Category

Best Startup

Product/Solution Name

BPR001

Date of Approval

N/A

Indications

Gastro-Intestinal Cancers

Therapeutic Categories

Oncology

Attached Files:

- 20230621_BIPER TX_ NC Slide Deck_Galien.pdf

Background information and need for solution/product

Most current treatment strategies for advanced cancers are either effective in only some patient populations or have high relapse rates. As an example, with an estimated one million cases worldwide* and an annual projected increase of 2%, the gastric cancer market is evolving rapidly. Despite the arrival of immunotherapies as a first line treatment and targeted therapies, there is still a high unmet medical need in this indication and all gastro-intestinal cancers indications as 50 % of patients remain without solutions* (up to 70% for Her2 negative patients). There is an urgent need for new class of therapeutics targeting new pathways.

Overexpression of BiP (GRP78), a key protein involved in cancer cells survival and resistance, is associated with very poor prognosis of patients in a broad range of cancer indications with a very high overexpression in gastro-intestinal cancers.

BiP has a key role in tumors thriving under adverse conditions, such as hypoxia, nutrient starvation, and oxidative stress, by adjusting their protein-folding and homeostasis capacity. BiP is a master regulator of the Endoplasmic Reticulum Stress Pathway and the folding of misfolded proteins. The ER Stress is a key survival and resistance mechanism in cancer cells controlled by BiP as a chaperone of the three ER Stress Effectors.

Inhibiting the ER Stress controller function of BiP lead to uncontrolled and unresolved ER Stress activating apoptosis and autophagy, two mechanisms of cancer cell death in tumors. Based on scientific, mechanistic and pharmaco-economic objective assessment & criteria, BiPER has developed BPR001 a first-in-class BiP inhibitor positioned to treat gastro-intestinal cancers with Gastric cancer as primary indication.

History of the development of the solution/product

BiPER Therapeutics' lead program is a first-in-class small molecule targeting GRP78/ BiP. BPR001 has a unique, selective mechanism-of-action that selectively kills cancerous cells. BPR001 induces strong and lethal ER Stress through selective GRP78 binding and inhibition, leading to cancer cellular death via apoptosis and autophagy. As cancer cells express permanent and high ER Stress level to survive, proliferate and become resistant to standard of care therapies – by targeting this pathway, BPR001 overcomes this survival mechanism and this resistance, improving outcomes in both sensitive and resistant cancers.

Large body of in vivo and in vitro efficacy and tolerability data support the proof-of-concept for BPR001 use as an oral anti-cancer therapy. BPR001 has demonstrated efficacy in a broad range of cancer indications in monotherapy and in combination associated with an excellent pharmacological and tolerability profile.
- BPR001 in oral administration induces tumor regression in combination with a chemotherapeutic agent (5FU) and inhibits tumor growth in murine gastric tumor xenograft mice in monotherapy
- BPR001 in combination with immunotherapy (anti-PD1), another reference treatment for gastric cancer, completely cured mice with colorectal cancer tumors
- BPR001 in oral administration reduces by 3 the volume of colorectal tumor in xenograft mice in monotherapy and reduces by 4 the tumor volume in combination with immunotherapy (anti-PDL1)
- The correlation between the downregulation of expression of BiP in mice sera and the sensitivity of BPR001 treatment in mice has been demonstrated

Moreover, ER stress is clearly established in gastric cancer and recognized as one of the tumor survival and resistance mechanisms for this indication. This program will likely target resistant patients HER2- in second line of treatment in combination with immune checkpoint inhibitors and/or chemotherapy (FOLFOX) or in 3rd line treatment for patient not responding or resistant to standards treatments which represent more than HER2- patients.

BiP, unlike other oncogenic markers, is very easily measured in the blood and tumors of patients. The correlation between intra-tumoral and circulating BiP has been demonstrated in retrospective studies. The huge advantage of having a biomarker like BiP that can be easily measured in the blood is that the selection and follow-up of patients on our treatment is based on a simple blood test. Two retrospective studies are launched with two French clinical

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

The inventing team from UCA and C3M (Nice) developed a new family of patented small molecules targeting selectively BiP. Extensive Medicinal chemistry led to the development of a clinical candidate, BPR001. BPR001, through extensive studies, optimization and formulation work, has demonstrated an excellent pharmacological profile in per os administration in terms of potency, selectivity, bioavailability and safety in vitro and in vivo, even in context of resistant cancer models. BPR001 has been demonstrated, by the team as well as by independent peer reviewed studies, to selectively bind BIP leading to BIP dissociation from key ER stress regulators (PERK, ATF6 and IRE1alpha).

BPR001 targets BIP (Binding Immunglobulin Protein), also known as GRP 78 (Glucose Regulated Protein 78) or HSPA5. BiP plays an essential role in endoplasmic reticulum stress management, a cell

survival mechanism that eliminates poorly designed or dysfunctional proteins. Cancer cells, inherently stressed by their transcriptional overactivity, their nutrient- and oxygen-deprived environment, and assaulted by natural defenses and radiation and chemotherapy treatments, overexpress BiP. Their level of endoplasmic reticulum stress is significantly higher than that of non-cancerous cells, enabling them not only to survive and proliferate, but also to resist treatments that target cancer cell-specific proteins mediated by endoplasmic reticulum stress.

When BPR001 binds to BIP, the latter no longer plays its regulatory role, and stress levels rise to such an extent that cancer cells can no longer keep up, triggering mechanisms leading to cell death. In other words, our compounds induce cancer cells (already stressed by nature) to burn-out and commit suicide, without affecting non-cancerous cells.

Our innovative molecules, focused on cancer cell metabolism and addressing unmet medical needs with high market potential, make our innovation unique.
Their anti-cancer properties via a novel and unique therapeutic pathway make them excellent drug candidates to treat a variety of cancers alone or in combination with standards of care with the following advantages:

- First-in-Class therapeutics with a unique mode of action and a new therapeutic pathway validated by numerous peer-reviewed publications
- Demonstrated potential in single agent use and/or in combination with standards of care such as immunotherapies and chemotherapies
- Excellent safety profile and proven selectivity on cancer cells with a broad therapeutic index
- Huge potential to treat a broad range of indications and to be not only administred to advanced stage cancer patents but also as neoadjuvant therapy at all stages
- A good pharmacological profile of our molecules, which can be administered orally where most treatments are intravenous, needs to have patient at the hospital to be treated thus resolving current problems of access to treatment, logistics and market extension.
- A simple synthetic route compatible with pharmaceutical standards and capable of addressing needs worldwide at a cost that is accessible to patients and payers, which is not the case with new treatments currently on the market or in development

Please provide appropriate references (ie Pubmed links)

Video : https://biper-tx.com/

Key Publications on Discovery from Co-founders
• Compounds Triggering ER Stress Exert Anti-Melanoma Effects and Overcome BRAF Inhibitor Resistance Cancer Cell
DOI:https://doi.org/10.1016/j.ccell.2016.04.013
• Discovery and Optimization of N-(4-(3-Aminophenyl)thiazol-2-yl)acetamide as a Novel Scaffold Active against Sensitive and Resistant Cancer Cells J. Med. Chem.
https://doi.org/10.1021/acs.jmedchem.6b00547
• New anti-cancer molecules targeting HSPA5/BIP to induce endoplasmic reticulum, stress, autophagy and apoptosis Autophagy
https://doi.org/10.1080/15548627.2016.1246107
• Structure activity relationship and optimization of N-(3-(2-aminothiazol-4-yl)aryl)benzenesulfonamides as anti-cancer compounds against sensitive and resistant cells

Bioorganic & Medicinal Chemistry Letters
https://www.sciencedirect.com/science/article/abs/pii/S0960894X17303025?via%3Dihub
· The GRP78/BiP inhibitor HA15 synergizes with mitotane action against adrenocortical carcinoma cells through convergent activation ER stress pathways Molecular and Cellular Endocrinology
https://doi.org/10.1016/j.mce.2018.02.010
· Development and in vivo evaluation of fused benzazole analogs of anti-melanoma agent HA15 Future medicinal chemistry
https://pubmed.ncbi.nlm.nih.gov/34096325/

Key Publications on BiP as target

· Prognostic role of BiP/GRP78 expression as ER stress in patients with gastric adenocarcinoma Cancer Biomark
https://pubmed.ncbi.nlm.nih.gov/34096325/
· Clinicopathological significance of endoplasmic reticulum stress proteins in ovarian carcinoma Nature
https://www.nature.com/articles/s41598-020-59116-x
· Elevated GRP78 expression is associated with poor prognosis in patients with pancreatic cancer Nature
https://pubmed.ncbi.nlm.nih.gov/26530532/
· Circulating GRP78 acts as a biomarker in the early diagnosis of lung cancer Int J Clin Exp Pathol.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6963050/#b27
· Serum GRP78 as a Tumor Marker and Its Prognostic Significance in Non-Small Cell Lung Cancers: A Retrospective Study Dis Markers.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4523661/