International Network for Sinonasal Cancer Research (INSICA): A Collaborative Group to Advance Research and Clinical Trials for Rare Sinonasal Malignancies

Nyall R. London Jr., MD PhD[1-4*], Glenn J. Hanna, MD[5], Neal S. Akhave, MD[6], Garret Choby, MD[7-8], Lot A. Devriese, MD PhD[9], François R. Ferrand, MD[10], Gary L. Gallia MD PhD[2-4], Lifeng Li, MD[11], Antoine Moya-Plana, MD PhD[12], Umar Rehman, BMBS[13], Teppei Takeda, MD PhD[14], Juliette Thariat, MD PhD[15], Robbie S. R. Woods, MD[16], Benjamin Verillaud, MD PhD[17], Matt Lechner, MD PhD[13*]

Affiliations:

[1]Sinonasal and Skull Base Tumor Section, Surgical Oncology Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health; Bethesda, MD, USA

[2]Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine; Baltimore, MD, USA

[3]Department of Neurosurgery, Johns Hopkins University School of Medicine; Baltimore, MD, USA

[4]Department of Oncology, Johns Hopkins University School of Medicine; Baltimore, MD, USA

[5]Center for Head and Neck Oncology, Dana-Farber Cancer Institute; Boston, MA, USA

[6]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center; Houston, TX, USA

[7]Department of Otolaryngology – Head and Neck Surgery, University of Pittsburgh Medical Center; Pittsburgh, PA, USA

[8]Department of Neurological Surgery, University of Pittsburgh Medical Center; Pittsburgh, PA, USA

[9]Division of Imaging & Oncology, Department of Medical Oncology, University Medical Center Utrecht, The Netherlands

[10]Department of Head and Neck Oncology, Gustave Roussy – Cancer Campus, 94805 Villejuif, France

[11]Department of Otolaryngology-Head and Neck Surgery, Beijing Tongren Hospital, Capital Medical University; Beijing, China

[12]Head Neck and Skull Base Surgery Department, Gustave Roussy Cancer Center – Paris Saclay University, Villejuif, France

[13]Division of Surgery and Interventional Science & UCL Cancer Institute, University College London, Charles Bell House,
43-45 Foley Street, London, W1W 7TS, United Kingdom

[14]Department of Otorhinolaryngology, The Jikei University School of Medicine, Tokyo, Japan

[15]Centre François Baclesse, Department of Radiation Oncology, Caen, Unicaen, France; Laboratoire de physique corpusculaire IN2P3/ENSICAEN, UMR6534, Unicaen, France

[16]Department of Otolaryngology-Head and Neck Surgery, Beaumont Hospital & Royal College of Surgeons in Ireland; Dublin, Ireland

[17]Department of Otolaryngology-Head and Neck Surgery, Lariboisière Hospital, Inserm U1141, Université Paris Cité; Paris, France

*These authors contributed equally as senior corresponding authors

Corresponding author:

Nyall R. London Jr., M.D., Ph.D., F.A.C.S.
Principal Investigator - Sinonasal and Skull Base Tumor Section
Surgical Oncology Program (SOP), Center for Cancer Research (CCR)
National Cancer Institute (NCI), National Institutes of Health (NIH)
Johns Hopkins University School of Medicine
Associate Professor of Otolaryngology – Head and Neck Surgery
INSICA President (2024-2026)
Email: nyall.london@nih.gov; nlondon2@jhmi.edu; Phone: +1-301-402-4216

Funding: This research was supported (in part) by the Intramural Research Program of the NIH, Center for Cancer Research, National Cancer Institute (NRL). This research was supported [in part] by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH author(s) were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered Works of the United States Government. However, the findings and conclusions presented in this paper are those of the author(s) and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services. This research was supported in part by the Head and Neck Cancer Research Fund (ML). The funders had no role in the design of the study; the collection, analysis, or interpretation of the data; or the writing of the manuscript. Manuscript clearance for peer review submission was obtained from the Intramural Research Program of the NIH.

Conflicts of Interest

N. London received research funding from Merck Sharp & Dohme, LLC regarding HPV-associated sinonasal carcinomas. G. J. Hanna receives research support to institution and

advisory/consulting fees from Coherus. M. Lechner received academic funding and university support for SSTR2 related research and serves as Pan-Cancer and Molecular Oncology Co-lead for Genomics England. All other authors declare no competing interests.

Data availability: There was no data generated or analyzed in this manuscript.

Abstract

Development of evidence-based treatment recommendations for rare cancers is challenging due to limited funding opportunities, spread of small numbers of patients across multiple institutions, and other obstacles. Malignancies of the sinonasal cavity are particularly rare with an overall incidence of approximately 0.56 cases per 100,000 population per year. Additionally, clinical behavior varies with a reported 5-year overall survival rate ranging from 22% - 67%. Here we describe our initial efforts including formation of an international network dedicated to sinonasal cancer research and highlight keys for successful study of rare tumors. This network first began with large multi-institutional retrospective collaborations of rare sinonasal tumors leading to improvements in staging for olfactory neuroblastoma and sinonasal melanoma. These efforts have been followed by a new emphasis on development of collaborative interventional trials as well as the development of position statements and recommendations to guide use of emerging molecularly targeted therapies. In order to be successful in studying rare malignancies, collaboration and teamwork is key along with an unrelenting drive for development of evidence to help guide treatment for rare cancers. This manuscript serves as an outline that may be applied by other interested groups to improve the study of other tumors in the human body.

Introduction

Sinonasal cancers arise from the nasal cavity and paranasal sinuses and comprise a wide spectrum of distinct histopathologic entities[1]. Diagnosis can be challenging due to the rare nature of these tumors and overlapping histopathological features, frequently leading to misdiagnosis which can result in poorer patient outcomes[2]. The most common sinonasal malignancy at 51.6% is sinonasal squamous cell carcinoma (SNSCC)[3]. Other sinonasal cancers include adenocarcinoma (12.6%), melanoma (6.6%), olfactory neuroblastoma (6.3%), and adenoid cystic carcinoma (6.2%)[3]. The clinical behavior of these malignancies varies with a 5-year overall survival rate ranging from 22% - 67%[3]. These tumors may invade the orbit, brain, and cranial nerves leading to numbness, visual changes, and other negative consequences on patients. Treatment strategies including surgery, radiation, and chemotherapy can also have lasting morbidity and treatment effects and may impact sense of smell, taste, and vision[3]. These rare tumors are best treated at high-volume centers with experienced multi-disciplinary teams[4,5]. Molecular advances and the discovery of actionable targets are actively transforming both diagnostic and therapeutic approaches for sinonasal malignancies[6]. Examples of recent molecular advances include the identification of frequent isocitrate dehydrogenase-2 (*IDH2*) activating mutations in sinonasal undifferentiated carcinoma (SNUC), characterization of a subset of aggressive sinonasal tumors deficient in SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily B, Member 1 (SMARCB1), and determining the biologic significance of the human papillomavirus (HPV) and actionable targets in HPV-associated sinonasal squamous cell carcinoma (HPV-associated SNSCC)[7-10].

Translational and clinical research are accelerated when working together, and multi-institutional and international collaborations are essential to make evidence-based advances for

rare malignancies such as sinonasal cancers. The starting key is innovation, teamwork, and an unrelenting drive for evidence-based advances in our field. These collaborative efforts can take many forms including retrospective and prospective case series, evidence-based treatment recommendations, interventional clinical trials, multi-institution translational studies, collaboration with patient organizations, and others. Many barriers and hurdles exist for conducting translational and clinical research for sinonasal malignancies. Firstly, due to the rare nature of these tumors, patient recruitment for clinical trials or for obtaining tumor tissue for research studies can be challenging. There may also be less research funding available for rare tumors compared to more frequently observed cancers. Both these challenges impact our ability to create *in vitro* and *in vivo* models to study sinonasal malignancies, which models are sorely lacking for this field. Significant tumor heterogeneity can also make treatment advances difficult as each tumor type may respond differently to each treatment strategy. Regulatory hurdles can also present additional challenges. Collectively, these barriers and hurdles underscore the importance of collaboration and teamwork, particularly when it comes to rare cancers such as sinonasal malignancies. Some potential solutions to these challenges include the formation of multi-institutional networks of interested physicians and scientists, the formation of centralized databases or tissue collection, and patient advocacy groups to help increase awareness.

Here, we describe the initial contributions of the International Network for Sinonasal Cancer Research (INSICA) and the goal of establishing a network for multi-institutional, international, interventional clinical trials for patients with sinonasal cancers. Our ultimate goal is to inspire collaborative efforts to collectively achieve evidence-based advances for rare sinonasal malignancies.

Initial contributions

The International Network for Sinonasal Cancer Research was initially founded in 2019 with a primary objective of facilitating large multi-institutional international collaborative retrospective studies. INSICA is led by a steering group (insica.org/about-us), and annual meetings have been held since 2022 combined with the European Network for Sinonasal Cancer Research (EUSICA)[11] in Madrid, Copenhagen[12], London, and Paris with the 2026 annual meeting planned for Bethesda, Maryland. The first study arising from INSICA collaborative efforts included 12 institutions from the United States, United Kingdom, and Europe and amassed clinical data from 404 patients with olfactory neuroblastoma (ONB), by far the largest retrospective study for this rare sinonasal malignancy[13]. Importantly, harnessing the power of these large numbers, this study showed the limitations of the currently used Kadish staging system, identified dural infiltration as a strong prognostic factor, developed an updated staging system (Kadish-INSICA), and provided stage-specific management recommendations. Furthermore, this study investigated the potential role of targeting Somatostatin receptor 2 (SSTR2), which is highly expressed in the majority of ONB and EBV-associated nasopharyngeal cancer and targetable with lutetium Lu 177 dotatate[14]. This form of peptide receptor radionuclide therapy (PRRT) showed potential efficacy against recurrent/metastatic ONB in a basket trial including 3 ONB patients reported as part of this study[13]. This was followed up by a large multi-institutional, international, retrospective collaboration including 505 patients with sinonasal melanoma and demonstrated survival benefit for patients treated with immune checkpoint inhibition and recommended modifications to the current TNM staging system[14]. Additional ongoing efforts are similarly aimed at SNUC, intestinal-type adenocarcinoma (ITAC) and SNSCC[15]. These initial INSICA efforts highlight the value and importance of multi-institutional collaborative studies for advancing evidence-based management of rare sinonasal tumors.

Establishment of a multi-institutional, international, clinical trial network

Development of evidence through interventional clinical trials is essential to guide treatment strategies and improve treatment options for our patients. However, there are many barriers to completion of successful trials including low patient volume for rare tumors, trial design flaws, funding, clinical trial staff support and turnover, collection and processing of patient specimens and patient-reported outcomes, challenges in obtaining the intervention of interest, and regulatory challenges that need to be considered. Prospective trials carry many advantages beyond assessing efficacy of the treatment of interest and are a stronger level of evidence than retrospective series. Scientific and clinical correlatives are a critical aspect of clinical trials and improve the investigators' ability to determine mechanisms of action and factors predicting disease response in a prospective manner. As sinonasal tumor patients are rare, it is important to carefully consider and design trials as there are a limited number of opportunities. Inclusion of multiple institutions and international institutions is also helpful as this assists in generating results that are broadly applicable across multiple centers. Physicians face challenges when confronted with patients that have failed standard treatments and are in dire need of alternatives. With the advent of genomics and molecular analyses, therapeutic targets can be identified and targeted therapy offered to some patients with recurrent or metastatic disease who have failed standard treatment approaches. However, we need to work together to develop collaborative prospective trials to evaluate these molecularly targeted therapies and develop evidence-based recommendations supported by larger patient cohorts rather than single patient case reports. While few interventional trials specifically for sinonasal malignancies have been reported, several have been completed or are currently in process (**Table 1-2**)[16-18].

On April 12, 2025, the INSICA group held the first international clinical trial planning meeting at L'Hôpital Lariboisière in Paris, France. The clinical trial planning meeting was led by Nyall R. London and Glenn J. Hanna with participating members also including Neal S. Akhave, Lot Devriese, François R. Ferrand, Gary L. Gallia, Lifeng Li, Antoine Moya-Plana, Teppei Takeda, Juliette Thariat, Benjamin Verillaud, Robbie S. R. Woods, and Matt Lechner (**Figure 1**). These members included specialists from Otolaryngology, Medical Oncology, Radiation Oncology, and Neurosurgery. The meeting was preceded by submission of trial ideas by attendees and selection of clinical trial proposals and consensus recommendations to discuss. The methodology for selection included trial design that was achievable to springboard towards future success, prioritization of trials focused on molecularly actionable subgroups or strong biomarker rationale, avoidance of overlap with currently ongoing trials, and commencing with the recurrent/metastatic patient population. The following topics include the main areas discussed.

Inverted papilloma-related sinonasal squamous cell carcinoma (IP-SNSCC) is commonly characterized by Epidermal Growth Factor Receptor (EGFR) exon 20 activation mutations in ~77% of cases[19-21]. Previous studies using irreversible small molecule inhibitors targeting EGFR exon 20 activating mutations have demonstrated efficacy *in vitro*[20]. A common challenge with targeted therapy is the tumor acquiring escape mechanisms to circumvent targeted pathway inhibition leading to persistent tumor growth. One potential option discussed for targeting IP-SNSCC is Amivantamab (**Table 3**). This is a bifunctional antibody targeting both EGFR as well as c-MET which acts to block a potential downstream escape pathway[22]. We would recommend assessing efficacy of Amivantamab or other similar compounds in available *in vitro* models of IP-SNSCC with known EGFR exon 20 mutations[20,23]. These tumors are very rare, thus multi-institutional collaboration will be necessary to achieve adequate patient numbers to determine

whether EGFR blockade in IP-SNSCC demonstrates efficacy. One could consider utilizing this approach in a neo-adjuvant rather than recurrent/metastatic setting. However, a small proportion of IP-SNSCC are associated with low-risk human papillomavirus (HPV) without EGFR exon 20 mutations, and diagnostic confirmation of IP-SNSCC on a biopsy specimen alone can be difficult, and many times is only made after surgical resection[19]. For these reasons and other challenges the group recommended commencing with a recurrent/metastatic setting for this tumor type.

A rising proportion of SNSCC have been found to be associated with high-risk HPV[24,25]. A key mechanism of tumorigenesis in HPV-driven head and neck cancer is the PI3K/AKT/mTOR pathway with characteristic hotspot mutations in PI3K having been identified particularly at E542K or E545K. Importantly, a recent study demonstrated that HPV can drive SNSCC and does not act as a neutral bystander in the sinonasal cavity[10]. PI3K hotspot mutations were noted in HPV-associated SNSCC and combination PI3K and transcriptional enhanced associate domain (TEAD) inhibition demonstrated synergistic reduction in colony formation. The clinical trial planning group therefore discussed the potential of first targeting PI3K alone in HPV-associated SNSCC with PI3K small molecule inhibitors demonstrating efficacy in pre-clinical models of head and neck cancer as well as SNSCC[10,26].

Immune checkpoint blockade has demonstrated efficacy in head and neck cancer as well as nasopharyngeal carcinoma[27-29]. However, the efficacy of immune checkpoint blockade in sinonasal cancers has only been investigated in small cohorts[30,31]. Multiple studies have been performed investigating the tumor immune microenvironment of many sinonasal malignancies including SNSCC, SNUC, and ONB[32-37]. The clinical trial planning group also discussed investigating the impact of immune checkpoint blockade in sinonasal cancer in a multi-institutional manner to accrue sufficient patient numbers to obtain a higher level of evidence

evaluating the efficacy of immune checkpoint blockade. The group concluded that it would be best to first start with tumors with a PD-L1 combined positive score ≥ 1. Many immune checkpoint options are available but given findings in other clinical trials the group suggested utilization of PD-1 inhibition as the initial point of investigation. Use of immune checkpoint blockade may also be an important treatment strategy in the neoadjuvant setting with several trials ongoing (**Table 2**).

Another potential targetable sinonasal malignancy discussed was SWI/SNF related BAF chromatin remodeling complex subunit B1 (SMARCB1)-deficient sinonasal carcinoma. These tumors often present at an advanced stage with a poor clinical prognosis. Loss of SMARCB1 is known to lead to epigenetic dysregulation and chromatin remodeling. It has been hypothesized that inhibition of enhancer of Zeste homolog 2 (EZH2), a histone methyltransferase, may be able to reverse this epigenetic dysregulation. Thus there has been interest in the use of an EZH2 inhibitor such as tazemetostat, which has shown efficacy in patients with epitheloid sarcoma[38-40]. However, pre-clinical evaluation of this approach in SMARCB1-deficient sinonasal carcinoma haven't yet been feasible due to a lack of available pre-clinical models. Another strategy discussed was the combination of EZH2 inhibition with immune checkpoint blockade. Indeed, there is an ongoing clinical trial exploring the combination of EZH2 inhibition with immune checkpoint blockade (NCT05407441). The clinical trial planning group therefore discussed the possibility of performing a similar interventional clinical trial with combinatorial EZH2 inhibition and immune checkpoint blockade for SMARCB1-deficient sinonasal carcinoma.

ONB is a rare malignancy of the olfactory epithelium. Approximately 80% of ONB cases express somatostatin receptor subtype 2 (SSTR2), enabling targeted treatment using peptide receptor radionuclide therapy (PRRT)[13]. ^{177}Lu-DOTATATE (Lutathera®), a radiolabelled somatostatin analogue, is approved for gastroenteropancreatic neuroendocrine tumours and has

demonstrated off-label efficacy in ONB based on case reports and small case series[13,41]. The INSICA group recommends considering ^{177}Lu-DOTATATE in patients with histologically confirmed ONB and documented SSTR2 expression on ^{68}Ga-DOTATATE PET/CT and/or immunohistochemistry, particularly in those with locally recurrent or metastatic disease classified as Kadish-INSICA stage DM that have failed standard of care treatment strategies. It was acknowledged that further multicenter trials on PRRT for ONB will be very challenging to perform for such a rare disease across multiple sites for a variety of reasons. However, evidence from the use in other disease types, results from basket trials and results from multicenter cohort studies were reviewed for Kadish-INSICA DM and a position statement outlining the recommendations of INSICA regarding the use of SSTR2-targeted PRRT/^{177}Lu-DOTATATE in the treatment of ONB was created and reviewed as part of the clinical trial planning meeting (**Supplemental Materials**). Key recommendations include: (1) patient management within a specialized tumor board (multidisciplinary team) with access to nuclear medicine expertise; (2) SSTR2 status assessment to guide PRRT eligibility; (3) pre-treatment renal and haematological evaluation to ensure adequate physiological reserve; (4) use of renal protection protocols during ^{177}Lu-DOTATATE administration; and (5) informed consent regarding off-label use.

Given the rarity of ONB, randomized clinical trial data on ONB specifically are unlikely to evolve and data from a basket trial support its use. Thus, INSICA advocates its use for locally recurrent or Kadish-INSICA DM disease that has failed standard of care treatment options and advocates centers to use the standardized protocol outlined in this statement (**Supplemental Materials**). This allows for the monitoring of clinical practice and clinical outcomes through standardization and centers are encouraged to prospectively collect outcome data on the use of PRRT/^{177}Lu-DOTATATE therapy for ONB at their respective institutions, under existing or newly

established IRB protocols. Centers may want to assess molecular changes that may occur following treatment with ^{177}Lu-DOTATATE which may also help in identifying potential combinatorial treatment options. All this will allow for refining therapeutic strategies and guidelines for PRRT use in ONB in the future.

We also encourage members and supporters of INSICA to prospectively collect clinical data and patient-reported outcome measures of all treated sinonasal cancers at their respective institutions, under existing or newly established IRB protocols. This shall also include the collection of clinical outcome data on the use of PRRT/^{177}Lu-DOTATATE therapy from ONB patients, who were treated according to the recommendations outlined in the Position Statement (**Supplemental Materials**) and from patients who were treated with targeted therapeutic agents based on molecular profiling and/or immunotherapy approaches.

Conclusions

Collaborative work is necessary to create evidence upon which the field can draw to guide treatment recommendations and improve patient outcomes for our patients with sinonasal malignancies. Here we described initial efforts to advance evidence through large multi-institutional collaborations. This has been followed by a new emphasis on development of collaborative interventional trials as well as the development of recommendations to guide use of emerging molecularly targeted therapies. We invite all interested members of the scientific community with an interest in this challenging field of research to join us and engage in this highly interesting field.

Acknowledgements

We would like to acknowledge and thank Ehab Hanna, Mario Hermsen, Peter Hwang, Dame Valerie J. Lund, and Christian von Buchwald for important guidance and mentorship. The authors would also like to acknowledge all the speakers and attendees at prior INSICA annual meetings for their engagement making these meetings a success as well as the many colleagues and friends who have supported INSICA initiatives and our multi-center work. We would like to also thank the many organizations who have given us an opportunity to present our initiatives through panel and talk invitations at meetings throughout the world. We would also like to acknowledge the invaluable support by the Head and Neck Cancer Research Trust and Dr. Amie Mertens (Chair of Trustees). This research was supported (in part) by the Intramural Research Program of the NIH, Center for Cancer Research, National Cancer Institute (NRL). This research was supported [in part] by the Intramural Research Program of the National Institutes of Health (NIH). The contributions of the NIH author(s) were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered Works of the United States Government. However, the findings and conclusions presented in this paper are those of the author(s) and do not necessarily reflect the views of the NIH or the U.S. Department of Health and Human Services. This research was supported in part by the Head and Neck Cancer Research Fund (ML). The funders had no role in the design of the study; the collection, analysis, or interpretation of the data; or the writing of the manuscript. Manuscript clearance for peer review submission was obtained from the Intramural Research Program of the NIH.

Table 1. Completed sinonasal malignancy-specific prospective interventional clinical trials of at least 10 patients

Name	Single or Multi-Institution	Tumor Type	Treatment of Interest	Results Summary
Phase 2 trial of induction chemotherapy for advanced sinonasal squamous cell carcinoma NCT00707473[16]	Single	Advanced SNSCC	Induction chemotherapy (docetaxel, cisplatin, 5-fluorouracil) with response directed chemoradiotherapy in responders and surgery with adjuvant radiation/chemoradiation in non-responders	1. Improved rates of organ preservation 2. No difference in overall survival
SINTART 1 NCT02099175[18]	Multi-institution	Resectable SNSCC, ITAC, SNUC, sinonasal neuroendocrine or small cell carcinoma, high grade ONB	Multi-modality treatment	1. 5-year progression free survival of 38% 2. Induction chemotherapy may select patients with favorable prognosis particularly SNUC
SINTART 2 NCT02099188[17]	Multi-institution	Unresectable SNSCC, ITAC, SNUC, sinonasal neuroendocrine or small cell carcinoma, high grade ONB	Multi-modality treatment	1. 5-year progression free survival of 26.8%
Phase 2 study of Bintrafusp Alfa in recurrent/metastatic olfactory neuroblastoma (BARON) NCT05012098	Single	Recurrent/metastatic ONB	Bintrafusp Alfa (Bifunctional blockade of PD-L1 and TGF-β)	Not yet reported

Table 2. Ongoing sinonasal malignancy-specific prospective interventional clinical trials of at least 10 patients

Name	Single or Multi-Institution	Tumor Type	Treatment of Interest	Trial Status
Enasidenib in IDH2-mutated malignant sinonasal and skull base tumors NCT06176989	Single	IDH2-mutated sinonasal and skull base tumors	Enasidenib (Small molecule inhibition of mutated IDH2)	Recruiting
PERI-SINO, Perioperative Chemoimmunotherapy with Toripalimab for Sinonasal Cancer NCT06940180	Single	Sinonasal SCC and SNUC	Chemoimmunotherapy prior to resection to assess pathologic response; followed by post-operative RT with immunotherapy or CRT	Recruiting
SANTAL (GORTEC 2016-02) Phase III Randomized Study of Chemo-radiotherapy Versus Radiotherapy Alone in the Adjuvant Treatment of Salivary Glands and Sinonasal Tumors NCT02998385	Multi-institution (France and Belgium)	Sinonasal non-squamous cell carcinomas	Concomitant cisplatin	Active, not recruiting
SinocaRT: Phase II Study of Intensity Modulated Radiotherapy in Dose Painting for Sinus Carcinomas After Endoscopic Surgery NCT05943119	Multi-institution (France)	Sinonasal carcinomas	Radiotherapy in painting dose on histoscannographic mapping	Recruiting
SNaC2 Study: Neoadjuvant Cemiplimab and Chemotherapy in Sinonasal Squamous Cell Carcinoma: A Phase 2 Trial ETCTN P10721 (NCT pending)	Multi-institution (NCI)	Sinonasal SCC	Two-arm randomized controlled trial of neoadjuvant chemotherapy vs. immunochemotherapy (cemiplimab); radiographic and pathologic response; followed by surgery + adjuvant therapy vs. definitive chemoradiotherapy	Approved; recruiting pending

I-NAPA study: Immunotherapy with chemotherapy and chemoradiation for advanced squamous cell cancer of nasal cavity/paranasal sinus NCT05027633	Single	Sinonasal SCC	Induction chemotherapy (cisplatin, docetaxel) with pembrolizumab with response directed chemoimmunoradiotherapy in responders and surgery with adjuvant radiation/chemoradiation in non-responders	Active, recruiting
Stereotactic Radiotherapy for Sinonasal Malignancy NCT06617910	Single	Sinonasal malignancies	Treatment outcomes and dosimetric analysis comparison between CyberKnife and volumetric modulated arc therapy based methods of stereotactic radiotherapy for sinonasal malignancy	Active, not recruiting
NeoScorch HN: Neoadjuvant Chemotherapy and Programmed Cell Death Protein 1(PD-1) Inhibition for Head and Neck Cancer Treatment De-escalation NCT07209189	Single	Advanced sinonasal malignancies	Neoadjuvant chemoimmunotherapy for advanced sinonasal malignancies	Approved; recruiting pending
Intensity-Modulated or Proton Radiation Therapy for Sinonasal Malignancy NCT01586767	Multi-institution (USA)	Advanced sinonasal malignancies	Intensity-modulated radiotherapy versus proton beam radiation for sinonasal malignancies	Active, not recruiting
PRISAM: Pre-Operative Radiotherapy and Immunotherapy for Sinonasal and Anorectal Melanoma NCT05546827	Single	Sinonasal melanoma	Pre-operative radiation therapy after starting immune checkpoint inhibition for sinonasal melanoma	Active, recruiting

Table 3. Proposed areas for intervention

Molecular target or disease subgroup	Potential intervention options
IP-SNSCC with EGFR exon 20 activation mutations	EGFR exon 20 inhibitor

SMARCB1-deficient sinonasal carcinoma	EZH2 inhibitor combined with immune checkpoint blockade
PD-L1 CPS ≥ 1	Immune checkpoint blockade
HPV-associated sinonasal carcinomas	PI3K inhibitor
ONB with SSTR2 expression	PRRT
Sinonasal adenocarcinoma and other sinonasal cancers	MEK inhibition

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331 **Figure Legends**

332 **Figure 1.** Map of participants' home institution (red star) in the clinical trial planning meeting.

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