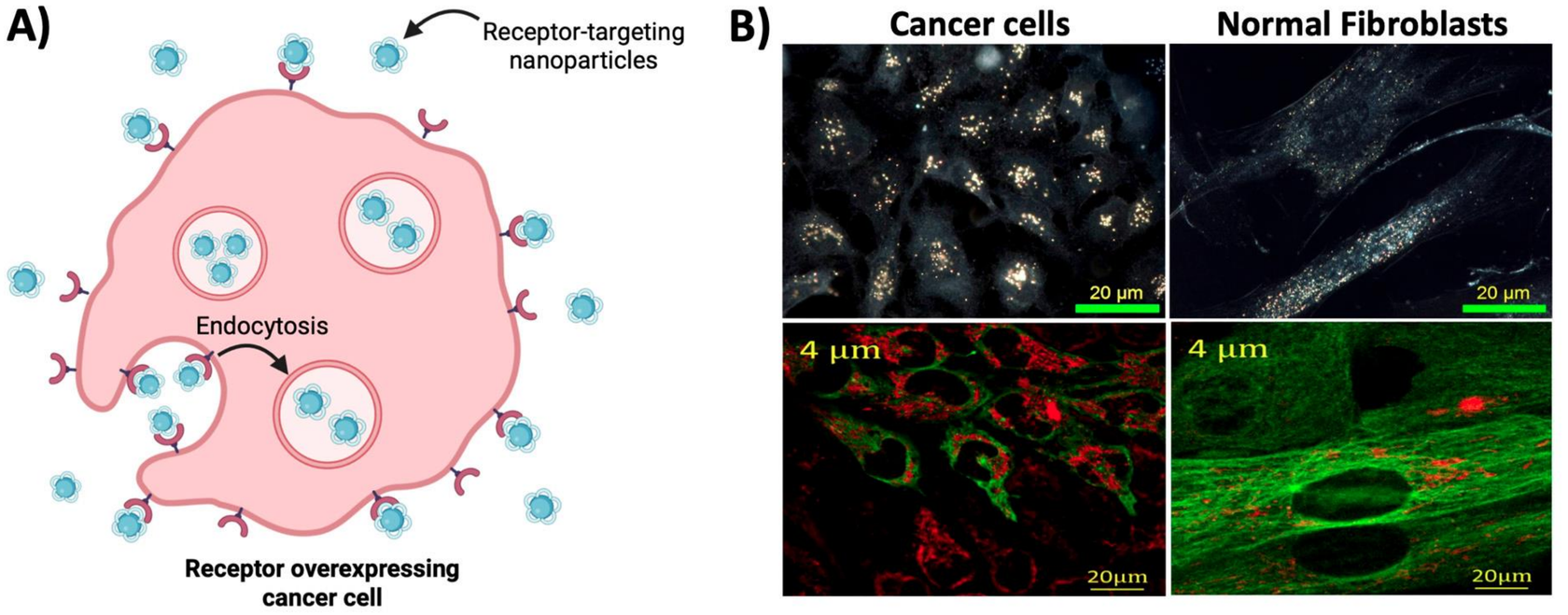




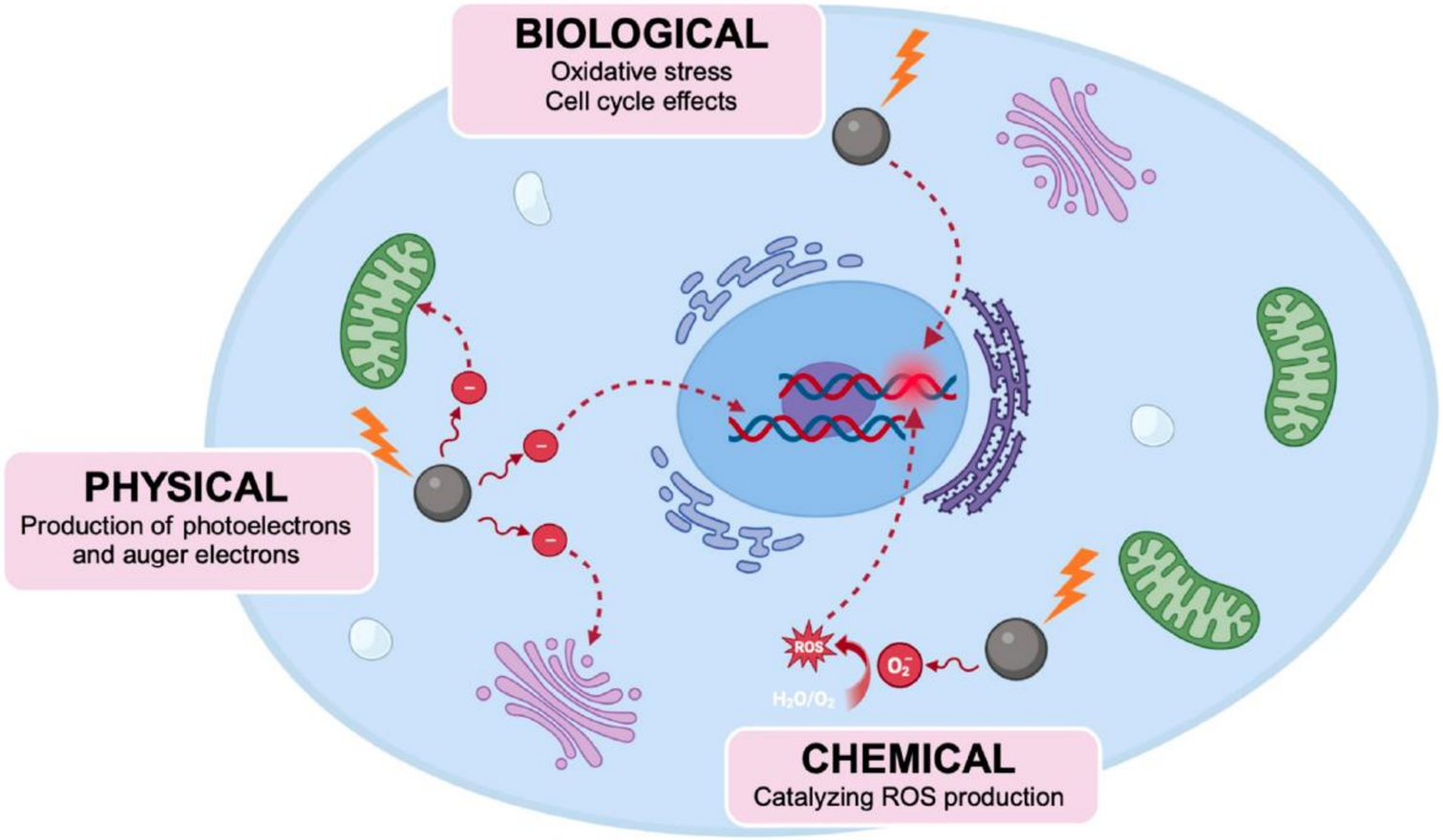
Tumor targeting of Nanoparticles

- Active

- Functionalization of NP’s targeting tumorcells



Mechanisms of Radiosensitization



Jackson et al, Molecules 2024

Table 1. Current clinical studies investigating the effects of high-Z NPs for radiotherapy.

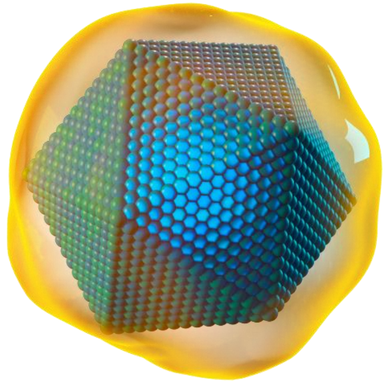
Nanoparticle	Condition	Phase	Status	Identifier
NBTXR3	Adult soft-tissue sarcoma	Phase I	Completed	NCT01433068
	Pancreatic ductal adenocarcinoma	Phase I	Recruiting	NCT04484909
	Lung non-small-cell carcinoma	Phase I	Recruiting	NCT04505267
	Metastatic malignant solid neoplasm	Phase I/II	Recruiting	NCT05039632
	Esophageal adenocarcinoma	Phase I	Recruiting	NCT04615013
	Head and neck squamous cell carcinoma	Phase II	Recruiting	NCT04862455
	Advanced cancers	Phase I	Recruiting	NCT03589339
	Head and neck squamous	Phase I	Active	NCT01946867
	Adult soft-tissue sarcoma	Phase II/III	Completed	NCT02379845
	Head and neck squamous cell carcinoma	Phase III	Recruiting	NCT04892173
AGuIX	Glioblastoma	Phase I/II	Recruiting	NCT04881032
	Brain metastases	Phase I	Completed	NCT02820454
	Brain metastases	Phase II	Recruiting	NCT03818386
	Gynecological cancers	Phase I	Recruiting	NCT03308604
	Brain metastases	Phase II	Recruiting	NCT04899908
	Lung tumors and pancreatic cancer	Phase I/II	Recruiting	NCT04789486
	Recurrent cancer	Phase I	Not yet recruiting	NCT04784221

What is NBTXR3?

NBTXR3 is a Suspension of Nano-sized Particles for One-Time Intratumoral Injection

NANOMETER SCALE

Mean size centered on 50 nm to fit into the cell



HAFNIUM OXIDE CORE

High atomic number (Z=72) and high electron density to increase absorption of ionizing radiation and cell damage

AMORPHOUS COATING

Negative surface charge for stability at neutral pH in aqueous medium and to facilitate tumor cell entry

BIOLOGICALLY INERT

NBTXR3 is inert (“off” status) in the absence of ionizing radiation. It is activated by ionizing radiation and increases energy dose deposit within cells (“on” status)

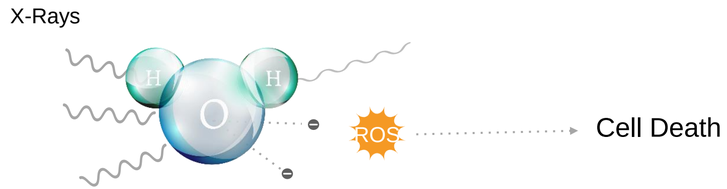
NBTXR3: A First-In-Class Radioenhancer

One-time intratumoral administration, remains in tumor

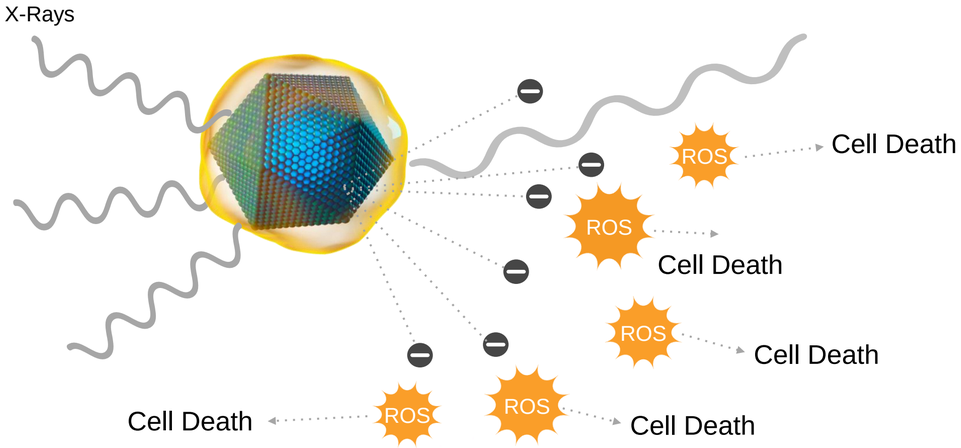
Efficacy and safety demonstrated in a randomized Phase II/III trial in locally advanced soft tissue sarcoma[1]

Universal mode of action targeting all solid tumors

Radiotherapy (RT) alone



NBTXR3 activated by RT



Increased absorption of ionizing radiation and cell death

[1]*Bonvalot et al. The Lancet Oncology (2019)*

Study Design – NBTXR3-102 Multicenter Phase I/II Trial

Key Inclusion Criteria

- **Ineligibility to cisplatin:**
  ≥ 70 years or
  ≥ 65 years with contraindication to cisplatin
- KPS ≥ 70
- **T3, T4 or Stage III/IVA** HNSCC* of the **oral cavity or oropharynx**
- Tumor amenable to intratumoral injection

Key Exclusion Criteria

- Tumor ulceration with vascular risk

Dose Escalation

Completed[1]

3 + 3 design: 4 dose levels
5%; 10%; 15%; 22%

N=19 patients
no DLT or TRAE grade ≥ 3

Dose Expansion

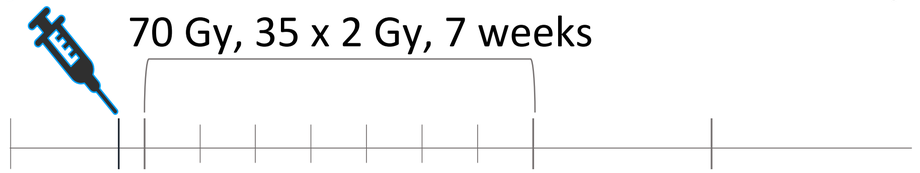
RP2D
N= 44 patients
NBTXR3 injected volume=22% of theoretical primary tumor volume
(height × length × width)

One-Time NBTXR3 Intratumoral Injection

Study Treatment

IMRT
70 Gy, 35 x 2 Gy, 7 weeks

Follow-up



Dose Expansion Endpoints

➢ **Efficacy**

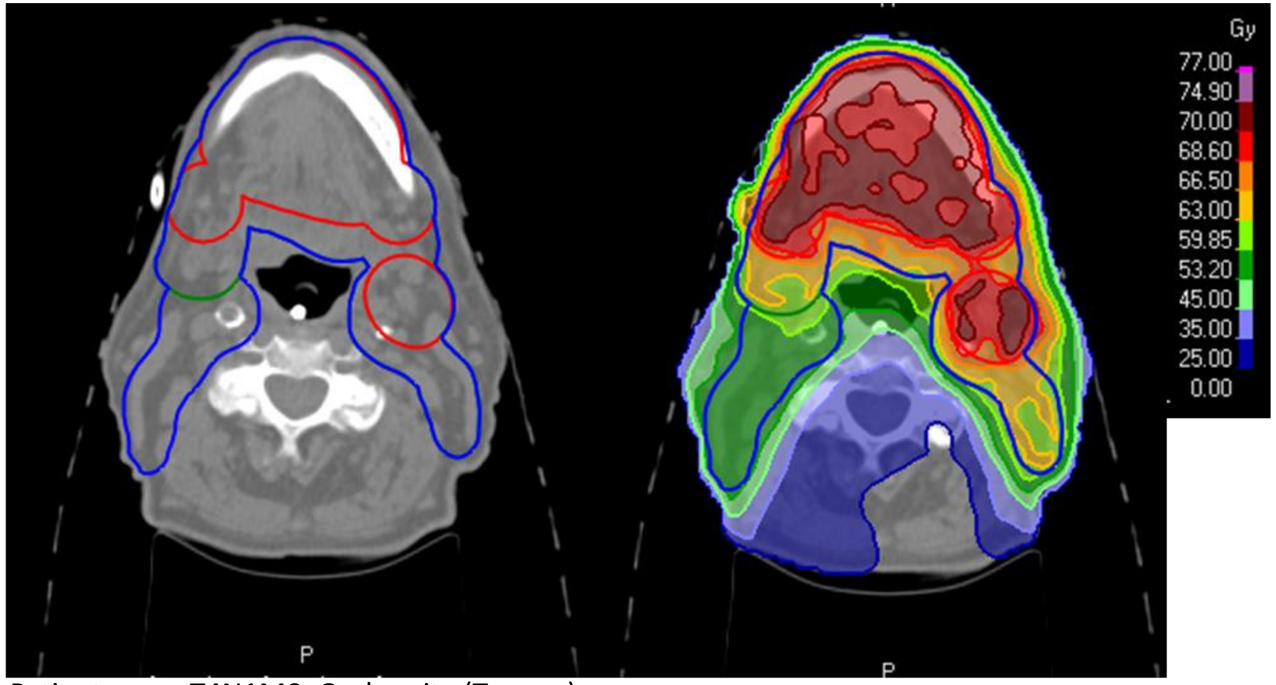
- ORR of primary tumor (injected lesion)
- ORR (injected and non-injected lesion)
- Duration of Objective Response
- PFS
- OS

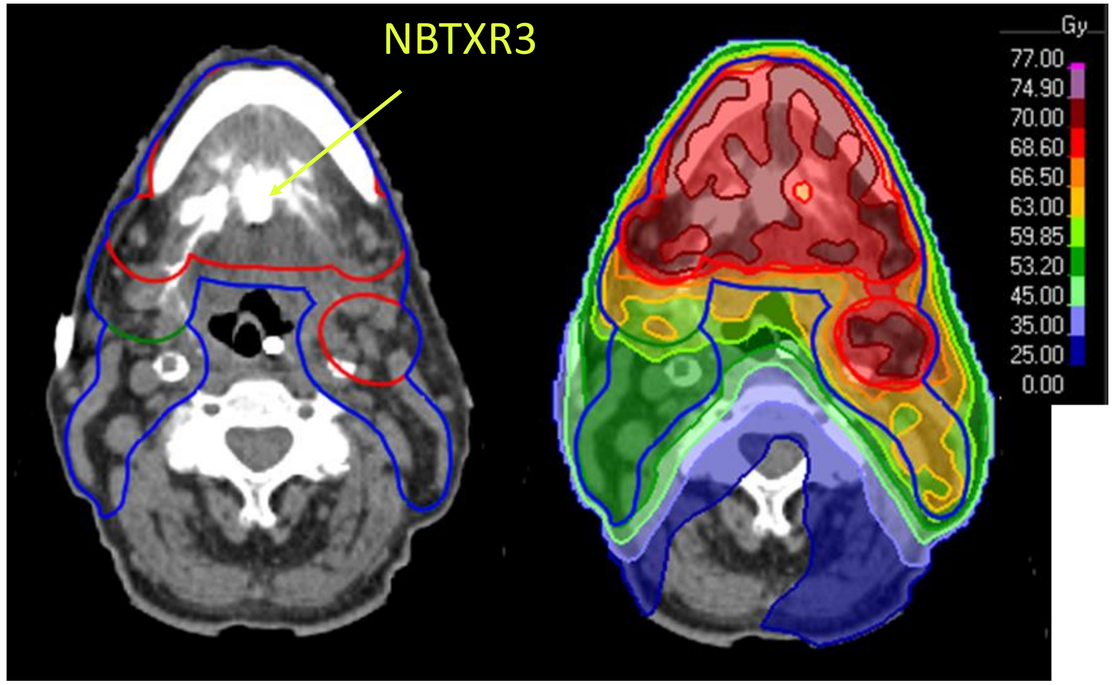
➢ **Safety**

*According to AJCC 7th edition for the dose escalation and 8th edition for the dose expansion; [1] *Hoffmann et al., Eur J Cancer (2021)*

RT of the Primary Tumor and Involved Lymph Nodes

- **Primary tumor injected with NBTXR3** and activated by IMRT (GTV_{70})
- **Involved lymph node(s)** are **non-injected** and treated with the same dose of RT as the primary tumor (GTV_{70})





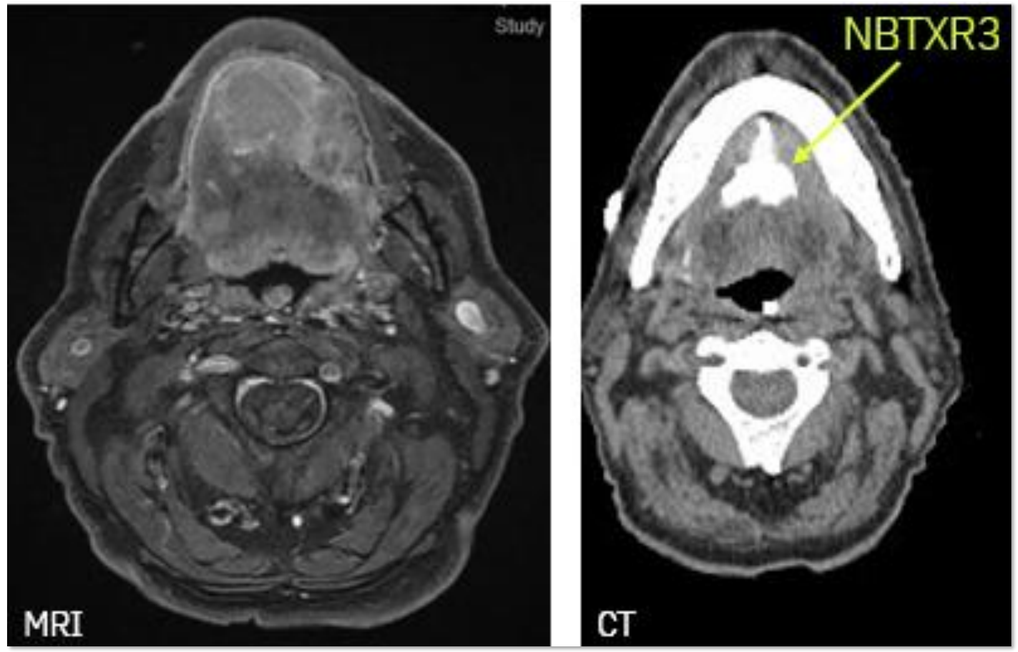
Patient case : T4N1M0, Oral cavity (Tongue)

Treatment Feasibility and Compliance

Feasibility of NBTXR3 Injection

All patients received at **least 90% of the planned injected volume of NBTXR3** in **Oral cavity or Oropharynx**

- **Injected Volume** median [Min, Max]: 13.60 ml [0.6, 57.1]
- **Injection Duration** median [Min, Max]: 11 min [3, 36]



Completion of IMRT

- IMRT completed in 50 patients (91%)

Safety

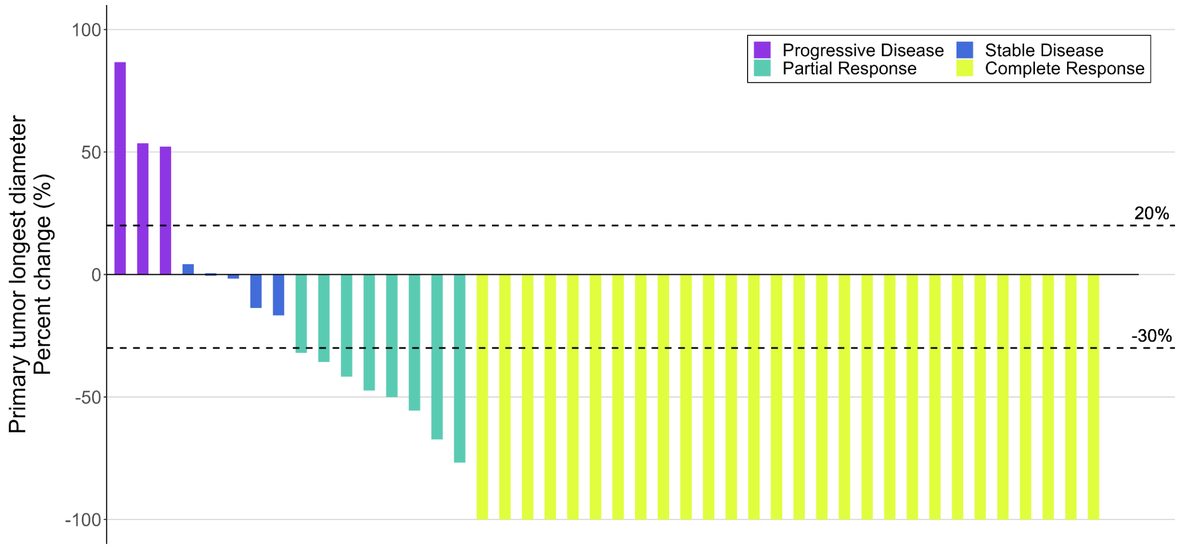
Treatment-Emergent Adverse Events (TEAE)	All Treated Population N=56
TEAE grade ≥ 3	43 (76.8)
TEAE related to NBTXR3	9 (16.1)
TEAE grade ≥ 3 related to NBTXR3	6 (11)
Stomatitis*	2 (3.6)
Tumor Pain	1 (1.8)
Lymphocyte Count Decreased	1 (1.8)
Sepsis*	1 (1.8)
Tumor Hemorrhage*†	1 (1.8)
TEAE related to injection	8 (14.3)
TEAE grade ≥3 related to injection	3 (5.4)
Tumor Pain	1 (1.8)
Hypertension	1 (1.8)
Swollen Tongue**	1 (1.8)
Oxygen Saturation Decreased**	1 (1.8)

***AEs related both to NBTXR3 and RT**

**** AEs reported in one patient**

† 45 days post RT due to lesion of both lingual arteries forming an aneurysm with subsequent bleedings

Local and Locoregional Control



Evaluable patients for objective tumor response

- Underwent at least one post-treatment assessment, and received at least 80% of the planned dose of NBTXR3 and 60 Gy of IMRT

12 patients were non-evaluable:

- Did not receive 60 Gy of IMRT: 4 patients (3 TEAE, 1 consent withdraw)
- No post treatment assessment: 8 early deaths (At 50 Gy, prior to end of treatment, objective response of injected lesion was reported in 6/8)

Best Overall Response Based on Investigator Assessment

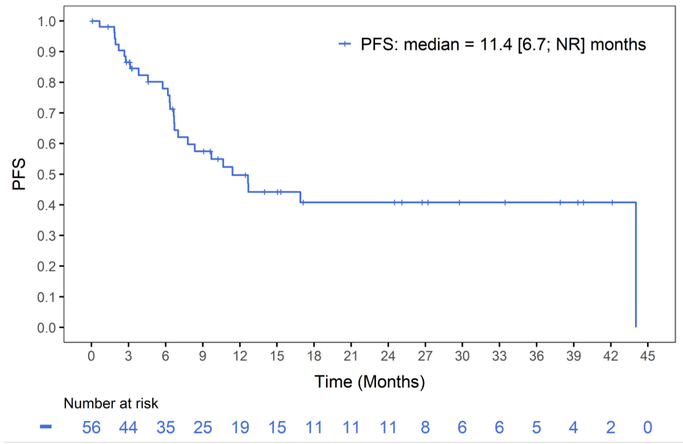
Measurement of tumor change as per RECIST v1.1

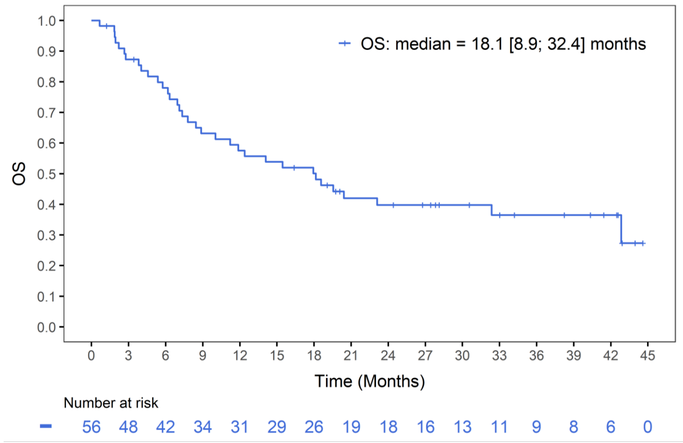
NBTXR3 Injected Lesion	Evaluable Patients (N=44)
Best Overall Response, n(%)	
CR	28 (63.6%)
PR	8 (18.2%)
SD	5 (11.4%)
PD	3 (6.8%)
ORR (CR + PR)	**36 (81.8%)**

Injected + Non-Injected Lesions	Evaluable Patients (N=44)
Best Overall Response, n(%)	
CR	23 (52.3%)
PR	12 (27.3%)
SD	4 (9.1%)
PD	5 (11.4)
ORR (CR + PR)	**35 (79.5%)**

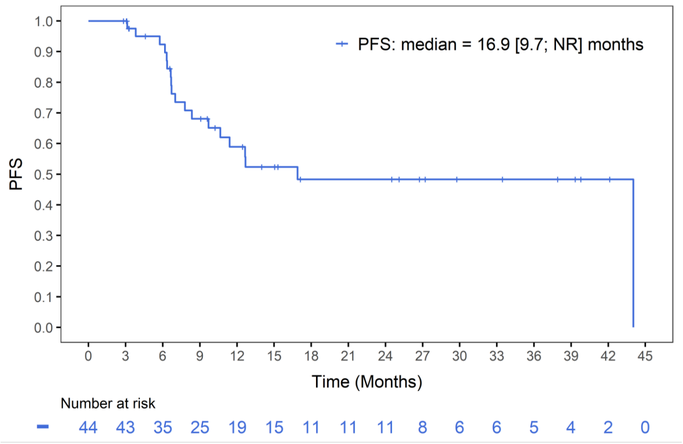
PFS and OS: Independent Central Review

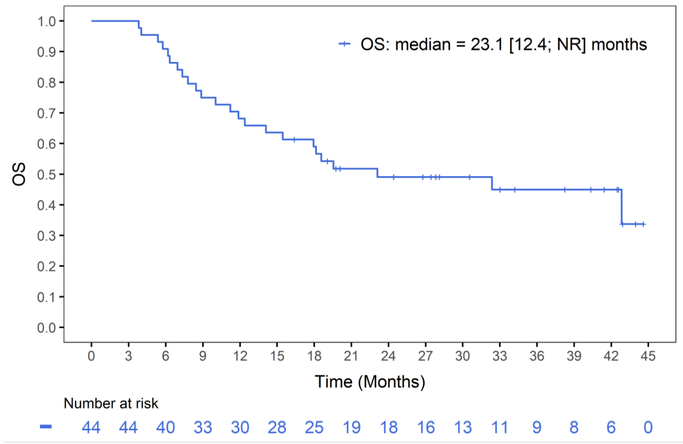
All Treated Population N=56





Evaluable Population* N=44





Of the 12 non-evaluable patients for objective tumor response, 9 had severe comorbidities (ACCI ≥ 4)

*Patients who underwent at least one post-treatment assessment, and received at least 80% of the planned dose of NBTXR3 and 60 Gy of IMRT

Conclusion phase I/II trial

- **NBTXR3 injection is feasible, with a manageable safety profile** in an elderly population with high burden of comorbidities
- **High ORR with increased ORR in the NBTXR3 injected lesion**
- **Prolonged PFS and OS** in an elderly population characterized by **poor prognostic factors** compared with historical data
- These results support the Phase III **NANORAY-312** trial (NCIT04892173) in which involved lymph nodes can also be injected

[1]Moye et al., Oncologist (2015); [2]Amini A, et al. Cancer (2016); [3]Shia et al. Cancers (2020)

Nanoray-312 : Global Phase III Design

Currently Enrolling

Key Inclusion Criteria

Age ≥60 years

Eligible for definitive RT

T3-T4 any N, or T2 if ≥N2 SCC of the Oral cavity, Oropharynx, Hypopharynx, or Supraglottic La (AJCC 8th)

At least one measurable and i injectable tumor

Ineligible for platinum-based chemotherapy

Ineligible for platinum-based chemotherapy

a. Estimated creatinine clearance ≥30 and <50 mL/min (calculated by Cockcroft and Gault)

b. Hearing loss or tinnitus Grade ≥2

c. Grade ≥2 peripheral neuropathy

d. Performance status : ECOG = 2 ; NYHA Class III

or

Aged 70-74 with Geriatric 8 (G8) score ≤14 or Aged ≥75 years

N=500

NBTXR3 dose: 33% of the Gross Tumor Volume

A

NBTXR3 + RT*

± Cetuximab (250 pts)

B

RT*

± Cetuximab (250 pts)

Endpoints

Primary: PFS

Key Secondary: OS

Secondary:

Local-regional control

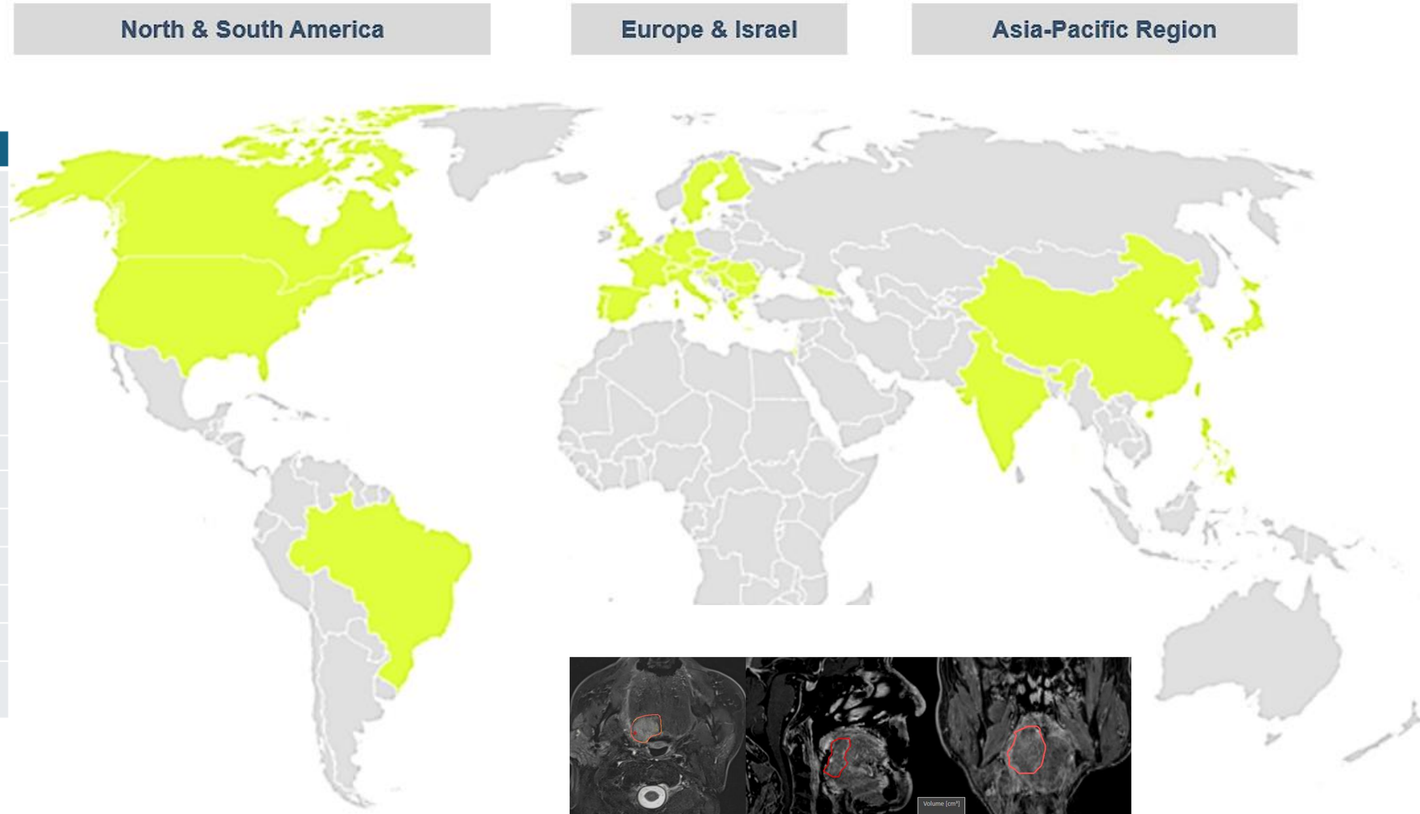
Distant control

QoL

Safety

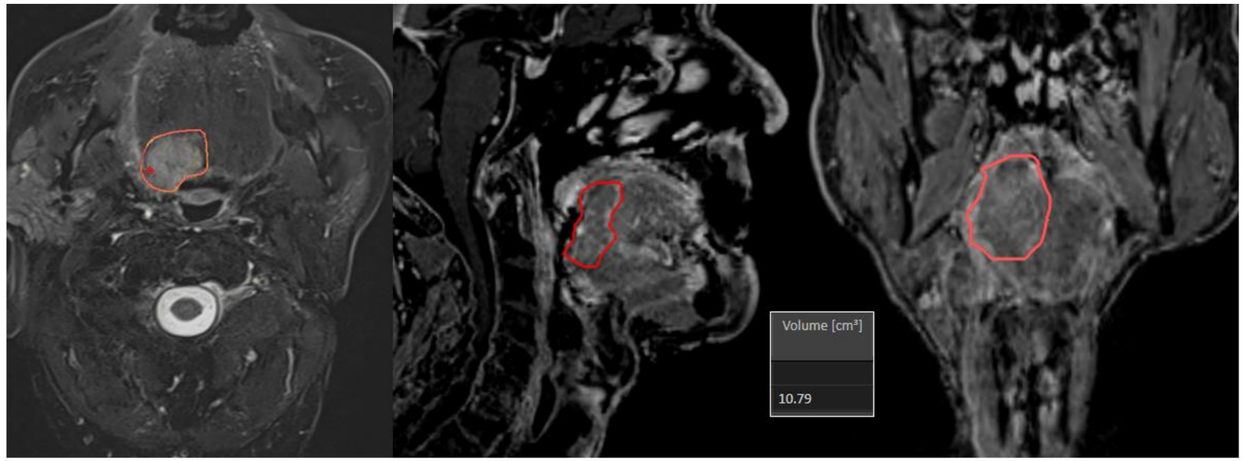
Nanoray-312 study

Account/Institution	PI Name
Hospital Universitario Marques de Valdecilla	García Castaño, Almudena
Hospital Universitario Cruces	Cacicedo Fernandez Bobadilla, Jon
Hospital Universitari Vall d'Hebrón	Giralt, Jordi
Hospital Clinic de Barcelona	Basté Rotllan, Neus
Hospital Regional Universitario de Málaga - Hospital General	Contreras Martinez, Jorge
Hospital Universitario 12 de Octubre	Iglesias Docampo, Lara Carmen
Institut Català d'Oncologia - Hospital Duran i Reynals (ICO L'Hospitalet)	Linares Galiana, Isabel
Hospital Universitario Lucus Augusti	Folgar Torres, Alicia
Hospital Universitario Virgen del Rocío	Flor Oncala, Maria Jose
Consorci Hospital General Universitari de València	Berrocal Jaime, Alfonso
IVO - Fundacion Instituto Valenciano de Oncologia	Aguilar Andino, Héctor
Hospital Universitario Fundación Jiménez Díaz	Rubio Perez, Jaime
Hospital Universitario HM Sanchinarro	Mihic Góngora, Luka
Hospitales Universitarios San Roque en Las Palmas de Gran Canaria - Centro Oncológico Integral Canario	Lara Jimenez, Pedro Carlos

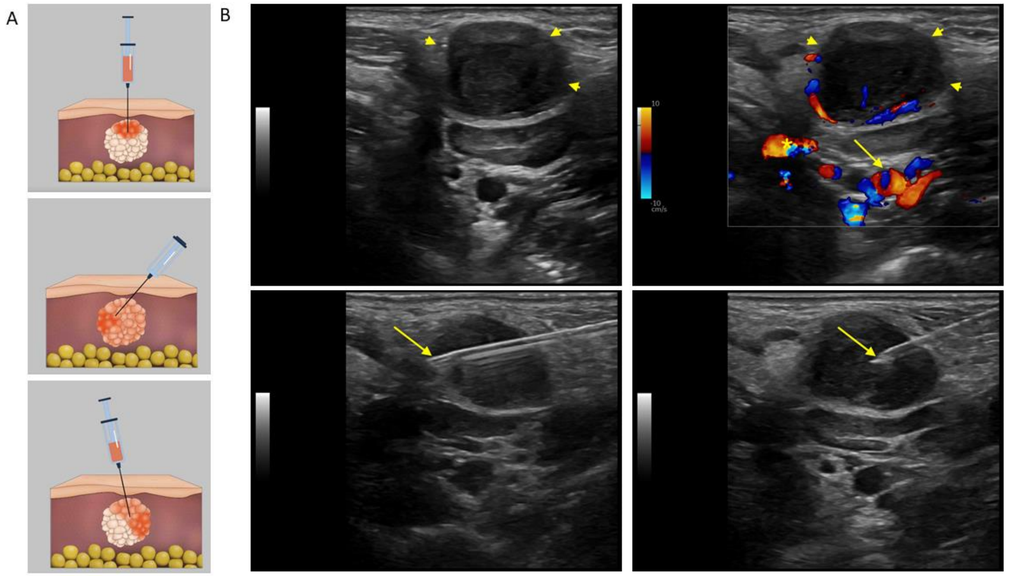


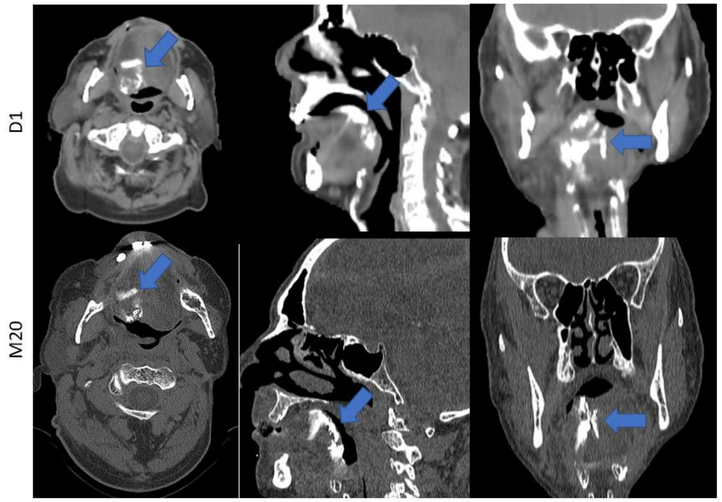
Measured tumor volume via MRI X 33% = Final volume of NBTXR3 to inject.

Nanoray-312 study



Measured tumor volume via MRI X 33% = Final volume of NBTXR3 to inject.





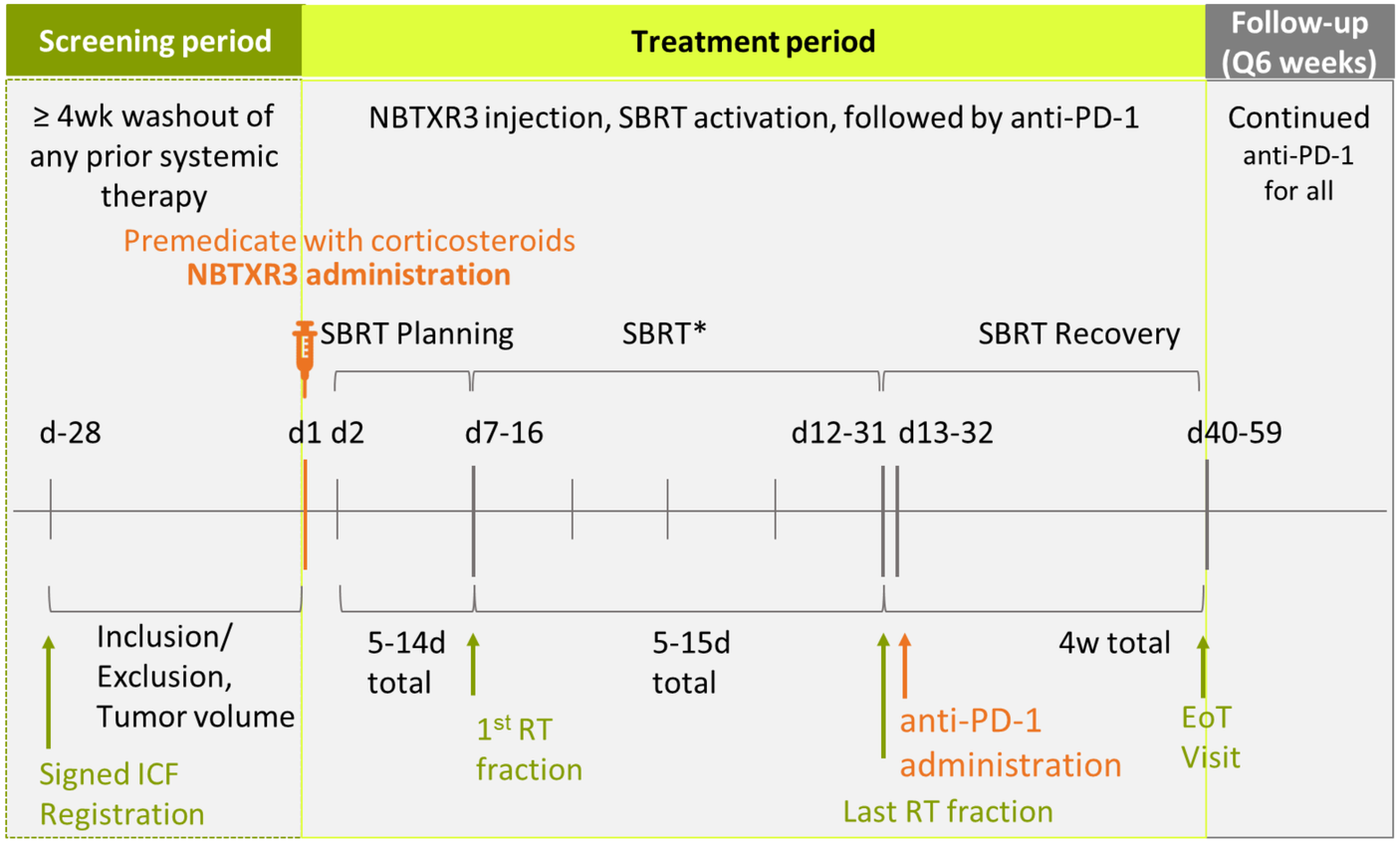
Study 1100 : Combination immunotherapy + SBRT

Multicenter Phase I dose escalation with dose expansion study to establish the RP2D of NBTXR3/RT/anti-PD-1 in 3 cohorts of anti-PD-1 resistant or naïve patients with advanced cancers (NCT03589339).

Anti-PD-1 Resistant
LRR or R/M HNSCC
(N=35)

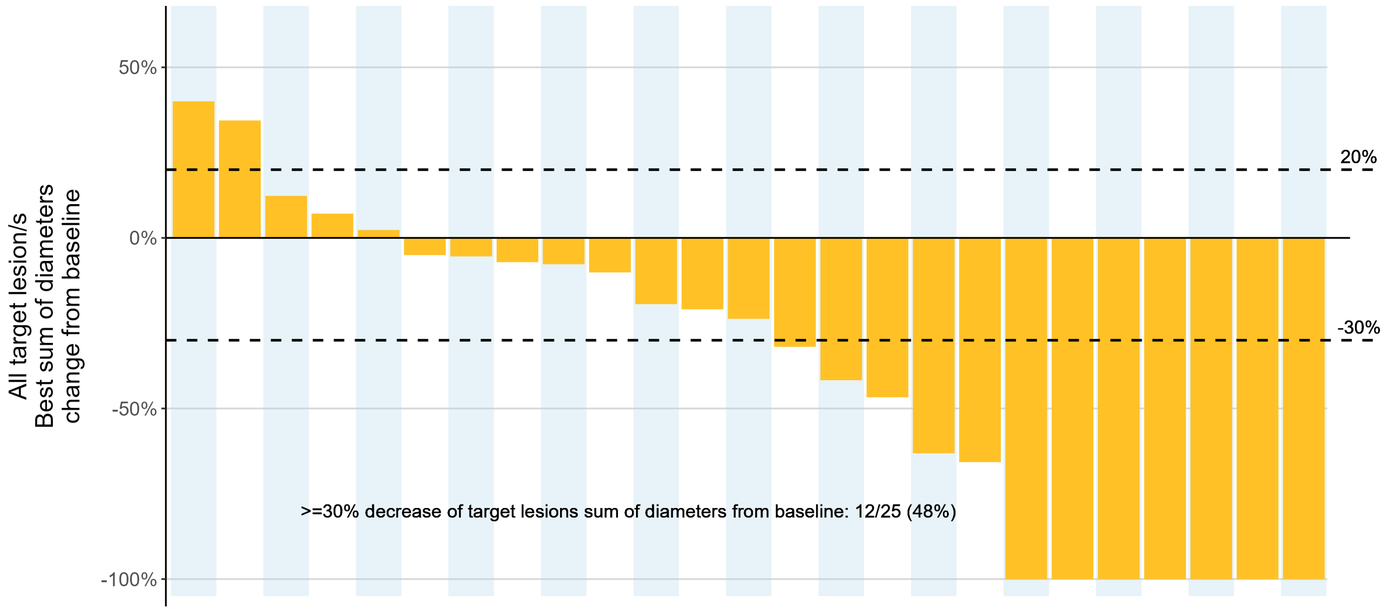
Anti-PD-1 Resistant
Lung / Liver / Soft Tissue Metastases
(N=35)

Anti-PD-1 Naïve
R/M HNSCC
(N=35)



*RT dose schedule to site of treatment as per site of treated lesion:
H/N 35 Gy/ 5 fxns; Lung 45 Gy/ 5 fxns; Liver 45 Gy/ 3 fxns; Soft tissue as per investigator

Best Change in All Target Lesions Diameter Sum from Baseline

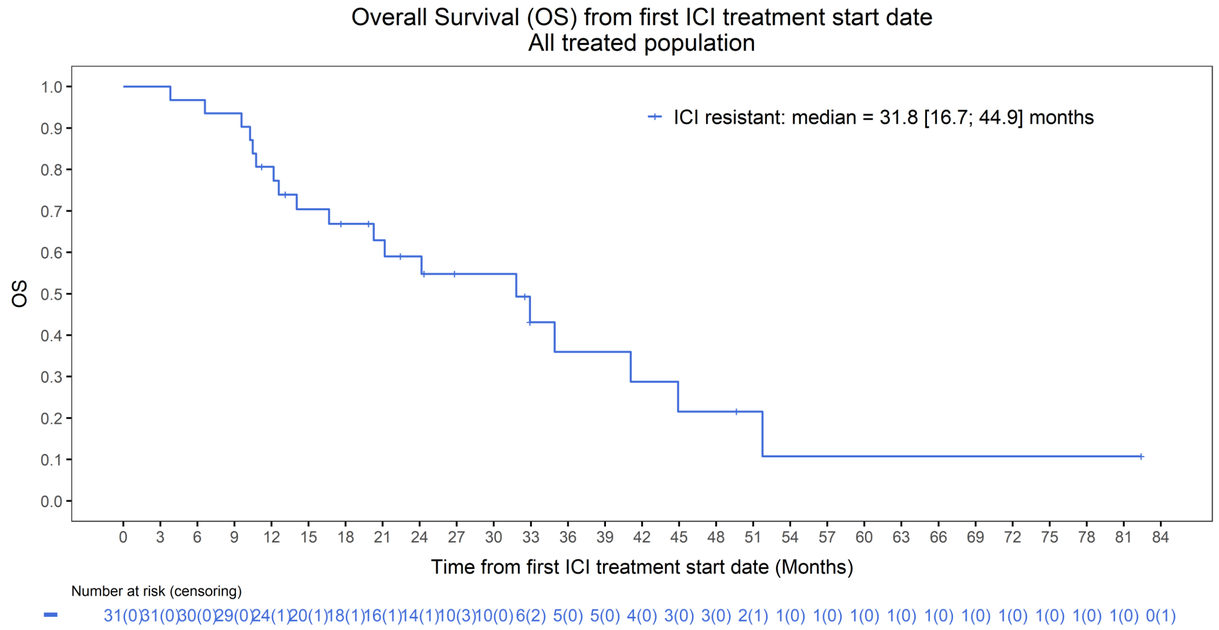


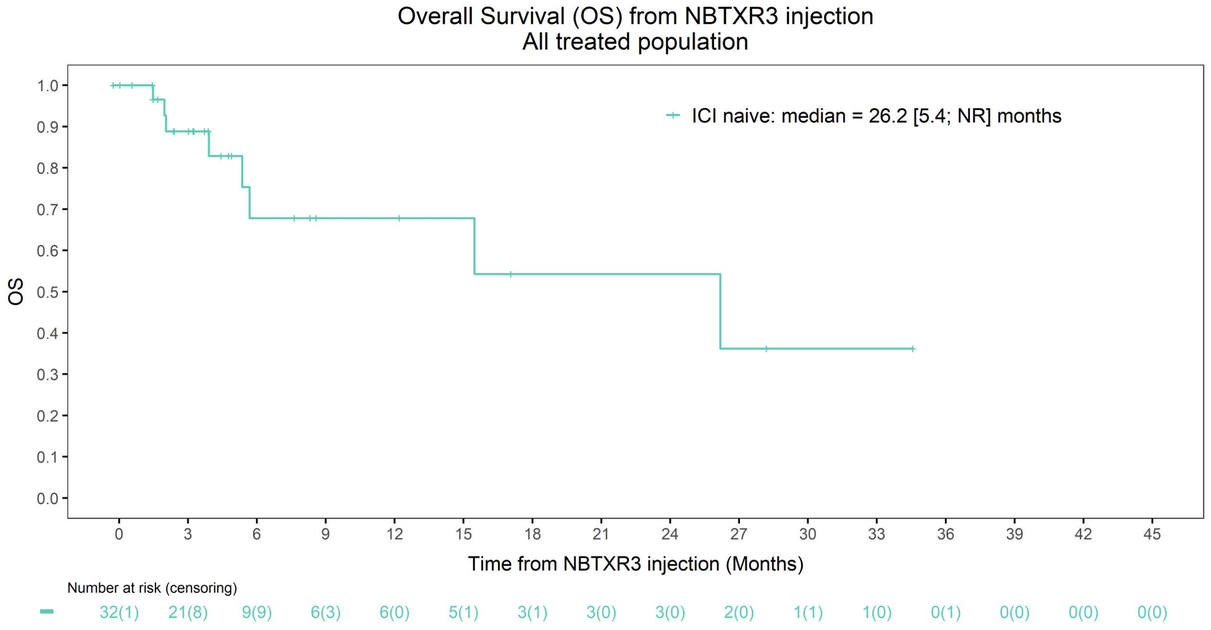
Overall Response (RECIST 1.1)	ICI Naive N=25
Complete Response	3 (12.0)
ORR (CR + PR)	**12 (48.0)**
95% CI	[27.8 - 68.7]
Median duration (days)(1))	54.0
DCR (CR + PR + SD)	**19 (76.0)**
95% CI	[54.9 - 90.6]
Median duration (days)(2)	65.0

(1) Number of days from first to last RECIST assessment with CR or PR
(2) Number of days from first to last RECIST assessment with CR, PR or SD

Best overall response have been derived as single best overall response observed for 11 subjects, either ongoing or with missing data (1 CR, 7 PR, 3 SD and 0 PD)

OS – ICI resistant and ICI naïve patients





Conclusion

- NBTXR3 intratumoral injection was feasible and safe in heavily pretreated patients with HNSCC, with Grade 3+ AEs related to NBTXR3 occurring in 2.9% of patients

- **In ICI Naïve patients:**
  - Overall tumor responses (ORR) were observed in 48% (12/25). Disease control was observed in 76% (19/25).
  - Median PFS was 7.3 months; median OS was 26.2 months.
- **In ICI Resistant patients:**
  - Overall tumor responses (ORR) were observed in 28% (7/25). Disease control was observed in 68% (17/25).
  - Median PFS was 4.2 months; median OS was 7.8 months. Median OS from first ICI treatment was 31.8 months.

- Overall, these results warrant further exploration in randomized trials for both ICI naïve and resistant HNSCC patients.

(2) Cohen EE, et al., Lancet. 2019. (3) Burtness B, et al., Lancet. 2019. (12) Ferris FL, et al., NEJM. 2016. (13) Topp BG, et al., Cancer Cell. 2023. (14) Haddad R, et al., Cancer. 2019.

Overal conclusion

- NBTXR3 intratumoral injection is feasible and safe in patients with LA HNSCC
- Encouraging signs of efficacy have been observed: ORR (81.8%), CRR (63.6%), and OS (17.9 months all treated; 23.1 months evaluable for efficacy population)
- Based on Phase I Study 102 results, a global registrational Phase 3 trial (Nanoray-312) is ongoing in platinum ineligible patients with LA HNSCC
- NBTXR3/SBRT followed by anti-PD-1 was feasible and safe in patients with advanced solid tumors, including R/M HNSCC in the Phase I Study 1100
- Promising early signs of efficacy were observed in HNSCC patients treated with NBTXR3/SBRT/anti-PD-1, including responses in patients resistant to anti-PD-1 and with metastatic disease, of whom many were HPV-
- Overall, these results support continued evaluation of NBTXR3 in patients with HNSCC

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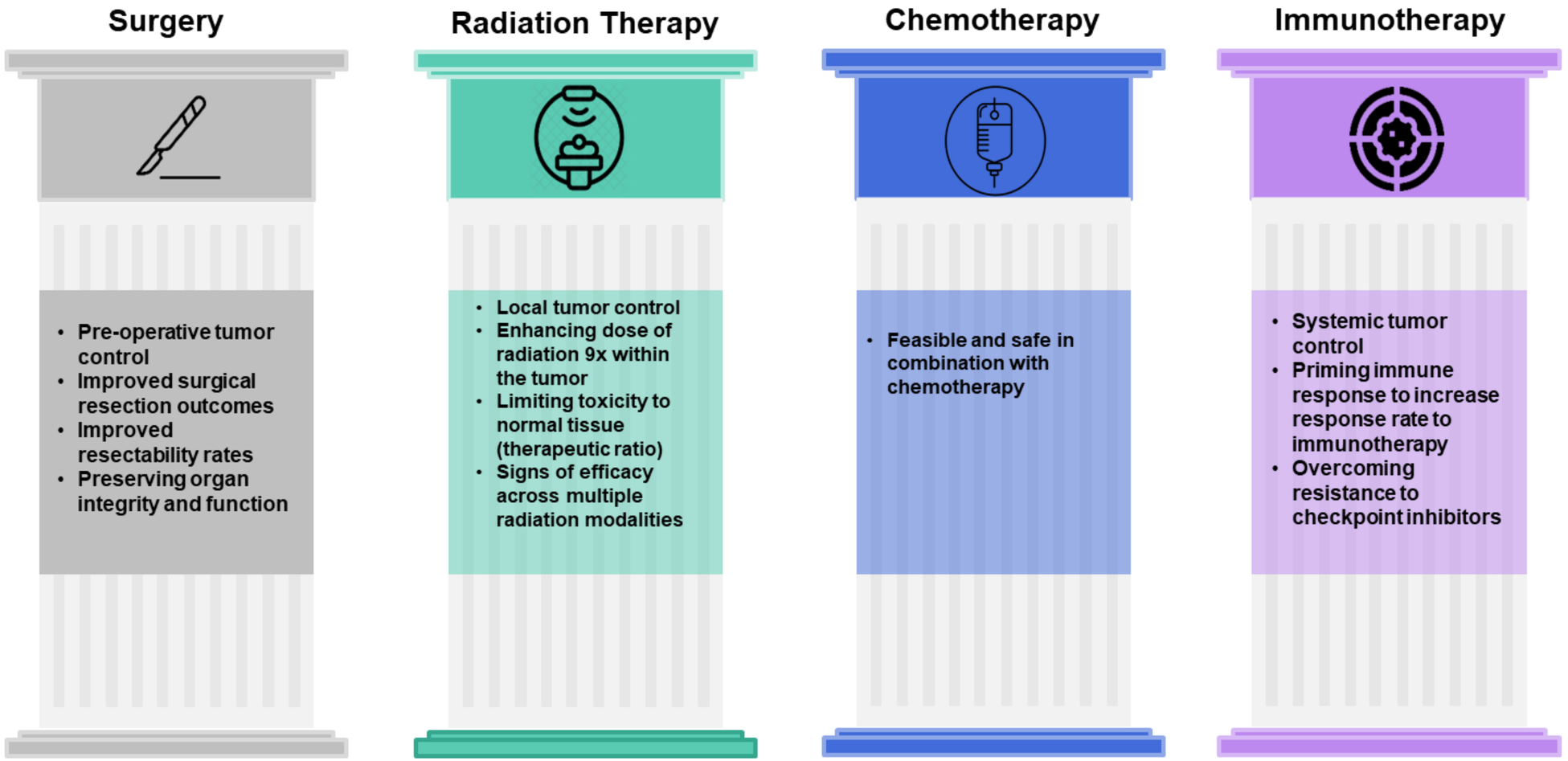

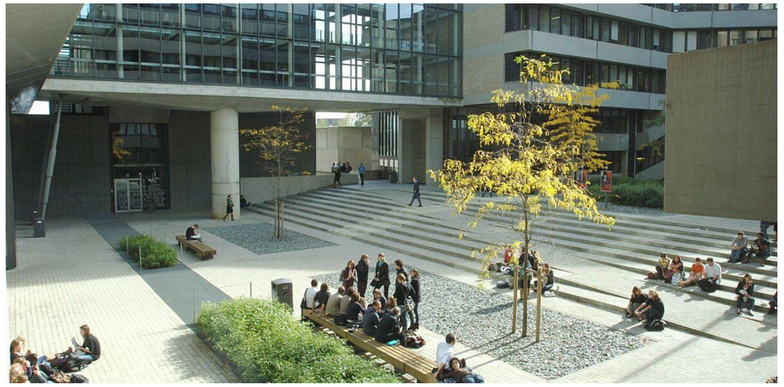

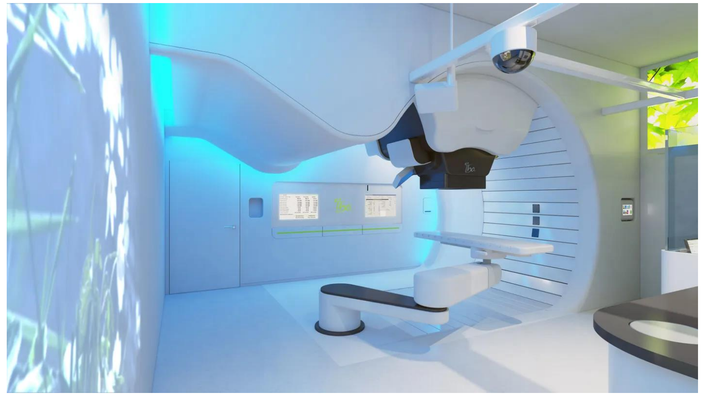


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