at a glance™

Of Note: ***Nuvectis is developing two precision cancer drug candidates (NXP800 and NXP900), initially for ovarian and gastric cancer (NXP800) and esophageal neck and head & cancer (NXP900); initial data flow from current Phase 1b trial of NXP800 expected by YE 2023. CEO Ron Bentsur previously led Keryx and UroGen to market caps of $2.2 billion and $1.1 billion, respectively.***

Key Considerations

- **Nuvectis is developing two drug candidates designed to inhibit key pro-cancer pathways with precision targeting.**
- **NXP800 targets a key defense mechanism that allows cancer cells to grow and flourish (HSF1 pathway). Current testing is focused on two sub-types of ovarian cancer of unmet medical need -- clear cell and endometrioid carcinomas and gastric cancer, also an unmet medical need.**
- **Data from an ongoing open label Phase 1b trial of NXP800 ARID1A-mutated ovarian cancer is expected by YE.**
- **Work continues to investigate the utility of NXP800 in other cancers such as esophageal, uterine endometrioid, urothelial, and pancreatic.**
- **NXP900 is the first small molecule shown to shut down both components (catalytic and scaffolding domains) of the SRC/YES1 kinase, a key signaling pathway that drives growth of various cancers.**
- **The initial target indications for NXP900 are esophageal and head and neck cancers. Additional indications based on potential sensitivity predictors such as YES1 gene amplification are being evaluated.**
- **Nuvectis expects IND acceptance of NXP900 in May/June and to commence human trial shortly thereafter.**
- **The NXP800 molecule was discovered and optimized by The Institute of Cancer Research (ICR) in England, the UK equivalent of America's National Cancer Institute. ICR also discovered Zytiga®, a leading drug for metastatic prostate cancer that generated more than $3 billion in annual sales before going generic.**

Nuvectis Pharma, Inc.

(Nasdaq: NVCT)

52-Wk Range:	**$3.08-20.92**
Recent Price:	**$14.74**
Shares O/S:	**14.75 Million**
Approx. Mkt Cap:	**$217 Million**
Fiscal Year Ends:	**Dec. 31**

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- **NXP900 was licensed from the University of Edinburgh in Scotland.**
- **A recent study published in Nature Communication by researchers at AstraZeneca suggests a potential utility for NXP900 as a combination therapy with AstraZeneca's blockbuster lung cancer drug, Tagrisso®. This represents independent validation for the potential of NXP900 in non-small cell lung cancer provided by the #1 player in the field, AstraZeneca.**
- **Nuvectis CEO Ron Bentsur previously held the CEO posts at Keryx and UroGen, leading those two companies to market caps of $2.2 billion and $1.1 billion, respectively. He and the Nuvectis management team have been responsible for four US FDA drug approvals, two European Union EMA approvals and a Japanese approval.**

Overview

The most commonly known medical treatments for cancer, namely chemotherapy treatments, are non-specific treatments, resulting in limited utility in specific cancers that require a targeted approach. Nuvectis is among a handful of cancer companies developing precision/targeted therapy medicines -- drugs that consider differences in peoples' genetic backgrounds and disease.

In cancer, precision drugs aim to target the unique features of a patient's cancer – notable are drugs that zero in on aberrant genes associated with pro cancer mechanisms that either upregulate the activity of cancer cells or control their defenders.

The move towards precision medicine is no longer the sole domain of large pharma. Smaller companies, witness Nuvectis and several others, are moving rapidly to field new science and novel approaches. There are numerous precision medicine/targeted therapy drug approvals in oncology that have occurred in the last ~10 years, so this is a proven approach.

Recent & Anticipated Milestones

-2Q22 – Reported positive pre-clinical data on NXP900 at American Association of Cancer Research Conference in New Orleans (April)

-2Q22 – FDA cleared US IND for NXP800 (June)

-4Q22 – Fast track designation granted by FDA for NXP800 in ARID1A-mutated ovarian cancer

-2Q23 – Initiated NXP800 Ph. 1b study in ARID1A-mutated ovarian cancer

-2Q23 – NXP900 IND acceptance by the FDA-enabling studies and file IND

-2Q23 – Initiate NXP900 Ph.1a dose escalation study

NXP800 is designed to shut down the HSF1 pathway, a major cancer defense mechanism, initially in patients with two sub-types of ovarian cancer and gastric cancer.

NXP900 employs precision targeting to preferentially shut down SRC/YES1 kinases, two kinases with pro-cancer activity driving tumor growth and metastases in various cancers.

Additional News - NXP900

Researchers at AstraZeneca last year published a paper in Nature Communication showing that the combination of NXP900 and Tagrisso® (Osimertinib) overcomes resistance to Tagrisso in non-small cell lung cancer (NSCLC) cells.

This represents significant, independent, and unsolicited validation of NXP900 (referred to as ECF-506 in the publication) from AstraZeneca which markets Tagrisso, the leading EGFR inhibitor with 2021 sales of about $5 billion. Acquired resistance to Tagrisso and other EGFR inhibitors that render them ineffective is a well-known limitation of this class.

About NXP800

NXP800 is a novel molecule that inhibits the Heat Shock Factor One, or HSF1, pathway, a major defense mechanism cancer cells use to promote tumor growth. In bench testing, researchers found that NXP800 possessed solid promise in inhibiting the HSF1 pathway, particularly in patients with the ARID1a gene mutation.

When they moved the program into in vivo animal testing, they quickly observed that two types of ovarian cancer – clear cell and endometrioid carcinomas, as well as gastric cancer—stood out as especially responsive to treatment with NXP800, and especially in cases in which the ARID1a gene was mutated. Ovarian clear cell and ovarian endometroid cancers, which represent unmet medical needs, are the current focus of Phase 1b clinical program. Additional cancer types will be added to the clinical program during 2023 of NXP800.

The Phase1a dose-escalation portion of the NXP800 clinical trial was designed to determine the optimal doses to take forward. The Phase 1b portion, initiated in April 2023, is designed for safety and efficacy signals.

The company believes that NXP800, which was granted Fast Track designation by the FDA in December 2022 for ARID1a-mutated ovarian clear cell carcinoma, may be the first drug approved for that indication as well as other cancers of unmet medical need.

According to the American Cancer Society, the US incidence of ovarian cancer is approximately 22,000 new cases a year. Of those, 4,500 are diagnosed as either clear cell or endometrioid. The subset of this group with the ARID1a mutation will provide NXP800 with an initial addressable market of approximately 2,500 patients annually.

Work is underway to potentially expand the indications for NXP800 in other ARID1a mutated cancers. In 3Q22, the company announced positive data for NXP800 in a preclinical xenograft model of ARID1a-mutated gastric carcinoma, another severe unmet medical need. Of the ~26,000 new cases of gastric cancer diagnosed annually, 25 percent harbor the ARID1a mutation.

About NXP900

Nuvectis expanded its portfolio of precision cancer drug candidates by licensing NXP900 from the University of Edinburgh in Scotland.

NXP900 is a novel molecule specifically designed to disrupt and completely shut down SRC-mediated signaling, one of the principal signaling pathways that promotes cancer cell growth and metastases.

NXP900 also potently targets the YES1 kinase, a key member of the SRC kinase family, a feature that is expected to provide additional development opportunities.

Think of the SRC and YES1 kinases as having two domains that are active in pro-cancer signal transduction—a scaffolding domain for receiving and storing cellular messages, and a catalytic domain for sending the messages along, telling the cancer cells what to do.

While several kinase inhibitors that have activity against the catalytic domain of SRC are approved, none are approved due to their anti-SRC activity but rather due to their activity against other targets. These drugs do not inhibit the scaffolding domain of the SRC kinase (i.e., a job half done) and their lack of specificity, in contrast to the highly specific NXP900, results in off-target toxicities such as immune suppression.

Industry analysts put the 2021 market for precision medicines at $66 billion, growing at a compound annual rate of 11.5 percent through 2030. In six years, the market value of precision drugs is expected to top $140 billion.

Nuvectis plans to seek initial indications for NXP900 in esophageal and head and neck cancers, as well as in other solid tumors with YES1 amplification (present in patients with various cancers, such as bladder urothelial cancers).

An IND acceptance by the FDA for clearance to start a Phase 1 clinical trial of NXP900 is expected in 2Q2023.

In vivo studies in xenograft models revealed yet another feature of NXP900 –its ability to cross the blood brain barrier. This finding led clinicians to postulate the potential of NXP900 in treating medulloblastoma, a rare pediatric brain cancer rife with SCR kinase.

In mid-June Nuvectis announced the presentation of positive data from NXP900 in a preclinical model of medulloblastoma, showing that treatment with NXP900 resulted in substantial tumor growth inhibition and a survival benefit vs. control.

If NXP900 is approved for this pediatric indication Nuvectis could be eligible to receive a Priority Review Voucher. The voucher is transferable. Current transactions suggest a value in the $100 million range.

Summary

- **Nuvectis has two precision medicine drug candidates in development, both designed to zero in on specific targets in tumors that are not adequately treated with current therapies.**
- **NXP800, currently in a Phase 1b safety and efficacy signal trial, has been shown to inhibit the HSF1 pathway with particularly high potency in ovarian cancers and gastric cancer with a mutated ARID1a gene, leading to the selection of clear cell and endometrioid ovarian and gastric cancers as the initial target indications for clinical development.**
- **Data releases from the Phase 1b trial of NXP800 are expected by YE 2023.**
- **NXP900 is a unique drug candidate that inhibits both domains of the target kinases (a feature not achievable with other SRC kinase inhibitors). NXP900 has completed the IND-enabling studies and a Phase 1 clinical trial is expected to start in 2Q2023.**
- **Composition of Matter and use patents have been issued in all principal jurisdictions that provide protection for NXP800 and NXP900 into the mid-2030s with extensions envisioned.**
- **Nuvectis CEO Ron Bentsur was previously CEO of Keryx, and UroGen, leading those companies to market caps of $2.2 billion and $1.1 billion, respectively. He and the Nuvectis management team have been responsible for four US and two European drug approvals in the last 10 years.**

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