Journal of the National Comprehensive Cancer Network

The goal of the Highlights of the NCCN Oncology Research Program (ORP) is to provide readers with more information on the ORP, including studies currently accruing patients.

For more information on specific trials, including patient selection criteria, please use the contact information listed with each study.

For more information on the NCCN ORP, including a complete detailing of the clinical studies currently underway at NCCN Member Institutions, please access the NCCN ORP pages at NCCN.org/clinical_trials/clinicians.asp.

## Highlights of the NCCN Oncology Research Program

The NCCN Oncology Research Program (ORP) strives to improve the quality of life for patients and reduce cancer-related deaths by advancing cancer therapies through research. Since the program's establishment in 1999, the NCCN ORP has brought millions of dollars in research grants to investigators at NCCN Member Institutions. Research grants are provided to NCCN through collaborations with pharmaceutical and biotechnology companies; these grants are in turn used to support scientifically meritorious cancer research efforts.

NCCN ORP studies typically explore new avenues of clinical investigation and seek answers to important cancer-related questions. All studies are approved and funded through a scientific peer-review process and are overseen by the ORP.

An NCCN study funded through the grant mechanism is highlighted below.

## Multicenter Phase II Study of Nintedanib for Patients With Advanced Carcinoid Tumors

**Principal Investigator:** Renuka Iyer, MD

**Conditions:** Carcinoid, metastatic carcinoid, and neuroendocrine tumors

**Institution:** Roswell Park Cancer Institute

**Participating Institution:** The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute

This is an open-label, multicenter phase II study in all patients with advanced low- and intermediate-grade neuroendocrine tumors (NETs), excluding pancreatic NETs. NETs, also known as carcinoids, are uncommon tumors arising from various primary sites. Although thought to be rare, the incidence of NETs is increasing. Nearly 50% of patients with NETs have metastatic disease at presentation, and 65% will die within 5 years of diagnosis. Carcinoids are generally slow-growing tumors, but in the advanced setting can be very disabling and can impact quality of life (QOL) due to diarrhea, bowel obstructions, pain, weight loss, depression, and fatigue. Many of the abdominal symptoms are caused by the dense adhesions. Midgut carcinoids often secrete serotonin that acts synergistically with platelet-derived growth factor (PDGF) and stimulates DNA synthesis in fibroblasts acting through 5-HT1B receptors coupled to a Gi-protein. This may partly explain the dense fibrotic reaction seen in small bowel carcinoids, and subsequent obstructive symptoms. Carcinoids are highly vascular, and vascular endothelial growth factors, (VEGFs), PDGFs, and fibroblast growth factors (FGFs) are all also thought to drive disease, with the additional serotonin-mediated fibroblast proliferation driving symptom progression.

Nintedanib (BIBF1120) is a potent, orally available triple kinase inhibitor targeting VEGF receptors, PDGF receptors, and FGF receptors. Therapy will consist of nintedanib (BIBF1120), 200 mg orally twice daily, plus octreotide (or lanreotide) administered every 4 weeks. Patients with progressing metastatic carcinoid tumors have no approved options and are a population with a clear unmet need. Targeting angiogenesis and mTOR pathways has been shown to improve outcomes in patients with pancreatic NETs, but has not proven to be beneficial in carcinoids. Studies suggest, however, that a subset of patients with carcinoid tumors may be sensitive to these therapies. Therapy is palliative and intended to improve QOL.

**Primary Objective:**

- Assess progression-free survival, defined as the interval from initiation of therapy to its cessation due to documentation of progressive disease or death

**Secondary Objectives:**

- Assess the clinical response (complete response + partial response) in all patients with measurable disease (using standard RECISTv1.1 criteria)
- Assess overall survival in all patients
- Assess changes in QOL throughout treatment, using the EORTC QLQ – GI.NET21 questionnaire for patients with gastrointestinal NETs, in all patients who have filled out at least 2 QOL questionnaires and will be reported by groups based on response (response, stable disease, or progressive disease)
- Analyze steady-state pharmacokinetics of nintedanib, biomarkers, regulatory T cells, and cytokine expression and growth factors in all patients, and report results in groups based on response
- Analyze gene mutations and copy number alterations in the mTOR pathway (will be performed only on the first 10 patients at MSKCC) and protein expression of activation of Akt (as well as other downstream targets)
- Closely monitor and tabulate all toxicities (graded using the NCI Common Terminology Criteria for Adverse Events, version 4.0)

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**ClinicalTrials.gov Identifier:** NCT02399215