
tiziana
LIFE SCIENCES
NASDAQ: TLSA
LSE AIM:TILS
Targeted Therapeutics for:
• NASH & Crohn's Disease
• Liver Cancer (HCC)
• Thymic Carcinoma & Thymoma
Kunwar Shailubhai, PhD, MBA | CEO & CSO
May 2019

DISCLAIMER & NOTICE OF FORWARD LOOKING STATEMENTS

Tiziana Life Sciences PLC (the "Company")

The content of this presentation has been prepared for the purpose of providing general information about, and an overview of, the Company and its business. It is not intended to be a complete review of all matters concerning the Company and nor has it been independently verified. Whilst the presentation has been prepared in good faith and the Company has taken all reasonable care to ensure the information and facts contained in this presentation are accurate and up-to-date, it does not make any representation or warranty, express or implied, as to the accuracy or completeness of any information included in this presentation. Neither the Company nor any of its directors, officers, employees or agents shall be liable for any loss arising directly or indirectly from the use of or reliance upon this presentation or in relation to the adequacy, accuracy, completeness or reasonableness of the information it contains. All and any such liability is expressly excluded to the fullest extent permitted by law. The information in this presentation is subject to updating, completion, revision, further verification and amendment without notice.

This presentation does not constitute or form part of any offer for sale or solicitation of any offer to buy or subscribe for any securities including ordinary shares in the Company nor does it constitute an invitation or inducement to engage in investment activity in relation to any securities, including the ordinary shares of the Company. It does not purport to contain information that shall form the basis of, or be relied upon in making such investment decisions. If you require any advice, please consult with a professional financial adviser. All investments are subject to risk. The value of securities may go down as well as up. Past performance cannot be relied on as a guide for future performance.

In the UK, this presentation has not been approved by an authorised person and is being distributed on the basis that each person in the UK to whom it is issued is reasonably believed to be such a person as is described in Article 19 (investment professionals) or Article 49 (high net worth companies, unincorporated associations etc.) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (SI 2005/1529) or are persons to whom an invitation or inducement to engage in investment activity (within the meaning of section 21 of the Financial Services and Markets Act 2000) in connection with the issue or sale of any securities may otherwise lawfully be communicated or caused to be communicated. Persons who do not fall within such descriptions may not act upon the information contained in this presentation.

This presentation is only being provided to persons that are (i) "Qualified Institutional Buyers", as defined in Rule 144A under the U.S. Securities Act of 1933, as amended (the "Securities Act"), or (ii) non-US persons outside the United States, in compliance with Regulation S under the Securities Act. By attending this presentation or by reading the presentation slides, you warrant and acknowledge that you fall within one of the categories (i) and (ii) above.

This presentation may contain certain forward-looking statements concerning the financial condition, results of operations and businesses of the Company. All statements other than statements of historical fact are, or may be deemed to be, forward-looking statements. Forward-looking statements are statements of future expectations that are based on management's current expectations and assumptions and involve known and unknown risks and uncertainties that could cause actual results, performance or events to differ materially from those expressed or implied in these statements. All forward-looking statements contained in this presentation are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. You should not place undue reliance on forward-looking statements. Each forward-looking statement speaks only as of the date of this presentation. The Company does not undertake any obligation to publicly update or revise any forward-looking statement as a result of new information, future events or other information. In light of these risks, results could differ materially from those stated, implied or inferred from the forward-looking statements contained in this presentation.

This presentation is not being distributed to persons outside of the UK and does not constitute or form part of any offer for sale or subscription of or solicitation or invitation of any offer to buy or subscribe for any securities, including in the United States, nor shall it or any part of it form the basis of or be relied on in connection with any contract or commitment whatsoever. However, any recipient of this presentation in jurisdictions outside the UK should inform themselves about and observe any applicable legal requirements. This presentation does not constitute an offer to sell or an invitation to purchase securities in the Company in any jurisdiction.

This presentation should not be copied or distributed by recipients and, in particular, should not be distributed by any means including electronic transmission, to persons with addresses in the United States of America, Canada, Australia, Republic of Ireland, South Africa, Japan or any other jurisdiction which prohibits the same except in compliance with applicable securities laws. Any such distribution contrary to the above could result in a violation of the laws of such countries. This presentation is confidential and is being supplied to you solely for your information and may not be reproduced, re-distributed or passed to any other person or published in whole or in part for any purpose. By accepting receipt of this presentation, you agree to be bound by the limitations and restrictions set out above.

INVESTMENT HIGHLIGHTS

- **Lead drug candidates, Foralumab and Milciclib, uniquely target the root cause of diseases with large unmet needs in multibillion dollar markets**
- **TLSA is undervalued at market cap $ 100M. High upside market potential for our two de-risked clinical drug candidates in NASH and hepatocellular carcinoma (HCC)**
- **Drugs have been de-risked through prior Phase II studies proving both safety and efficacy**
- **Robust and growing IP portfolio covering breakthrough inventions in fully human antibodies & oral and nasal delivery of drugs**
- **Drugs target the root cause of disease, thereby offering efficacy for all patients in the disease population, as compared to current standard of care which is only effective in a small fraction of the patient population**
- **NASH is $35 billion global market**
- **Liver cancer, a $1.5 billion market, is underserved by FDA approved drugs which only work in small percentage of patients**

EQUITY HIGHLIGHTS

- **NASDAQ:TLSA* (also listed on LSE AIM: TILS)**
- **Price Per ADS: $6.89****
- **52 Week Trading Range: $5.00 - $12.17**
- **Market Cap: ~ $105 M**
- **ADS Outstanding: 13.6 M**
- **Analyst Coverage:**
  - **Laidlaw & Company: Price Target $17 as of April 2018**
  - **H.C. Wainright & Co.: Buy Rating on AIM Listed Stock as of May 2018**
  - **Stockdale: Buy Rating on AIM Listed Stock as of December 2018**

***Equity information as of April 19, 2019**

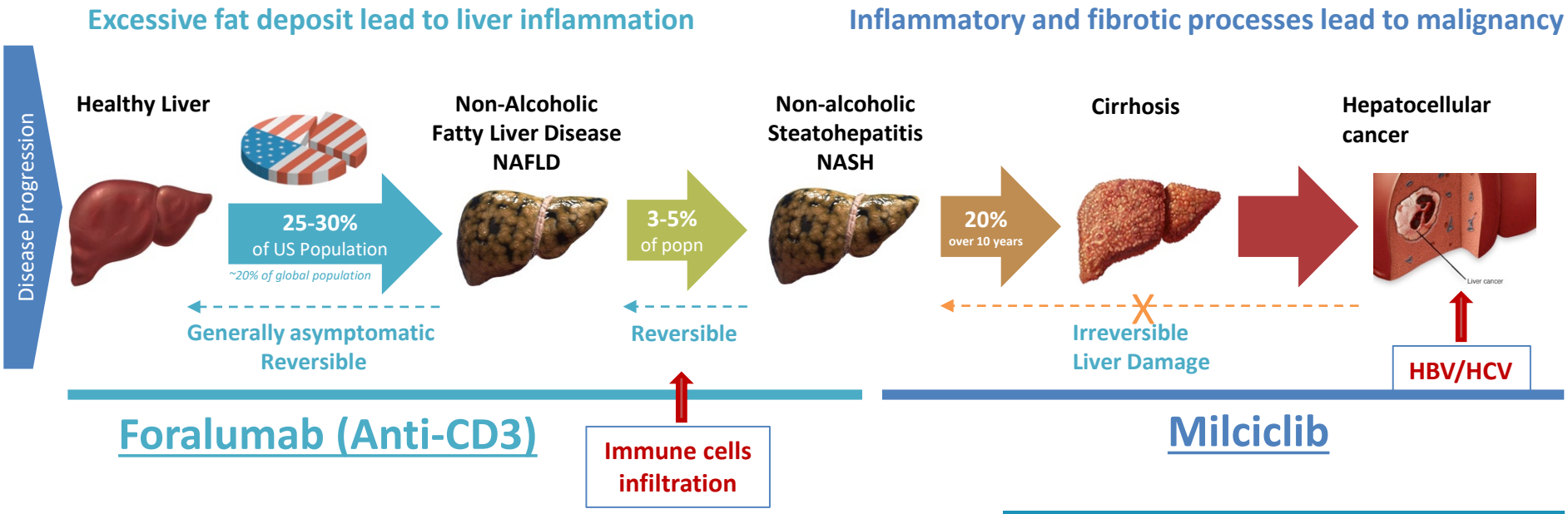
****Each ADS traded on NASDAQ represents 10 ordinary shares traded on LSE AIM**

MULTIPLE CATALYSTS UPCOMING

CATALYST	WHEN
Report Phase II Results from Liver Cancer Study with Milciclib	July 2019
Initiate Phase I Oral Dosing of Foralumab in Healthy Volunteers	2H 2019
Report Phase I Oral Dosing of Foralumab in Healthy Volunteers (Safety, Tolerability & Biomarkers of anti-inflammation)	1H 2020
Report Phase I Nasal Dosing of Foralumab in Healthy Volunteers (Safety, Tolerability & Biomarkers neurodegenerative disease)	2H 2019
Initiate Phase IIb Liver Cancer Study of Milciclib in Combination with a TKI	2H 2019
Initiate Phase II in Crohn's disease and NASH with Oral Foralumab	2H 2020

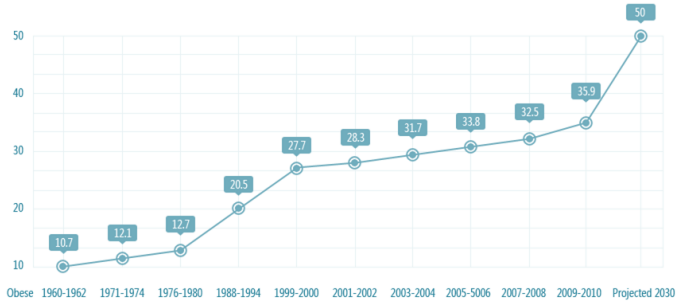
BOTH DRUGS TARGET LIVER DISEASES
$20 B MARKET U.S., $35 B GLOBAL

tiziana LIFE SCIENCES



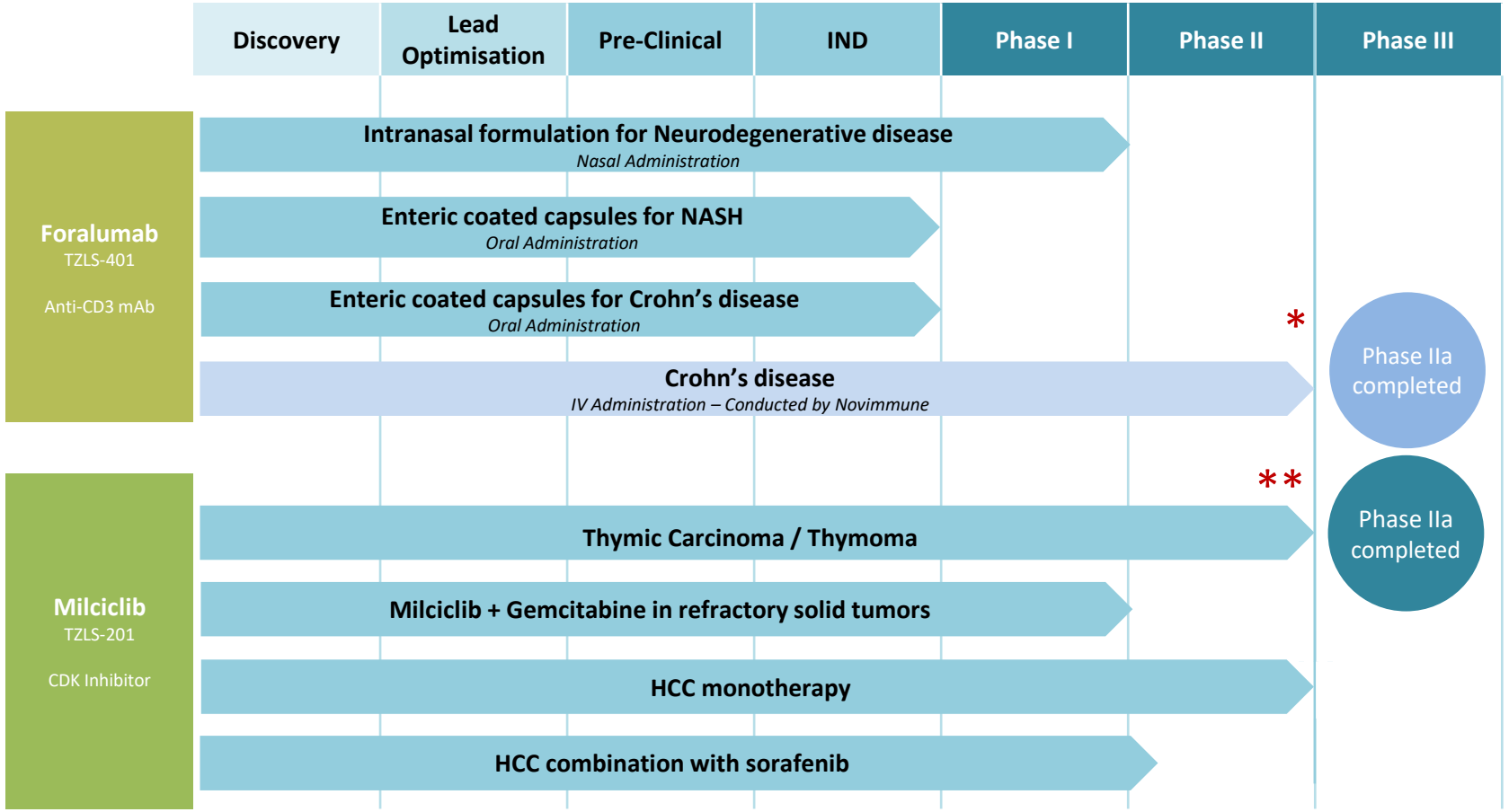
- **Non-alcoholic fatty liver disease (NAFLD) the most common liver disease**, affecting one-third of the Western world, driven by obesity and diabetes epidemic[1]
- **NASH predicted to become leading cause of liver transplantation** in USA by 2020[2]
- **Hepatocellular carcinoma (HCC) is primary cause of obesity-related cancer death** in middle-aged men in the USA[1]
- **No currently approved drugs** – liver transplant only option for end-stage patients
- **Market estimated to reach US $20.27 bn by 2025** (10.7% CAGR from 2015 to 2025)[1]

Prevalence of obesity, US adults aged 20-74



1 Transparency Market Research "Nonalcoholic Steatohepatitis Therapeutics Market - Global Industry Analysis, Size, Share, Growth, Trends, and Forecast 2015 – 2025
2 Y Ilan. Aliment Pharmacol Ther 44 (11-12), 1168-1182. 2016
3 Wree A, Broderick L, Canbay A, Hoffman HM, Feldstein AE. From NAFLD to NASH to cirrhosis-new insights into disease mechanisms. Nat Rev Gastroenterol Hepatol 2013; 10: 627–36.

CLINICAL DEVELOPMENT PIPELINE



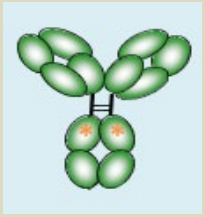
* The trial in Crohn's Disease (IV administration) conducted by Novimmune produced encouraging clinical response. TILS strategy is to pursue oral administration with foralumab in NASH and CD.

** We will seek guidance from regulatory authorities for next steps

TZLS-401: FORALUMAB IS A FULLY HUMAN ANTIBODY USED TO MODULATE IMMUNE RESPONSE VIA MUCOSAL IMMUNE SYSTEM

tiziana LIFE SCIENCES

TZLS-401



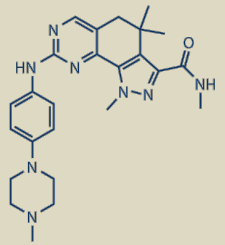
Fully human, anti-CD3 monoclonal antibody (mAb) acting locally on mucosal immune cells lining gut and nasal passages to induce tolerance and reduce inflammation systemically

Mechanism	Indications	Opportunity	Competitive Edge	IP/Ownership
• Interacts with immune cells lining the gut and nasal mucosal surfaces to suppress immune response locally and systemically • Binds to T cell receptors (TCR complex) inducing immunomodulation and tolerance • Non-parenteral administration	• NASH (oral) • Crohn's Disease (oral) • Diabetes, Type 1 (oral) • Multiple Sclerosis (progressive) (nasal) • Autoimmune diseases, e.g. Lupus, arthritis etc. • Recent article (Boden et al., In Press) demonstrated that orally administered OKT3, a murine anti-CD3 mAb, reduced gut inflammation in moderate to sever UC patients	• Novel mode of action (oral and nasal administration) • Improved safety compared to parenteral administration • Extensive POC in human and animals studies and pre-clinical • May be used in combination with anti-IL6-R (TZLS-501) • >$35 billion market	• First-in-class mode of action. Foralumab acts locally on immune cells lining gut and nasal mucosa • Large molecule drugs and mAbs are usually administered by IV or Sub Q (parenteral) • Only fully human anti-CDA mAb unlike competitors	• Exclusive license from Novimmune • Compositions and Method of Use patents provide protection to 2025 • Combination and formulation patents from TLSA are pending and expected to expire in 2037

TZLS-201: MILCICLIB IS A CELL CYCLE (CYCLIN DEPENDENT KINASE) INHIBITOR FOR TARGETED CANCER THERAPY

tiziana LIFE SCIENCES

TZLS-201



Small molecule, broad spectrum, cell cycle inhibitor targeting aggressive, heterogeneous, solid cancers, especially HCC and thymic cancer

Mechanism	Indications	Opportunity	Competitive Edge	IP/Ownership
• Potent pan-CDK Inhibitor of CDKs 1,2,4,5 and 7 and Src family kinases • Arrests cell cycle resulting in tumor cell death and inhibition of tumor growth/spread • Targets a root cause of HCC. Reduces levels of miRNAs that control gene expression in HCC and other cancers	• Hepatocellular carcinoma (HCC) • Thymic cancer (orphan) • Cholangiocarcinoma • Solid cancers	• Improved safety profile compared to current Standard of Care (SOC) drugs (sorafenib, lenvatinib, regorafenib) • Useful as monotherapy or combination therapy (additive/synergistic effect) with SOC drugs • Combination with conventional chemotherapy agents • >$1.4 billion global market	• Reduced toxicity and adverse events compared to SOC drugs • Different mechanism of action from SOC drugs (tyrosine protein kinase inhibitors) reducing likelihood of tumor “escape” when used in combination therapy • Orally bioavailable	• Exclusive license from Nerviano Medical Sciences • Composition and Method of use in combination patents providing protection to 2030

tiziana LIFE SCIENCES

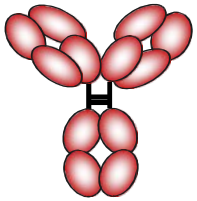
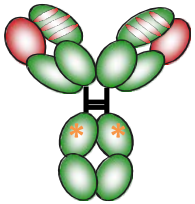
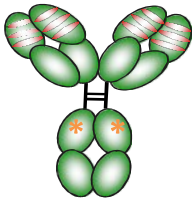
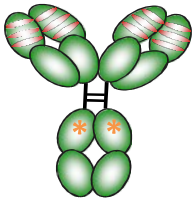
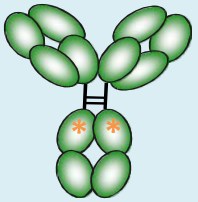
CLINICAL DEVELOPMENT PIPELINE

Foralumab: A fully human anti-CD3 mAb

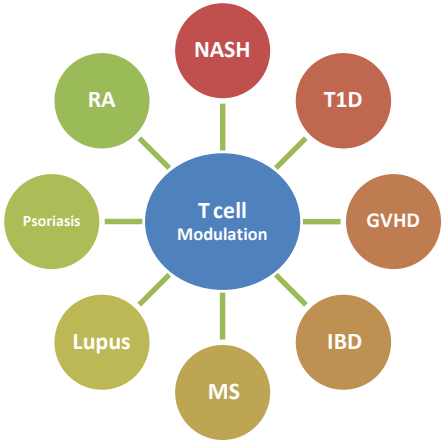
- Ongoing Phase I trial at Harvard Medical School with healthy volunteers to study safety, tolerability and biomarkers for neurodegenerative disease with an intranasal formulation for nasal delivery (Completing May 29, 2019)
- Upcoming Phase I trial in healthy volunteers to study safety, tolerability and biomarkers for indications in NASH and Crohn's Disease with an enteric coated capsule formulation for oral administration
- Upcoming Phase II trial in Crohn's Disease and NASH with oral administration

FORALUMAB – THE ONLY FULLY HUMAN ANTI-CD3 MAB

CD3-specific monoclonal antibodies in clinical development[1]

OKT3 Muromonab	ChAglyCD3 Otelixizumab	Nuvion Visilizumab	hOKT3γ1(Ala-Ala) Teplizumab	NI-0401 Foralumab
				
IgG2a	IgG1 *Agly	IgG2 *AA	IgG1 *AA	IgG1 *AE
Fully Mouse	*Chimeric & Humanized*	*Humanized*	*Humanized*	***Fully Human***
Approved by the FDA for solid organ transplantation immuno-suppression				

Oral and Nasal Administration

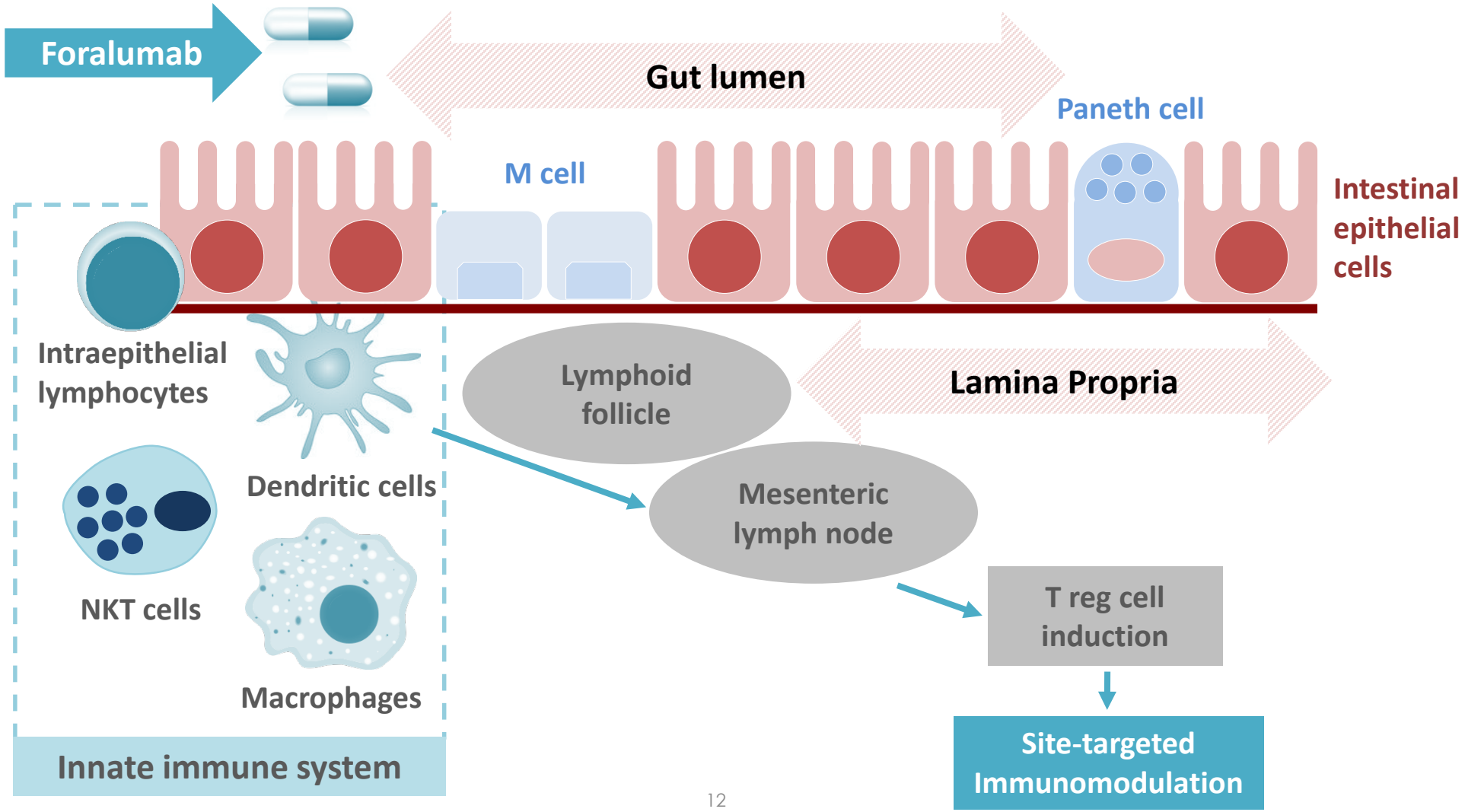


Oral and nasal administration with foralumab could potentially be a game changer to enhance efficacy and reduce toxicity

Source: (1) Therapeutic anti-CD3 monoclonal antibodies: from bench to bedside, Kuhn C, Weiner HL, Immunotherapy, 2016 Jul;8(8):889-906.

HOW DOES ORALLY ADMINISTERED FORALUMAB WORK?

A novel method for immune modulation without immune suppression



FIRST PATENT ON ORAL FORMULATION WITH ANTIBODY

Nasal administration of Foralumab

- Successfully developed nasal formulation of foralumab
- Proof-of-concept for nasal administration demonstrated in animal studies
- IND for nasal administration for neurodegenerative diseases with Brigham and Women's Hospital, Harvard University
- In-licensed nasal delivery technology from Brigham and Women's Hospital, Harvard Medical School

Covers foralumab and other mAbs

ANTI-CD3 ANTIBODY FORMULATIONS

Applicant(s): Tiziana Life Sciences PLC

Inventor(s): SHAILUBHAI, Kunwar

US Non-Provisional Patent Application No.:62/380,652, filed August 29, 2017

PCT Application PCT/US2017/049211, filed, Aug 29, 2017

Claims

- Composition of matter of a first oral formulation of the fully human antibody, foralumab comprising an enteric-coated lyophilized capsule with stabilizers and antioxidants to treat autoimmune and inflammatory diseases such as NASH
- General methods for the production of a lyophilized NI-0401/CD3 antibody dosage form for use in oral formulation

PROOF-OF-CONCEPT IN NASH PATIENTS BY ORAL TREATMENT WITH MURINE ANTI-CD3 (OKT3): *EFFECTIVE IN A PHASE II TRIAL WITH NASH*[1]

tiziana LIFE SCIENCES

Study design

- 36 subjects with NASH and type II diabetes
- Randomized, single-blinded
- 9 per group, not powered for statistical significance
- 0.2, 1.0, 5.0 mg or placebo daily for 30 days
- Primary endpoints: safety and trends in immunomodulation
- Secondary endpoint: indication or trend of efficacy through biomarkers
- Follow up: Days 0, 14, 30, 60
- Hadassah Medical Center, Jerusalem Israel

Safety

- No treatment-related adverse events
- Safe and well tolerated
- No change in CD3+ lymphocyte count
- Normal blood chemistry and blood cell counts

Immunological

- Increases in Treg markers consistent with induction of Tregs
- Anti-inflammatory markers ↑
- CD4+CD25+LAP+ Treg cells ,TGFβ ↑

Efficacy biomarkers

- Positive trends, some of which were statistically significant
- AST ↓ – liver enzyme indicating reduced liver inflammation
- Glucose ↓ – favorable for subjects with type-2 diabetes
- Insulin ↓ – favorable for subjects with type-2 diabetes

OKT3 withdrawn from the market due to severe side effects being a murine mAb
Foralumab is fully human anti-CD3 mAb

Source: (1) Lalazar, G., Mizrahi, M., Turgeman, I., Adar, T., Ya'Acov, A. B., Shabat, Y., . . . Ilan, Y. (2015). Oral Administration of OKT3 MAb to Patients with NASH, Promotes Regulatory T-cell Induction, and Alleviates Insulin Resistance: Results of a Phase IIa Blinded Placebo-Controlled Trial. Journal of Clinical Immunology, 35(4), 399-407.

FORALUMAB IS AS GOOD AS OKT3

Oral Treatment with Foralumab, a fully human anti-CD3 monoclonal antibody, prevents skin xenograft rejection in mice with human immune systems

Mineko Ogura, Songyan Deng, Paula Preston-Hurlburt, Hideki Ogura, Kunwar Shailubhai, Chantal Kuhn, Howard L Weiner, and Kevan C. Herold

Clinical Immunol, 2017. 183: 240-246

Clinical Immunology 183 (2017) 240–246

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Oral treatment with foralumab, a fully human anti-CD3 monoclonal antibody, prevents skin xenograft rejection in humanized mice

Mineko Ogura [a], Songyan Deng [a], Paula Preston-Hurlburt [a], Hideki Ogura [a], Kunwar Shailubhai [d], Chantal Kuhn [b], Howard L. Weiner [b], Kevan C. Herold [a,c,*]

[a] Department of Immunobiology, Yale University, New Haven, CT, United States
[b] Ann Romney Center for Neurologic Diseases, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02115, United States
[c] Department of Internal Medicine, Yale University, New Haven, CT, United States
[d] Tiziana Life Sciences, R&D Center, 3805 Old Easton Road, Doylestown, PA 18902, United States

ARTICLE INFO

Article history:
Received 8 May 2017
Received in revised form 14 July 2017
Accepted with revision 14 July 2017
Available online 21 July 2017

Keywords:
Anti-CD3
Monoclonal antibody
Oral biologic
Immune tolerance

ABSTRACT

Oral administration of biologics may be a feasible approach for immune therapy that improves drug safety and potentiates mechanisms of tolerance at mucosal barriers. We tested the ability of a fully human non-FcR binding anti-CD3 mAb, foralumab, to prevent skin xenograft rejection in mice with human immune systems. At an intragastric dose of 15 μg, the drug could transit through the small bowel. Serum absorption and binding of lymphoid cells was seen and proliferative responses of splenic CD8 + T cells to mitogen were reduced. Five consecutive daily doses, then weekly dosing led to indefinite graft acceptance without depletion of peripheral T cells. Proliferative and cytokine responses to activation of splenocytes with PHA were reduced. The serum levels of IL-10 but not TNF were increased 6 days after application of the skin graft. Oral treatment with anti-CD3 mAb may represent a feasible approach for immune modulation.

© 2017 Elsevier Inc. All rights reserved.

1. Introduction

One of the most effective biologics used for modifying immune responses has been anti-CD3 monoclonal antibodies (mAbs) [1]. Beginning with OKT3, modifications of the Fc region of the antibody have been made to reduce T cell activation and cytokine release and improve their tolerability. Subsequently, many reports have described the clinical use of these reagents for preventing unwanted immune responses ranging from allograft rejection to treatment of autoimmune diseases such as Type 1 diabetes, psoriatic arthritis, and inflammatory bowel disease [2–10]. These modifications also changed the mechanisms of the mAbs which have been shown to involve the production of IL-10 or TGFβ as well as partial exhaustion of T cells and, most recently, the induction of regulatory cells [11–14]. We and others have previously described a mechanism for induction of regulatory cells in anti-CD3 mAb treated mice and humanized mice following migration to the gut wall [15,16].

However, despite better tolerability of the second generation of anti-CD3 mAb with mutated Fc regions, parenteral administration of the mAbs continues to have limitations because of the need for intravenous administration in a medical facility, and potential for cell activation.

Ochi et al. first described the immune modulating effects of oral dosing of anti-CD3 mAb in experimental autoimmune encephalitis, a model of multiple sclerosis [17]. They described the induction of CD4 + CD25- Latency Associated Peptide (LAP) + T cells that exhibited regulatory properties [18]. Subsequently, oral anti-CD3 mAb was shown to suppress low-dose streptozotocin induced and NOD diabetes, models of Type 1 diabetes and murine lupus, by induction of IL-10-secreting CD4 + CD25-LAP + regulatory cells [19,20]. In a model of inflammation and insulin resistance, Ilan et al. also reported induction of LAP + Tregs when oral anti-CD3 mAb was given with β-glucosylceramide which induced NKT cell dependent immunoregulation [21]. Other groups have reported similar efficacy with oral anti-CD20 mAb [22]. More recently, in a small T1D when given with anti-CD20 mAb OKT3 to patients Phase IIa trial, Lalazar et al. administered oral murine OKT3 to patients with NASH and reported that there was improvement in liver function tests and an increase in CD4 + CD25 + LAP + T cells [23]. Anti-CD3 mAb was not identified in the serum or found on the surfaces of T cells in the peripheral blood suggesting that the activity of the drug was restricted to interactions with gut-resident T cells.

Although these previous studies suggest efficacy of oral anti-CD3 mAb administration, the mechanism of action of the oral drug, its absorption, and how polyclonal intestinal Tregs that may be targeted by the oral drug can modify systemic immune responses has not been explained. Understanding the basis for the immunologic effects of biologics in humans can be challenging because of limited access to target

* Corresponding author at: Department of Immunobiology, Yale University, 300 George St, #353E, New Haven, CT 06520, United States.
E-mail address: kevan.herold@yale.edu (K.C. Herold).

https://doi.org/10.1016/j.clim.2017.07.005
1521-6616/© 2017 Elsevier Inc. All rights reserved.

Key Findings

- **Foralumab is as potent as OKT3**
- **Oral treatment with foralumab is effective in animal studies**
- **Mechanism of action is *via* activation of Tregs that systemically circulate to elicit targeted immunomodulation**

A recent article (Boden et al., In Press) demonstrated that orally administered OKT3 showed clinical activity in moderate to severe ulcerative colitis patients

tiziana LIFE SCIENCES

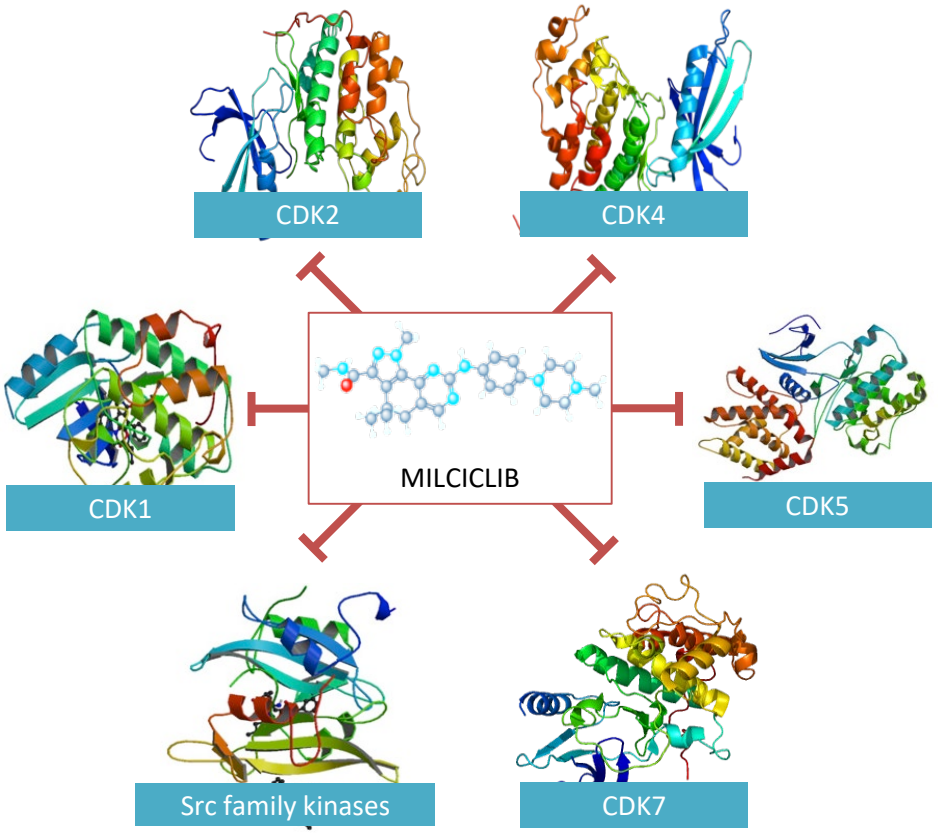
CLINICAL DEVELOPMENT PIPELINE

Milciclib: A pan-inhibitor of CDKs and Src kinase

- Ongoing Phase IIa trial in liver cancer with milciclib
- Upcoming Phase IIb trial in liver cancer with combination of milciclib and a TKI

MILCICLIB, A SMALL MOLECULAR PAN-INHIBITOR OF CDKS

- A novel small molecule with potent anti-tumor activity in a wide range of animal models with remarkably low toxicity
- Inhibitor of a wide range of kinases associated with cancer cell growth including CDK2, CDK1, CDK4 and CDK5 and src-family kinases
- Treatment of cancer cells with milciclib induces reduction in STAT3, MAPK, AKT, YES and S6, effectors of signaling pathways relevant to hepato-carcinogenesis
- Shown to be very well tolerated in over 296 patients, supplied for oral administration – a key issue for patients with underlying liver disease
- Anticipated improved toxicity profile over the current standard of care



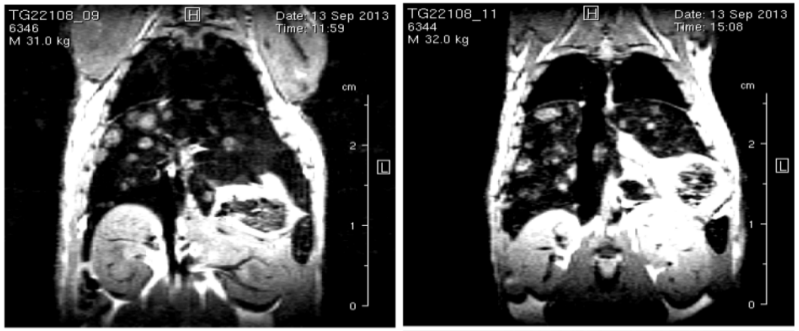
Potentially the next-gen Sorafenib/Nexavar with fewer side effects

MILCICLIB INHIBITS MIR221/222 TO SUPPRESS HCC TUMOR GROWTH IN MICE

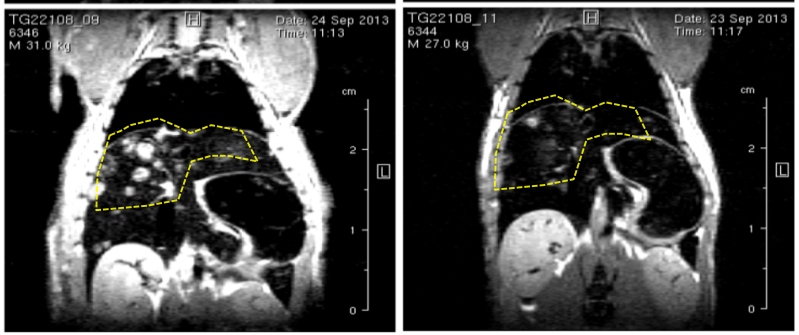
MR images, control vs. milciclib treated mice, pre-/post-treatment

CONTROL | MILCICLIB (40mg/kg/day)

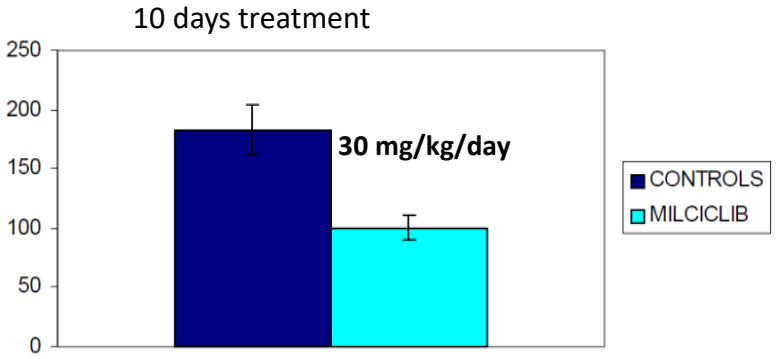
PRE



POST (Day 8)



% tumour growth, pre-/post- treatment

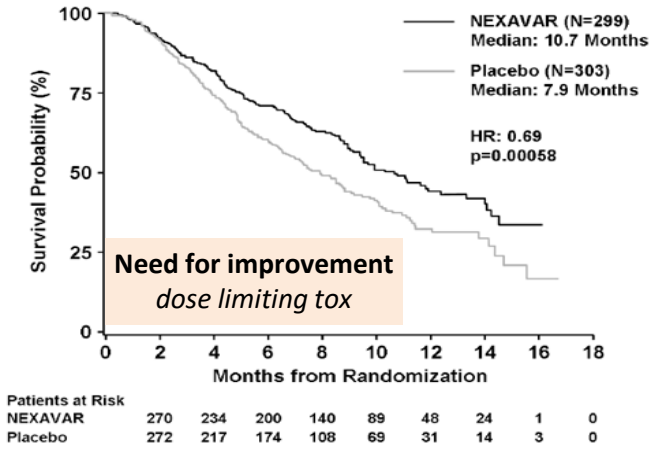


TG 221/DENA mice

- Short and robust MOA based transgenic mouse model for HCC development, dependent on mir221 expression
- Tumor development is induced by DENA

Impressive milciclib effect, with clear reduction in the number and volume of lesions observed after treatment

MILCICLIB AND SORAFENIB MAY HAVE SYNERGISTIC EFFECT



Need for improvement
dose limiting tox

Synergistic effect on HCC with sorafenib expected

Sorafenib

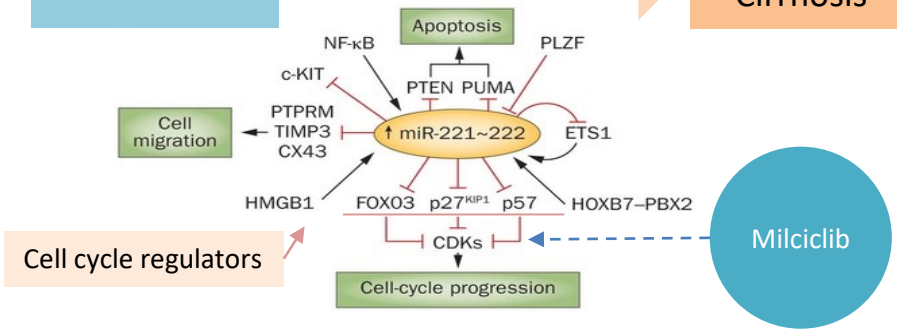
- MTK ↑
- PI-3K ↑
- Akt ↑
- VEGF ↑
- PDGF ↑

Milciclib

- miRNA 122 ↓
- miRNA 221 ↑ ↓
- miRNA 222 ↑ ↓

Normal Liver → HBV/HCV → Fibrosis Cirrhosis → Chronic Inflammation / dysregulation of cell cycle → HCC

↑↓ **HCC mediated alteration**



OVEREXPRESSION OF miR-221/222 is often associated with development of sorafenib resistance in HCC patients

ANIMAL STUDIES DEMONSTRATING SYNERGISM BETWEEN MILCICLIB AND TK INHIBITORS TO TREAT HCC PRESENTED AT AASLD (NOV 9-13, SAN FRANCISCO)

Oral Treatment with Milciclib either alone or in Combination with Sorafenib Inhibited Tumor Growth in an Orthotopic Model of Hepatocellular Carcinoma

Aastha Jindal[1] , Vaseem Palejwala[2] and Kunwar Shailubhai[1,2]

[1]Baruch S. Blumberg Institute and [2]R & D Center, Tiziana Life Sciences, 3805 Old Easton Road, Doylestown, PA 18902

INTRODUCTION

Hepatocellular carcinoma (HCC) is a multifactorial and complex disease frequently caused by chronic hepatitis (HBV and HCV), metabolic diseases or exposure to toxic agents. Overexpression of cyclin dependent kinases (CDKs), tyrosine kinases (TKs) and microRNAs (miR-221 & miR-222) is associated with HCC. Curative therapies are resection, liver transplantation and pharmaceutical interventions to delay its onset. Nexavar® (sorafenib) is approved as first line therapy. Lenvima (lenvatinib) was recently approved as first-line therapy and Opdivo (nivolumab) and Stivarga (regorafenib) were approved for sorafenib-refractory patients. However, TKIs are not entirely satisfactory due to severe toxicities and high recurrence rates. Thus, there is a need for development of therapeutic agents, preferably with new mechanism of action, to improve treatment options. Milciclib (PHA-848125AC) is a broad spectrum inhibitor of multiple CDKs, c-src kinase, TRKA and wee-1 & 2 kinases [1,2]. Oral treatment with milciclib in combination with gemcitabine was well tolerated and produced clinical responses in patients with refractory solid malignancies [3,4]. Interim data from an ongoing phase 2a clinical study in sorafenib-resistant HCC patients with milciclib suggested that the treatment was well-tolerated and it produced clinical benefits. **Since HCC is primarily intrahepatic metastases, an effective treatment intervention suppressing proliferation and metastatic potential may be a better clinical options.**

The objectives of this study were to

a) Determine the effects of milciclib alone and in combination with select tyrosine kinase inhibitors (TKIs) on the proliferation, viability, apoptosis and invasive potential on human liver cancer cell line MHCC97H and

b) Mechanistic evaluation of orally administered milciclib either alone or in combination with sorafenib on inhibition of tumor growth in an orthotopic mouse model of HCC

METHODS

IN VITRO

Cell Proliferation: This assay was performed in human liver cancer cell lines MHCC97H, MHCC97L and HepG2.215 using WST-1 reagent according to manufacturer's instructions (Sigma Aldrich, cat # 5015944001).

IN VIVO

Orthotopic Athymic Nude Mice: MHCC97H cells in PBS were mixed with 20% Matrigel and then inoculated orthotopically into the right flank of female Balb/c nude mice. After 7 days the mice were randomized based on AFP. Milciclib (30mg/Kg), Sorafenib (20 mg/Kg), Milciclib + Sorafenib or the vehicle was given orally to individual mice once daily from day 12 until day 47. After completion of the treatment at day 48, animals were euthanized and blood, liver tissues and tumor were collected for gene expression and mechanistic assays.

AFP ELISA: Human serum levels of alphafetoprotein were determined on day 0,6,12,18,24,30,36,42 & 48 using High Range AFP kit.

miRNA isolation & expression analysis: miRNA was isolated from total RNA using TaqMan Advanced miRNA assay. Results were normalized to has-miR-192-5p as reference miRNA.

Real time PCR: Real-time qPCR was employed using TaqMan Fast Advanced Master Mix and TaqMan Gene Expression probes. The expression of target genes was normalized to housekeeping gene GAPDH in each sample.

Western blotting analysis: Tumor lysates were used for immunoblotting with antibodies for PTEN, AKT, p-AKT (ser473), c-Myc, cyclin D1 and β-actin.

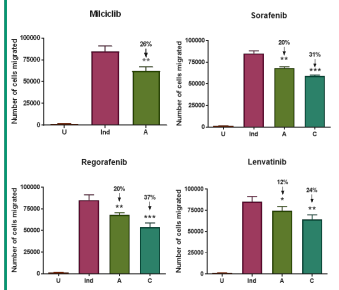
RESULTS

Synergistic effect on inhibition of cell proliferation, viability and induction of apoptosis by milciclib with other TKIs on MHCC97H cells

MHCC97H + Protein Kinase Inhibitors	KI IC50 (μM)	TKI IC50 (μM) with 1.3 μM Milciclib	Viability with 1.3 μM Milciclib IC50 (μM)	Apoptosis IC50 (μM)
Milciclib	1.3	NA	NA	NA
Sorafenib	12.0	6.7	6.4	9.7
Regorafenib	4.7	1.9	2.5	10.3
Sunitinib	30.4	17.2	15.4	27.4
Lenvatinib	0.3	0.1	0.12	0.5

(T)KI – Tyrosine Kinase Inhibitor; IC50 of Milciclib for viability and apoptosis was comparable to that observed for proliferation

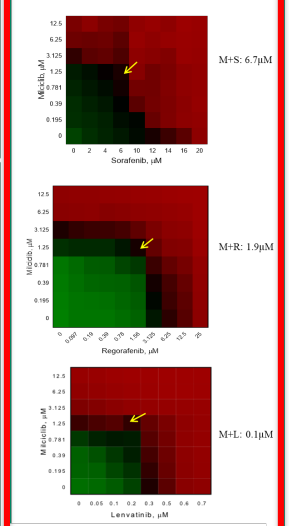
Synergism between milciclib and TKI also observed in inhibition of epithelial to mesenchymal transition of MHCC97H cells



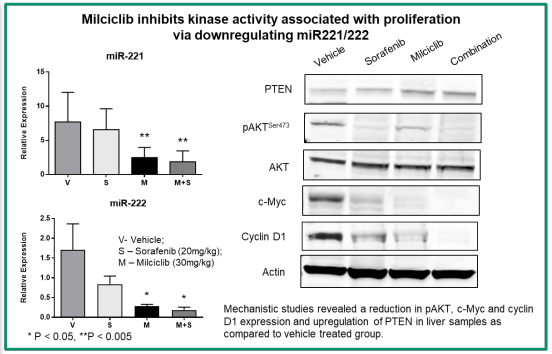
* P < 0.05, ** P < 0.005, *** P < 0.001

U= Uninduced; Ind = EMT induced; A = Indicated inhibitor alone @ IC50 ; C = Combination 0.5X IC_{50} of indicated TKI with milciclib at IC50

Heat Map depicting synergism between combinations of milciclib with TKIs on proliferation of MHCC97H Cells



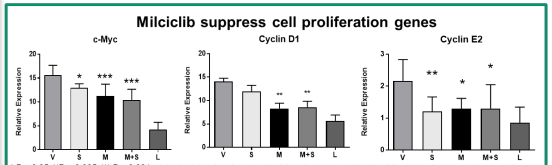
Milciclib inhibits kinase activity associated with proliferation via downregulating miR221/222



* P < 0.05, **P < 0.005

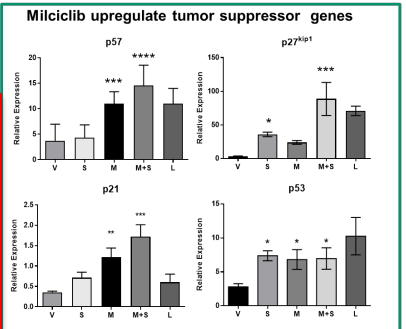
Mechanistic studies revealed a reduction in pAKT, c-Myc and cyclin D1 expression and upregulation of PTEN in liver samples as compared to vehicle treated group.

Milciclib suppress cell proliferation genes



* P < 0.05, **P < 0.005, *** P < 0.001 V- Vehicle; S – Sorafenib (20mg/kg); M – Milciclib (30mg/kg); L- Normal human liver

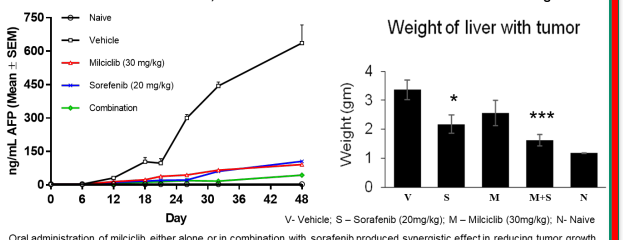
Milciclib upregulate tumor suppressor genes



V- Vehicle; S – Sorafenib (20mg/kg); M – Milciclib (30mg/kg); L- Normal human liver

* P < 0.05, **P < 0.005, *** P < 0.001

Effect of administration of milciclib, sorafenib alone or in combination of liver tumor weight & AFP

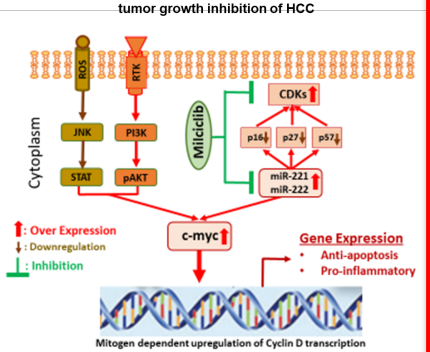


V- Vehicle; S – Sorafenib (20mg/kg); M – Milciclib (30mg/kg); N- Naive

Oral administration of milciclib either alone or in combination with sorafenib produced synergistic effect in reducing tumor growth [milciclib -20% (p<0.002) or sorafenib -21% (p<0.001) vs combination -38% (p<0.0002) as compared to vehicle.

MECHANISM

Possible mechanism for Milciclib mediated cell cycle arrest and tumor growth inhibition of HCC



The ongoing mechanistic and gene expression studies suggest that milciclib exerts its effect via downregulation of miR-221, miR-222 , oncoprotein c-Myc, and possibly through cyclin D1 resulting in upregulating p27kip1 and p57 and endogenous CDK inhibitors. *Since HCC is primarily intrahepatic metastases, an effective treatment intervention suppressing proliferation and metastatic potential may have better clinical options.*

CONCLUSIONS

- Milciclib treatment either alone or in combination with TKIs inhibited proliferation, induced apoptosis and reduce epithelial to mesenchymal transition (EMT) in HCC cell lines (MHCC97H, MHCC97L & HepG2.215)
- Milciclib produced synergistic effect with TKIs in all of the above assays
- Oral treatment with milciclib induced synergistic effect on reduction of tumor growth in combination with sorafenib
- Mechanism of action studies revealed a significant reduction in miR-221 and miR-222, cyclin D1, c-Myc and p-AKT expression and upregulation of tumor suppressors such as p27, p57 and p21 in liver samples
- Milciclib reduced the human serum AFP levels alone or in combination with sorafenib
- Our data demonstrate that milciclib follows a distinct mechanism to produce anti-HCC activity

REFERENCES

1. Albanese C, Alzani R, Amboldi N, et. al. Mol. Cancer Ther, 2010; 10.1158/1535-7163
2. Brasca MG, Amboldi N, Ballinari D, et. al. J Med Chem, 2009; 52(16):5152-63
3. Aspeslagh S, Shailubhai K, Bahleda R, et. al. Cancer Chemother Pharmacol, 2017; 79(6): 1257-1265
4. Weiss GJ, Hidalgo M, Borad MJ, et. al. Invest New Drugs, 2012; 2334-43.

DISCLOSURES

Kunwar Shailubhai and Vaseem Palejwala are employees and stockholder of Tiziana LifeSciences. Aastha Jindal has no conflicts of interests to declare.

INTERIM ANALYSIS DATA FROM MILCICLIB PHASE 2A TRIAL IN SORAFENIB-RESISTANT HCC PATIENTS

tiziana LIFE SCIENCES

- **Why interim analysis:** Since this was the first exposure of milciclib in HCC patients with, it was important to ensure safety of patient with underlying cirrhosis

- **Trial design**: Oral administration with milciclib (100 mg/day). Total patients 30 to be enrolled.
  Duration 6 months
  Primary end point: safety
  Secondary end points: PFS, ORR & TTP
  Exploratory: AFP and miRNA profiling
- **Compassionate use**: On request of patients with EC approval

- **Data from 27 evaluable sorafenib-resistant HCC patients:**
  - Ten patients completed treatment as per protocol. Seven approved for compassionate use. Three patients completed 9, 13 and 16 months, respectively. No sign of severe toxicity or deaths.
  - Milciclib treatment was well-tolerated
  - IDMC recommended to continue enrolling patients
  - Toxicities were manageable

- **Enrollment Complete**

- **Anticipated Topline data: July 2019**

MILCICLIB OVERCOMES DRUG RESISTANCE

Key Findings

- **Milciclib was well-tolerated with manageable side effects in patients with refractory solid tumors**
- **Oral treatment with milciclib in combination with gemcitabine demonstrated clinical activity in patients who were non-responder to existing chemotherapeutic drugs**
- **Recommended phase 2 dose (RPD) was found to be 150 mg/day (7 day off/7day on cycle)**
- **Overall response rate was 36%**
- **Results suggest further evaluation of milciclib in other solid cancers either as monotherapy or combo-therapy**

Cancer Chemother Pharmacol (2017) 79:1257–1265
DOI 10.1007/s00280-017-3303-z

CLINICAL TRIAL REPORT

Phase I dose-escalation study of milciclib in combination with gemcitabine in patients with refractory solid tumors

Sandrine Aspeslagh[1] · Kunwar Shailubhai[2] · Rastilav Bahleda[1] · Anas Gazzah[1] · Andréa Varga[1] · Antoine Hollebecque[1] · Christophe Massard[1] · Anna Spreafico[3] · Michele Reni[3] · Jean-Charles Soria[1]

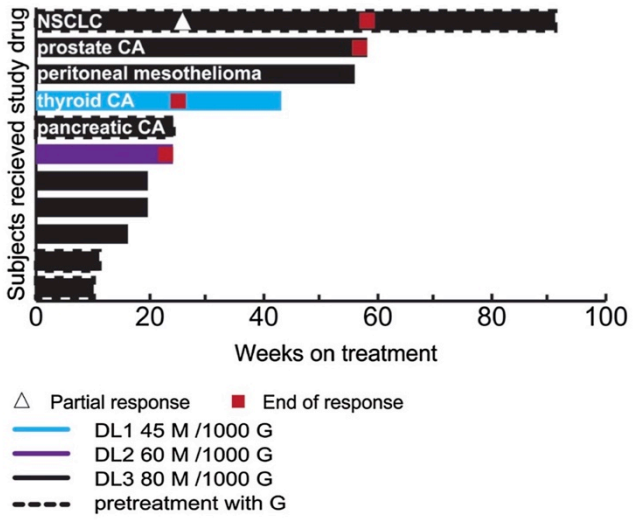


Fig. 1 Swimmerplot showing treatment duration. Tumor type was indicated for patients having a prolonged stable disease or a partial response. *M* milciclib; *G* gemcitabine

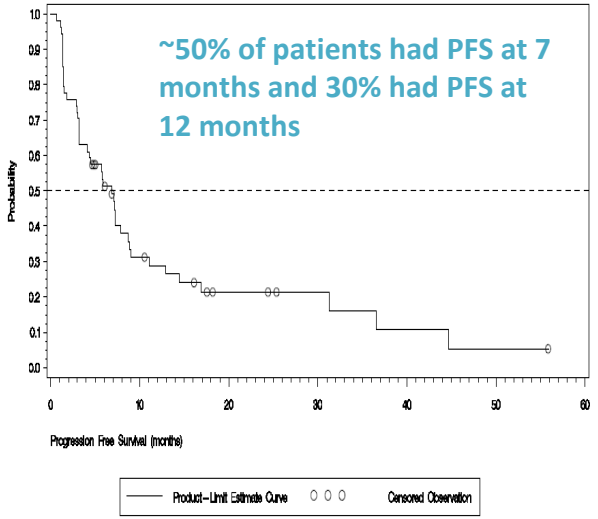
THYMIC CARCINOMA AND THYMOMA UPDATES

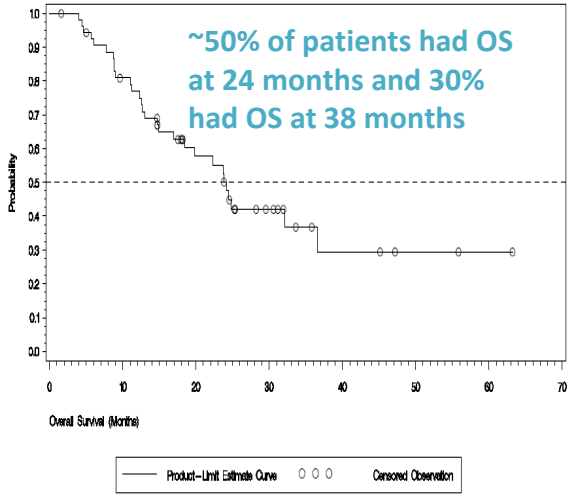
- **Two Phase 2 trials with Milciclib in US, Italy and France**
  - Trial 006: Thymic carcinoma and Thymoma mixed population (72 patients)
  - Trial 007: Thymic carcinoma and Thymoma mixed population (30 patients)
- **Rare cancers with very few cases: Orphan Disease Indications**
- **Positive clinical data**
- **Primary endpoint (PFS) and secondary endpoint (OS) met in both trials**
- **Thymic carcinoma is an aggressive metastatic cancer and it has no approved therapy**
- **Milciclib as a single agent met primary as well as secondary endpoints in thymic carcinoma in both trials**
- **Seeking guidance from FDA/EMA regarding conditional marketing approval**

TWO PHASE 2 TRIALS DEMONSTRATED CLINICAL ACTIVITY AND SAFETY OF MILCICLIB IN THYMIC CARCINOMA AND THYMOMA PATIENTS

CDKO-125a-006

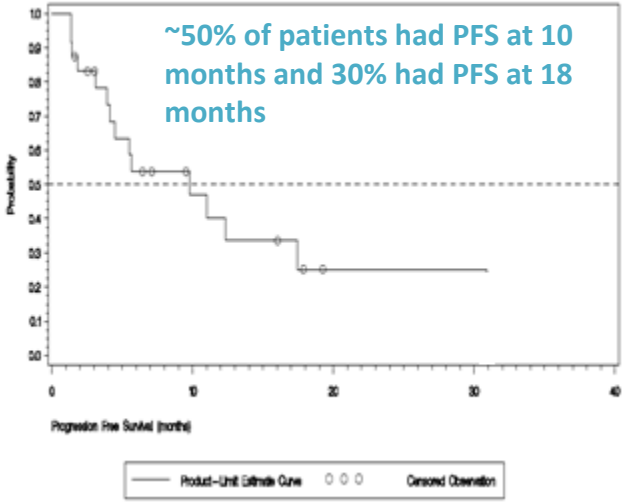
Thymic Carcinoma and Thymoma mixed population

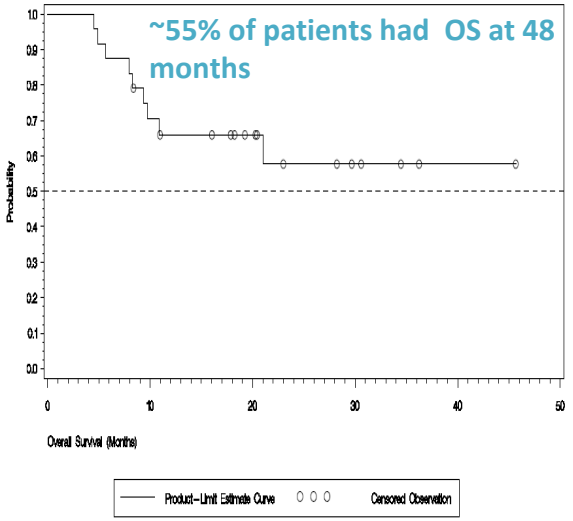




CDKO-125a-007

Thymic Carcinoma and Thymoma mixed population





Source: (1) TILS press release - Tiziana Life Sciences Announces Safety of Milciclib in a Phase 2a Trial in Unresectable or Metastatic Hepatocellular Carcinoma (HCC) Patients, Dec 8, 2017

PRECLINICAL PIPELINE

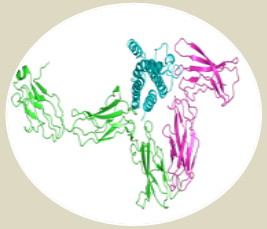
TZLS-501, a fully human anti-IL6 receptor mAb, a preclinical candidate

- **Multiple Myeloma**
- **Rheumatoid Arthritis**

TZLS-501: ANTI IL-6 RECEPTOR IS A FULLY HUMAN ANTIBODY

tiziana LIFE SCIENCES

TZLS-501



Fully human anti-interleukin-6 receptor (IL-6R) monoclonal antibody (mAb) to treat inflammatory disease

Mechanism	Indications	Opportunity	Competitive Edge	IP/Ownership
• Interleukin-6 (IL-6) is a potent cytokine regulating cell growth and differentiation as well as immune responses. • Excessive production of IL-6 and its receptor IL-6R are key drivers of chronic inflammation and inflammatory disease	• Multiple Myeloma • Could potentially be used in combination with foralumab for NASH and other inflammatory diseases such rheumatoid arthritis	• Anticipated to exert synergistic effect with foralumab for inflammatory diseases • >$35 billion market	• Differs from other anti-IL-6R mAb's (e.g. tocilizumab), by acting not only on membrane-bound IL-6R, but also on soluble IL-6R, and is also able to deplete circulating levels of IL-6 in blood	• Exclusive license from Novimmune (NI-1201) • Method of use in combination with anti-CD3 patent pending

tiziana
LIFE SCIENCES

IP PORTFOLIO

STRONG INTELLECTUAL PROPERTY PORTFOLIO

Family	Subject	Priority	Status	Expires	Jurisdiction
Foralumab TZLS-401	Methods of Use (Autoimmune or Inflammatory diseases and disorders)	2004	Issued/ Pending	2025	Australia, Canada, China, Hong Kong, Israel, Japan, Mexico, Norway, Singapore, South Africa, Ukraine, Armenia, Austria, Azerbaijan, Belgium, Belarus, Switzerland, Germany, Denmark, Spain, France, United Kingdom, Ireland, Italy, Kyrgyzstan, Kazakhstan, Luxembourg, Moldova, Netherlands, Portugal, Russian Federation, Sweden, Tajikistan, Turkmenistan,
	Composition and methods of use	2004	Issued/ Pending	2025	US, Armenia, Australia, Austria, Azerbaijan, Belarus, Canada, China, Denmark, France, Germany, Hong Kong, India, Israel, Italy, Japan, Kazakhstan, Kyrgyzstan, Mexico, Moldova, Netherlands, Norway, Republic of Korea, Russian Federation, Singapore, South Africa, Spain, Switzerland, Tajikistan, Turkmenistan, and Ukraine Pending: Brazil, Japan (divisional), Singapore (divisional), US (divisional)
	Methods of Use (In combination with anti-IL-6/IL-6R antibodies)	2011	Pending	2032	US
	Formulations and dosing regimen	2016	Pending	2037	US, Australia, Canada, China, Europe, Israel, Japan
	Methods of Use (CNS disorders)	2017	Pending	2038	PCT
	Methods of Use (gastrointestinal/autoimmune/inflammatory)	2018	Pending	2039	Provisional
Milciclib TZLS-201	Composition of matter, methods of use, process of manufacturing	2003	Issued/ Pending	2024	US, Europe, Eurasia, Africa, Algeria, Antigua & Barbuda, Argentina, Australia, Barbados, Bosnia & Herzegovina, Brazil, Canada, Colombia, Costa Rica, Croatia, Cuba, Ecuador, Egypt, Georgia, Iceland, India, Indonesia, Israel, Japan, Korea, Kosovo, Malaysia, Mexico, Mongolia, Montenegro, New Zealand, Nicaragua, Norway, Pakistan, Philippines, Serbia, Singapore, South Africa, Sri Lanka, Taiwan, Thailand, Trinidad & Tobago, Tunisia, Ukraine, Uzbekistan, Venezuela, Vietnam
	Methods of use (multiple indications)	2008; 2009	Issued	2029; 2030	US, EU, China, Hong Kong, Japan
	Methods of use (combination therapies with cytotoxics)	2008; 2009	Issued	2029; 2030	US, EU, China, Hong Kong, Japan
	Compositions of related entities, formulations and methods of treatment	2009	Issued	2030	US, EU, China, Hong Kong, Japan
	Methods of use (combination therapies with therapeutic antibodies)	2006	Issued	2027	US, EU, China, Japan
	Formulations of milciclib and therapeutic combinations of the same for use in the treatment of cancer	2017	Pending	2038	US, PCT
Anti-IL6R antibody TZLS-501	Composition of Matter and Methods of use	2009	Issued	2029	US, Austria, Australia, Belgium, Canada, China, Denmark, France, Germany, Ireland, Italy, Japan Luxembourg, Mexico, Netherland, Spain, Sweden, Switzerland and UK Pending: US (divisional), Japan (divisional), India

New patent applications have been submitted for milciclib and foralumab

LEADERSHIP TEAM & BOARD OF DIRECTORS

MANAGEMENT

Kunwar Shailubhai PhD, MBA
CEO & CSO

- Co-founder , EVP & CSO of Synergy Pharmaceuticals, NASDAQ: SGYP
- The pioneer of GC-C agonist technology inventor of TRULANCE approved for Chronic constipation and IBS-C
- VP, Callisto Pharmaceuticals
- Group Leader, Monsanto Co.

Tiziano Lazzaretti
Chief Financial Officer

- Previously Group Finance Director at Pharmentis –Teva Ratiopharm spin off
- Executive Director at Alliance Boots, Snia, Accenture and FIAT Group
- MBA, Bocconi University, Milan
- Corporate Finance, London Business School. BSc Accounting and Finance

Key Strengths of the Management Team

- Successful credentials in entrepreneurship
- Several biotechnology deals
- Proven 'Bench to market' record
- Strong credentials in Science and Business

BOARD

Gabriele Cerrone
Executive Chairman

- Proven track record & experience in financing biotechnology companies
- Served chairman of 2 biotech companies with market cap over 2 B
- Inhibitex sale $2.5Bn
- Synergy / Trovagene / Gensignia / Rasna / Contravir / Siga Technologies
- MBA, Stern School of Business, NY, USA

Leopoldo Zambeletti
Non-Executive Director

- Former head of Life Sciences M&A for Credit Suisse, EU
- Investment Banking experience at JP Morgan and Credit Suisse
- Created biggest deals in biotech. CD drug: Nogra to Celgene: AAA Accelerator to Novartis: 3.9 B
- Non-exec. director several biotech companies

Willy Simon
Non-Executive Director

- Career as a executive in the banking and corporate finance sector and director of publicly listed companies
- Kredietbank N.V., Citibank, Generale Bank NL, CEO of Fortis Investment Management
- Chairman of Bank Oyens & van Eeghen, Partner at Redi & Partners

SCIENTIFIC ADVISORY BOARD

SCIENCE ADVISORY

Howard Weiner, MD

- Professor of Neurology at Harvard Med
- Director and Founder of the Partners MS Center and Co-Director of the Ann Romney Center for Neurologic Diseases
- Pioneered investigation of the mucosal immune system for the treatment of autoimmune and other diseases

Napoleone Ferrara MD

- Inventor of Avastin® ($6.67Bn/yr)*; 2010 Lasker Award
- Senior Deputy Director Basic Sciences, Moores Cancer Center, UC San Diego
- Distinguished Prof of Pathology, School of Medicine, UC San Diego

* Roche Investor Update – February 2018

Kevin Herold, MD

- Professor of Immunobiology and Medicine and Deputy Director, Yale Center for Clinical Investigation
- Director of the Yale Diabetes Center and Director of the TrialNet Center at Yale
- Expert in autoimmune diseases and anti-CD3 monoclonal antibody therapies

Arun Sanyal MD

- Charles Caravati Distinguished Professor and Chair, Division of Gastroenterology, Hepatology and Nutrition at Virginia Commonwealth University School of Medicine
- World leader in the field of liver diseases

tiziana
LIFE SCIENCES

THANK YOU

LSE AIM:TILS