

APRIL 6, 2017

[SN38 GOES DIRECTLY TO TUMOR](#)

Time to shine, Intezyne: Nanoparticle enters clinic, GRP78 work marching on

By Randy Osborne, Staff Writer

Intezyne Technologies Inc. should find itself “on an IPO trajectory for late 2018 or early 2019,” its chief financial officer (CFO), Russell McAllister, told *BioWorld Today*, “coinciding with potential licensing deals for both” lead candidates owned by the Tampa, Fla.-based company.

He forecast “a lot of interesting things on the financing and licensing fronts,” as the firm raises money privately while gathering data on both candidates that could spark deals.

First-in-human trials have just begun with Intezyne’s topoisomerase-1 inhibitor, IT-141, which encapsulates within a tumor-targeting micelle nanoparticle SN-38, the active metabolite of New York-based Pfizer Inc.’s colorectal cancer drug, Camptosar (irinotecan), and Cambridge, Mass.-based Merrimack Pharmaceuticals Inc.’s Onivyde (liposomal irinotecan) for pancreatic cancer. At the start of the year, Merrimack sold Onivyde along with its generic version of Doxil (liposomal doxorubicin hydrochloride, Janssen Products LP) to Ipsen SA, of Paris, in a potential \$1 billion-plus deal – “quite large dollars, given Onivyde’s commercial sales to date,” McAllister said. (See *BioWorld Today*, Jan. 10, 2017.)

Intezyne CEO Kevin Sill said the company is “currently screening patients [for the IT-141 trial]. We hope to dose within the next two weeks. I imagine next week, but I’ll say two weeks to be safe. The study is active and recruiting.”

Sill noted that irinotecan is “used off label in many gastrointestinal cancers, including gastroesophageal, pancreatic, lung, ovarian, all sorts of different indications. It’s widely known to be effective, but delivering or getting more of the drug to the tumor environment and less to healthy tissues should allow for a much more effective yet safer treatment option.” IT-141, he said, is “well positioned to be a next generation of the irinotecan class of compounds,” and Intezyne is “the only group that’s delivering SN38 directly. That way we’re able to bypass one of the metabolism limitations of irinotecan. We’re hoping to access the patient population that is intolerant of irinotecan or does not respond well.”

CFO McAllister said IT-141, as a new entrant into the class, is “not specifically targeting irinotecan-resistant patients or irinotecan

treatment failures” but aiming for a “really broad audience” made of many solid tumor types. “That’s based on approvals for irinotecan, but also there have been a lot of investigator-sponsored studies not specifically on label,” he said.

Despite inefficient delivery (less than 4 percent of irinotecan successfully converts into SN-38, of which only a fraction reaches the tumor), Camptosar became one of Pfizer’s blockbuster products, generating sales of more than \$1 billion annually. It remains on the World Health Organization (WHO) List of Essential Medicines. IT-141 was developed in-house, CEO Sill said. “The company was founded around the [nanoparticle] delivery technology. We’ve been working on this for many years.”

At this week’s American Association for Cancer Research meeting, another Intezyne candidate, IT-139 – a glucose-regulated protein 78 (GRP78) inhibitor and the most clinically advanced one in development for solid tumors – was featured in a symposium. The phase I trial with IT-139 showed that it was well-tolerated with manageable side effects, and turned up antitumor activity in numerous types. “We’ve seen synergy both in vitro and in vivo with essentially all classes of compounds that we’ve evaluated,” Sill said. “The challenge for us is to carefully consider all of these data and identify the true lead indications and how we’re going to best utilize this drug.”

EVIDENCE MOUNTS FOR GRP78

CFO McAllister said IT-139 goes after a proliferation and survival pathway that, although known, “was off the radar until relatively recently” but “has gained prominence and fits very well into the current thrust of cancer treatment,” since it combines well with other therapies. “While the data from the phase I showed it has potential as a monotherapy, we’re really focused on adjunctive use,” in order to “defeat resistance to many anticancer agents,

©2017. REPRINTED WITH PERMISSION FROM CLARIVATE ANALYTICS
FORMERLY THE IP & SCIENCE BUSINESS OF THOMSON REUTERS.



including the PD-L1s. That should be very exciting to people, because a lot of these compounds are very effective and then lose that effectiveness within three to six months. We think we could extend that window significantly."

IT-139 is in the lead "from a clinical perspective," McAllister said, although the current focus of the company is on IT-141. "We are manufacturing IT-139 and that's a somewhat lengthy process, so we won't have clinical material available until late this year," he said. The question of which compound might benefit the company most is "a tricky one. I would tend to think IT-139 probably has greater overall market potential, because it could be used with drugs from lots of different classes. We'll put it back into [the clinic with] a phase Ib in early 2018."

As long ago as 2004, research published in *Cancer Cell* established GRP78 as worthy of investigation. Work done by scientists from the University of Texas M.D. Anderson Cancer Center in Houston and the University of Sao Paulo, Brazil, began when the protein GRP78 was discovered on the cell surface of metastatic prostate tumors. Inside the cell, GRP78 is involved in the cellular stress response. Specifically, it was found to be a chaperone protein that interacts with other proteins and helps

them fold into shape. (See *BioWorld Today*, Oct. 1, 2004.)

Last October, scientists at Wake Forest Baptist Center succeeded in enhancing and restoring sensitivity to an estrogen-blocking drug in estrogen-responsive tumors in an animal model. Breast cancer is the most frequently diagnosed cancer among women, with estrogen receptor-positive being the most common type. The research findings were published in *Cancer Research*. Scientists first tested a GRP78-targeting molecule called a morpholino, which can modify gene expression.

The morpholino compound successfully inhibited GRP78 and restored sensitivity to the estrogen modulator tamoxifen in the resistant tumors. Metabolic analysis of breast cancer cells showed that suppressing GRP78 increased the intracellular concentrations of essential polyunsaturated fats, including linoleic acid, which could mean GRP78 plays a part in mediating cellular lipid metabolism. The same tumor-bearing mice were treated with different doses of linoleic acid and it turned out that this approach had the same effect as targeting GRP78 in restoring tamoxifen sensitivity to the tumors, Wake Forest said.