UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): April 13, 2021

MEI Pharma, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**000-50484**	**51-0407811**
(State or other jurisdiction of incorporation or organization)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

11455 El Camino Real, Suite 250
San Diego, California 92130
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: (858) 369-7100

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which registered
Common stock, $0.00000002 par value	**MEIP**	**The NASDAQ Stock Market LLC**

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

☐ Emerging growth company

☐ If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to section 13(a) of the Exchange Act.

Item 2.02. Results of Operations and Financial Condition.

The information set forth below under "Investor Presentation" in Item 8.01 below is incorporated by reference herein.

Item 8.01 Other Events.

Investor Presentation

MEI Pharma, Inc. (the "Company") is furnishing this Current Report on Form 8-K in connection with the disclosure of information contained in an investor presentation to be used by the Company at various meetings with institutional investors and analysts. A copy of the presentation is filed herewith as Exhibit 99.1 and is incorporated into this Item 8.01 by reference.

Press Release

On April 13, 2021, the Company and Kyowa Kirin issued a press release titled "MEI Pharma Announces Completion of Patient Enrollment in Follicular Lymphoma Primary Efficacy Population of Global Phase 2 TIDAL Study Intended to Support Potential Accelerated Approval Application from U.S. Food and Drug Administration (FDA)". A copy of the press release is filed herewith as Exhibit 99.2 and is incorporated into this Item 8.01 by reference.

Poster Presentation

On April 10, 2021, the Company posted a poster presentation titled "Voruciclib, a CDK9 inhibitor, downregulates MYC and inhibits proliferation of KRAS mutant cancers in preclinical models" on the Company's website. A copy of the press release is filed herewith as Exhibit 99.3 and is incorporated into this Item 8.01 by reference.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Investor Presentation
99.2	Press release dated April 13, 2021
99.3	Poster Presentation titled "Voruciclib, a CDK9 inhibitor, downregulates MYC and inhibits proliferation of KRAS mutant cancers in preclinical models"

Signatures

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

MEI PHARMA, INC.
By: /s/ Daniel P. Gold
Daniel P. Gold
Chief Executive Officer

Dated: April 13, 2021

Exhibit 99.1

Building a Leading Oncology Franchise

April 13, 2021

NASDAQ: MEIP

Forward-Looking Statements

- This presentation contains, and our officers and representatives may from time to time make, statements that are "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. Examples of forward-looking statements include, among others, statements regarding our development strategy; potential advantages of our product candidates; the initiation and completion of preclinical and clinical studies and the reporting of the results thereof; the timing of regulatory submissions and actions; the sufficiency of our existing cash; and all other statements relating to our plans, objectives, expectations and beliefs regarding future performance, operations, financial condition and other future events (including assumptions underlying or relating to any of the foregoing).
- These forward-looking statements rely on a number of assumptions concerning future events and are subject to a number of risks, uncertainties, and other factors, many of which are outside of our control. Important factors that could cause our actual results and financial condition to differ materially from those indicated in forward-looking statements include, among others: uncertainties relating to the initiation and completion of preclinical and clinical studies; whether preclinical and clinical study results will validate and support the safety and efficacy of our product candidates; the outcome of regulatory reviews of our product candidates; varying interpretation of research and development and market data; the impact of the COVID-19 pandemic on our industry and individual companies, including on our counterparties, the supply chain, the execution of our clinical development programs, our access to financing and the allocation of government resources; risks and uncertainties relating to intellectual property and the other factors discussed under the caption "Item 1A. Risk Factors" in our most recent annual report on Form 10-K and our most recent quarterly report on Form 10-Q.
- Any forward-looking statement made by us in this presentation is based only on information currently available to us and speaks only as of the date on which it is made. In addition, we operate in a highly competitive and rapidly changing environment, and new risks may arise. Accordingly, you should not place any reliance on forward-looking statements as a prediction of actual results. We disclaim any intention to, and undertake no obligation to, update or revise any forward-looking statement. You are urged to carefully review and consider the various disclosures in our most recent annual report on Form 10-K, our most recent Form 10-Q and our other public filings with the SEC since the filing of our most recent annual report.

MEI Pharma: Who We Are

- Clinical Development Company Building a Leading Oncology Franchise with 4 Clinical-Stage Programs: Focus On HemOnc

- Zandelisib (f/k/a ME-401) Potential Best-in-Class PI3Kδ Inhibitor in Phase 2 Study Intended to Support Accelerated Approval Application with U.S. FDA

- Well Capitalized with ~$164.6 Million*

* As of March 31, 2021, MEI had preliminary $164.6 million in cash, cash equivalents, and short-term investments with no outstanding debt (Unaudited).

Zandelisib Topline TIDAL Study Data on Track to be Reported in the Fourth Quarter of CY2021

Announced Today:

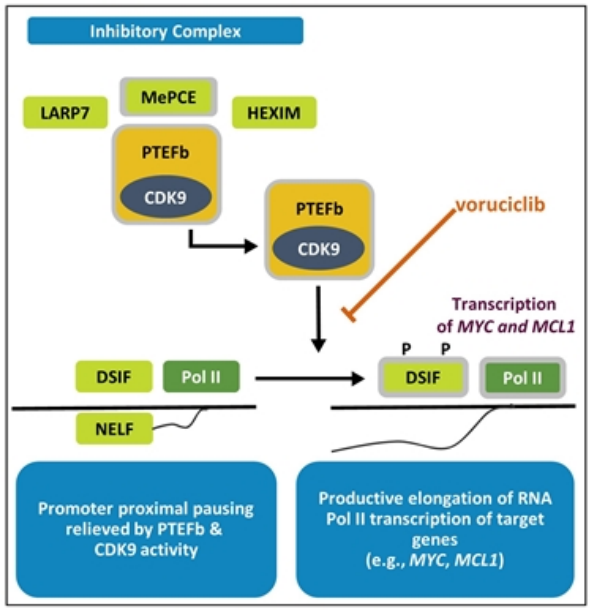
Enrollment Complete in Follicular Lymphoma Primary Efficacy Population of Global Phase 2 TIDAL

The complete Phase 2 TIDAL study data are intended to be submitted to FDA to support accelerated approval applications

Voruciclib: Oral CDK Inhibitor with Potent CDK9 Activity

Preclinical Data

CDK9 Regulates *MYC and MCL1* Transcription by RNA POL II



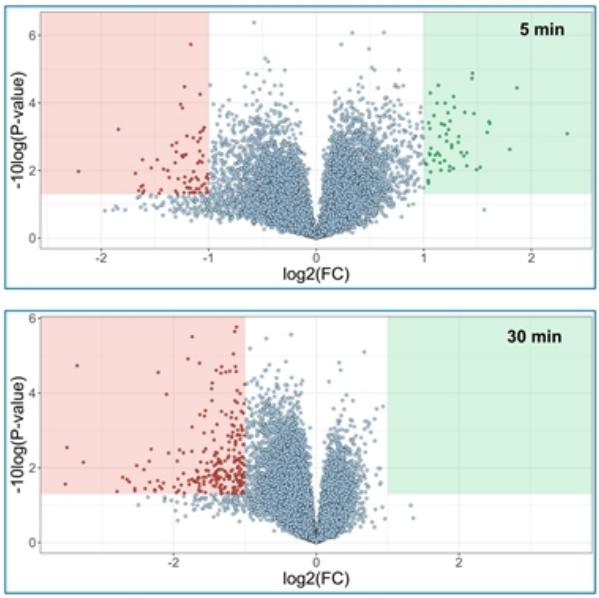
Wiley et al, AACR 2021

Voruciclib Induces Rapid Down Regulation of RNA POL II Associated Proteins That Control *MYC and MCL1* Transcription

Summary of Phosphoproteomics Analysis	
Total Peptides	98,140
Total Proteins	5,753
Phosphoproteins (n)	**4,806**
Phosphosites (n)	**21,384**

Voruciclib (min)	Downreg Phospho-peptides (n)	Downreg Phospho-proteins (n)
5	72	67
15	33	28
30	237	174
60	159	117

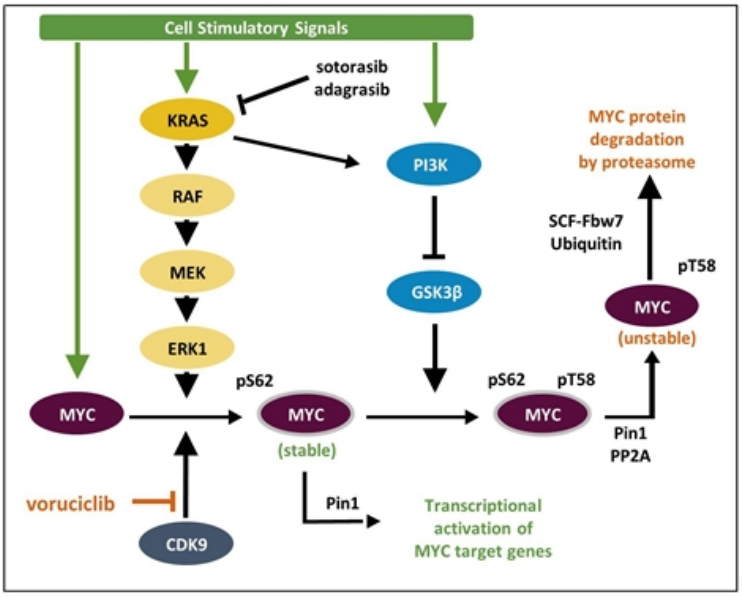
16-plex TMT labelling, IMAC phosphopeptide enrichment, HPLC fractionation, and analysis by LC-MS/MS.



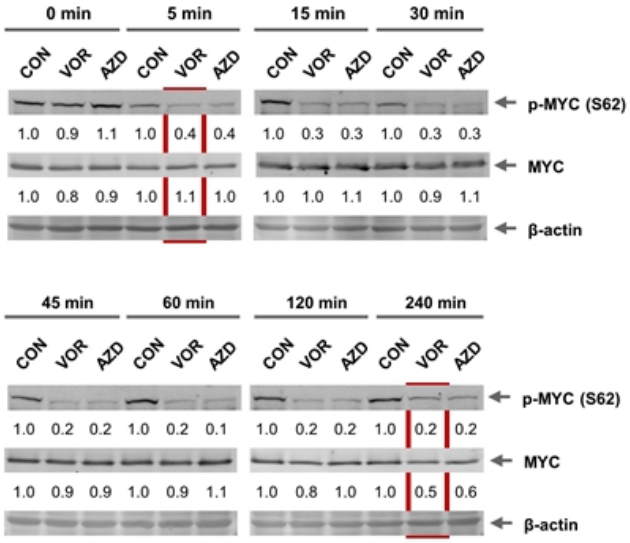
Database ID	Gene Symbol	Role in RNA Pol II Regulation
P24928	POLR2A	RNA Pol II complex
Q96ST2	IWS1	
O60885	BRD4	pTEFb complex
Q03111	MLLT1	
Q7L2J0	MEPCE	pTEFb regulation
O00267-2	SUPT5H	RNA Pol II regulation
Q15648	MED1	
P23193	TCEA1	
Q9UHB7	AFF4	

Wiley et al, AACR 2021

CDK9 Regulates *MYC* Protein Stability



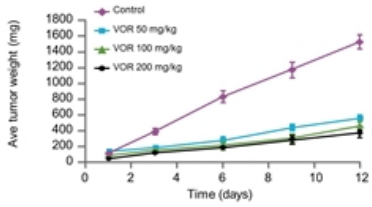
Voruciclib Causes Rapid Inhibition of MYC pSer62 Phosphorylation and Reduces MYC Protein Levels



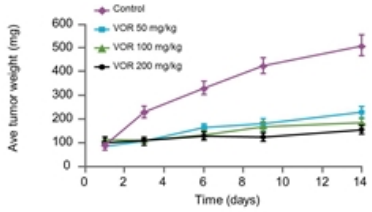
Wiley et al, AACR 2021

Voruciclib Inhibits *KRAS* Mutant Cell Growth *In Vitro* and *In Vivo in Xenograft Mice*

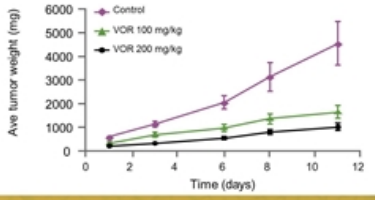
Cell Line	Indication	*KRAS* Mut	IC_{50} (μM)
Gp2D	CRC	G12D	0.8
HCT-116	CRC	G13D	1.8
LS-513	CRC	G12D	0.6
SW-480	CRC	G12V	3.9
SW837	CRC	G12C	2.1
KYSE-410	Esoph	G12C	1.9
RPMI-8226	MM	G12A	2.4
A-549	NSCLC	G12S	1.5
Calu-1	NSCLC	G12C	2.0
HCC1171	NSCLC	G12C	3.0
HCC44	NSCLC	G12C	0.8
NCI-H460	NSCLC	Q61H	3.1
NCI-H1373	NSCLC	G12C	1.2
NCI-H1792	NSCLC	G12C	1.4
NCI-H2030	NSCLC	G12C	1.1
NCI-H23	NSCLC	G12C	1.2
NCI-H358	NSCLC	G12C	0.6
TOV-21G	Ovarian	G13C	1.7
AsPC-1	PDAC	G12D	2.3
HPAF-II	PDAC	G12D	1.9
MIA PaCa-2	PDAC	G12C	1.1
Panc 04.03	PDAC	G12D	1.4



HCT-116
(CRC, KRAS G13D)



SW-480
(CRC, KRAS G12V)



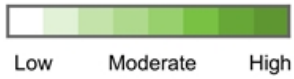
H460
(NSCLC, KRAS Q61H)

Wiley et al, AACR 2021

Leveraging CDK9 Regulation of MYC: Exploring Synergy with Direct KRAS Inhibitors

VORUCICLIB SYNERGIZES WITH *KRAS* G12C INHIBITORS *IN VITRO*

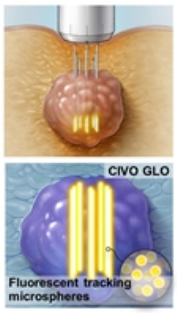
Cell Line	*KRAS* mut	Sensitivity to G12C Inhibitors	Synergy Scores: Voruciclib + Sotorasib	Synergy Scores: Voruciclib + Adagrasib
NCI-H23	G12C	High		
HCC1171	G12C	High		
MIA Paca-2	G12C	High		
SW837	G12C	Moderate - High		
NCI-H2030	G12C	High		
Calu-1	G12C	Moderate - High		
HCC-44	G12C	Moderate - High		
NCI-H1373	G12C	Moderate - High		
NCI-H358	G12C	High		
NCI-H1792	G12C	Moderate - High		
KYSE-410	G12C	Low - High		
Panc 04.03	G12D	Low		
Gp2D	G12D	Low		
LS-513	G12D	Low - Moderate		
AsPC-1	G12D	Low		
HPAF-II	G12D	Low		
TOV-21G	G13C	Low		



Non-small cell lung cancer cell lines
Pancreatic adenocarcinoma cell lines
Colorectal cancer cell lines
Esophageal cancer cell line
Ovarian cell line

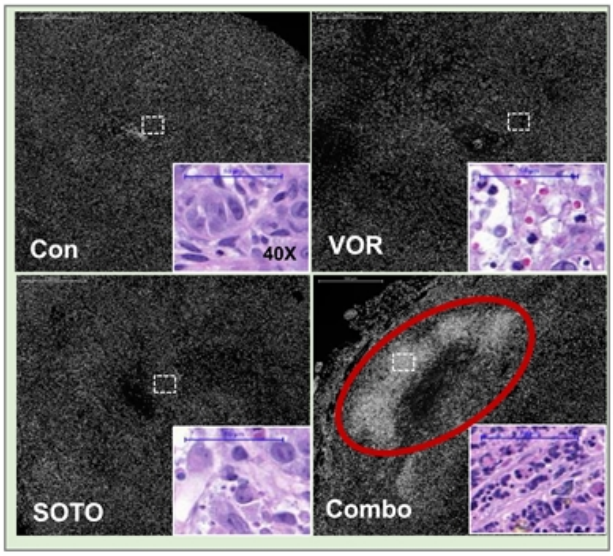
Wiley et al, AACR 2021

Leveraging CDK9 Regulation of MYC: *In Vivo* Synergy with Sotorasib in MIA PaCa-2 Tumors



Intratumoral injection of drugs & fluorescent microspheres with Presage CIVO technology

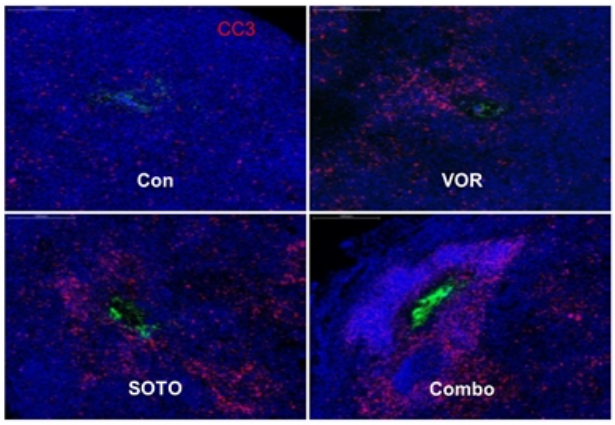
Processing of tumors for IHC & staining with DAPI, CC3, H&E

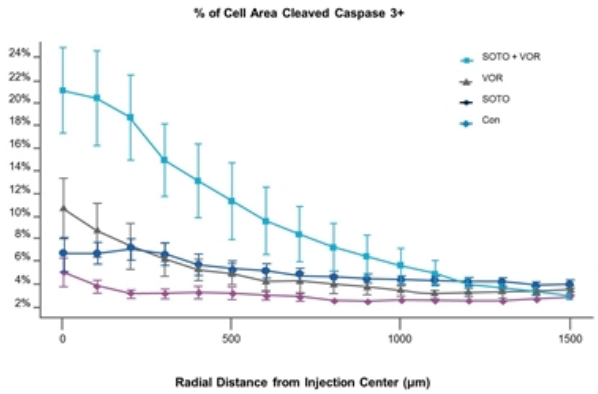


Representative IHC images of DAPI and H&E staining in a Murine Xenograph Model

Wiley et al, AACR 2021

Leveraging CDK9 Regulation of MYC: *In Vivo* Synergy with Sotorasib in MIA PaCa-2 Tumors





Data represents 5 tumors with duplicate combination and SOTO injection sites per tumor, single injection sites other conditions; 4 sections imaged per tumor (Murine Xenograph Model) .

CONCLUSIONS

- MYC is implicated in *KRAS* mutant tumors. CDK9 is a known regulator of *MYC* transcription and a modulator of MYC protein phosphorylation at Ser62
- Treatment of *KRAS* G12C mutant MIA PaCa-2 pancreatic cancer cells with voruciclib resulted in a rapid decrease in both phosphorylation of proteins that regulate transcription of *MYC,* and in phosphorylation of MYC protein on Ser62 that was followed by a reduction in total MYC protein
- In *in vitro* and *in vivo* preclinical models, voruciclib demonstrated single agent activity against multiple *KRAS* mutant cancer cell lines harboring various G12, G13, and Q61 mutations
- Voruciclib acted synergistically with KRAS G12C inhibitors in killing *KRAS* G12C mutant cancer cell lines, both *in vitro* and *in vivo*
- Collectively, these experiments suggest that voruciclib could be an attractive therapeutic option for cancers driven by KRAS-MYC

Voruciclib: Oral CDK Inhibitor with Potent CDK9 Activity

Clinical Experience

Piramal Monotherapy Phase 1 Studies in Solid Tumors

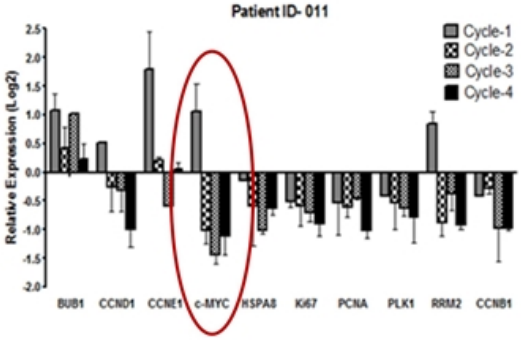
- 2 weeks on, 1 week off schedule
  - 75 to 850 mg
  - 29 pts in dose escalation / expansion at 600 mg cohorts
  - 41% disease control rate
    - 1 PR and 8 SD lasting 2 to 6 months
- Daily continuously schedule
  - 75 to 500 mg
  - 39 pts in dose escalation / expansion at 350 mg cohorts
  - 31% disease control rate
    - 12 SD lasting a median of 15 weeks
- Safety profile
  - Most common AEs involved GI tract
  - 9 Drug related SAEs
    - 2 at doses <350 mg: infectious diarrhea, hematuria due to low platelets
    - 7 at doses 350-850 mg: Diarrhea (2), renal failure (2), death/hypokalemia, death/abdominal pain, increased INR
  - No evidence of myelosuppression

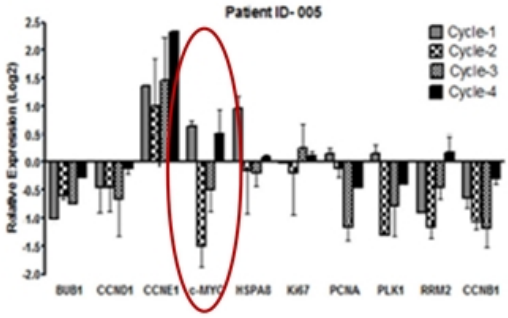
MEI pharma

Data on file.

Decreased c-MYC Expression in Solid Tumors

- 10 gene biomarkers evaluated in Phase 1 daily dosing study
- c-MYC expression decreased in 17/25 patients (68%) tested





Data on file.

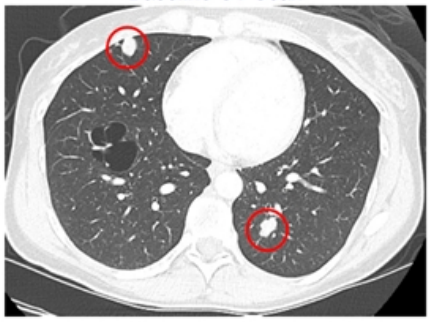
Piramal Study of Voruciclib + Vemurafenib in BRAF-mut Advanced/Inoperable Malignant Melanoma

- Voruciclib 150 mg daily plus vemurafenib 720 mg or 960 mg BID in 28-day cycles
- 9 pts treated before study termination for business reasons
- 8 patients evaluable for efficacy
  - 5 patients were BRAFi refractory
    - ➢ Best Response = PD
  - 3 patients were BRAF/MEK naïve
    - ➢ **1 CR and 2 PR ongoing for 3 to 14 months**
- Most common AEs were fatigue, constipation, diarrhea, arthralgia and headache
  - 1 DLT = grade 3 fatigue
  - No SAEs related to voruciclib

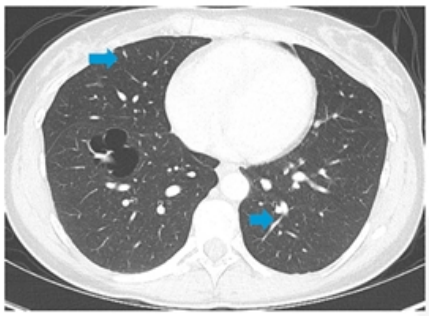
Diab et al, ASCO 2015

CR in a Patient with Pulmonary Metastases

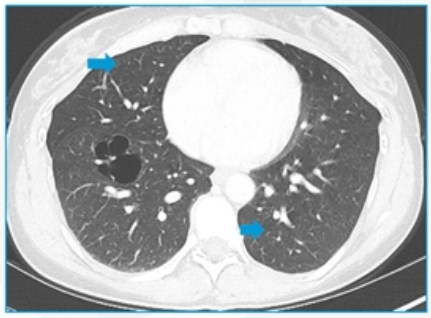
Baseline CT Scan



2 months after starting the trial
(Radiological CR (based on official radiology report)



14 months after starting the Trial
Patient remained on trial for 12 months only, and CR remained durable for 14 months. Patient still alive as of January 2017



Data on file.

Leveraging CDK9 Regulation of MCL1: Phase 1 Study in R/R B-Cell Malignancies and AML

- Study population
  - Relapsed/Refractory B-cell malignancies
  - Relapsed/Refractory AML
- Dose escalation with standard 3+3 design

- Endpoints
  - Safety and tolerability
  - Pharmacokinetics
  - Biologic correlative studies
    - BH3 profiling, MCL-1 expression (Dana Farber)
    - Molecular mutations analysis (City of Hope)
  - Response rates

Voruciclib single agent dose escalation/optimization - Enrolling

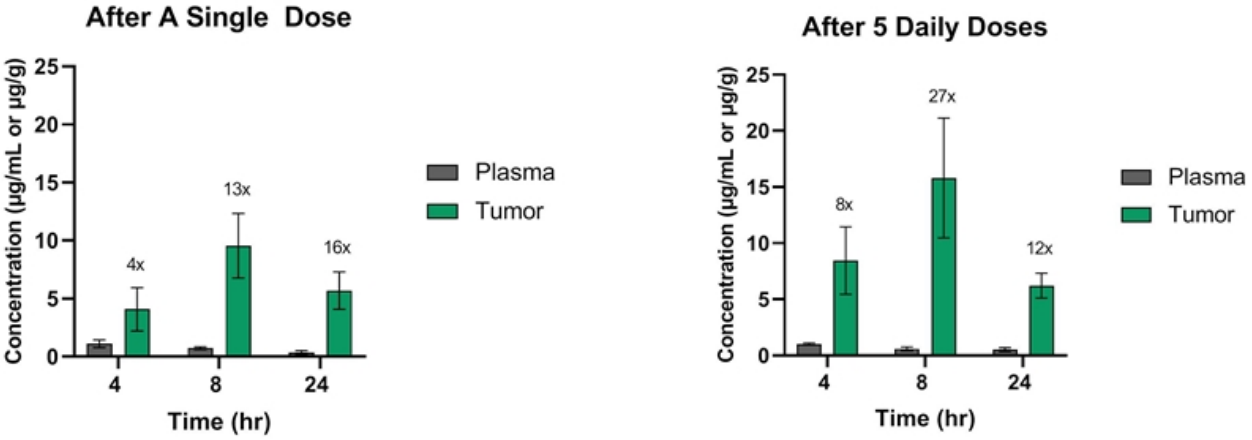
50 mg > **100 mg** > **150 mg** > **200 mg**

Phase 1 Study in Hematologic Malignancies

- 24 pts treated in 3 dose levels
  - 10 AML and 14 B-cell malignancies
- No drug related GI toxicity or neutropenia at doses studied
- Favorable PK profile across all voruciclib studies
  - Half life 24-28 hours supports once-a-day dosing
  - Dose proportional Cmax and AUC
  - High volume of distribution indicates broad entry into tissues
- Doses of 150-200 mg projected to achieve plasma concentrations sufficient to inhibit molecular target

Data on file.

Voruciclib Shows Preferential Tumor Accumulation in Preclinical Model



HCT-116 CRC cell xenograft in SCID mice. 8 mice per time point (2 control, 6 orally dosed with voruciclib at 100 mpk). Voruciclib fold increase in tumors relative to plasma are indicated.

Data on file.

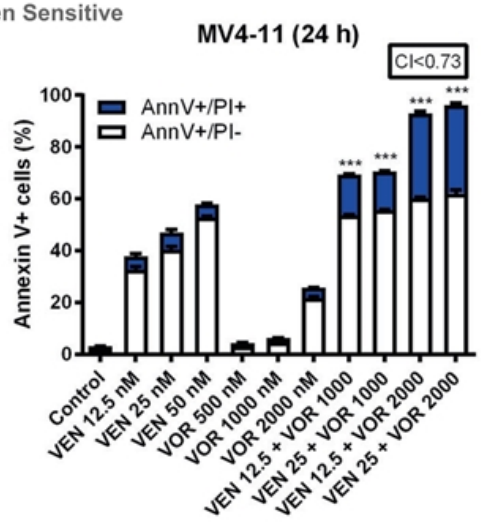
Evidence of Biologic Activity in AML

- Suspected Differentiation syndrome seen in 5 pts (50%)
  - Increased WBC without increased in blasts, bone pain, and/or pulmonary symptoms
  - Response to corticosteroids
- Differentiation syndrome reported with ATRA, IDHi, and other AML targeted therapies

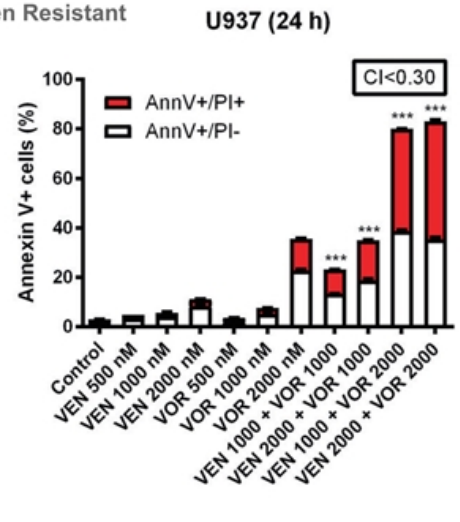
Data on file.

Voruciclib Synergizes with Venetoclax in Venetoclax Sensitive and Resistant Cell Lines

Ven Sensitive



Ven Resistant



Luedtke, et al. Nat Sign Trans and Targ Ther. 2020

Phase 1 Study of Voruciclib + Venetoclax in AML
Planned Amendment

- Study population
  - Relapsed/Refractory B-cell malignancies
  - Relapsed/Refractory AML
- Dose escalation with standard 3+3 design

- Endpoints
  - Safety and tolerability
  - Pharmacokinetics
  - Biologic correlative studies
    - BH3 profiling, MCL-1 expression (Dana Farber)
    - Molecular mutations analysis (City of Hope)
  - Response rates

Voruciclib single agent dose escalation/optimization – Enrolling

50 mg > 100 mg > 150 mg > 200 mg

Voruciclib + Venetoclax dose escalation (Pending FDA approval)

V^2

100 mg > 150 mg > 200 mg

Key Upcoming 12 Month Milestones Across Portfolio

- **Zandelisib**
  - TIDAL, study intended to support accelerated approval application for R/R follicular lymphoma:
    - Announce top-line data fourth quarter CY2021
  - New clinical studies to expand development, including:
    - COASTAL, intended confirmatory Phase 3 study + Rituxan® in 2L FL/MZL
    - TIDAL study arm: 3L MZL
    - 1L DLBCL + RCHOP (IIT)
  - Initial data of Phase 1b evaluating zandelisib with zanubrutinib under clinical collaboration with BeiGene: Mid CY2021
- **Voruciclib**
  - Initial data, Phase 1 monotherapy and +BCL2i data updates
- **ME-344**
  - Institute plan to leverage clinically demonstrated anti-tumor activity in combination with anti-VEGF
- **Pracinostat**
  - Program / Phase 2 MDS Helsinn Update

Q&A

NASDAQ: MEIP

Building a Leading Oncology Franchise

April 13, 2021

NASDAQ: MEIP

MEI Pharma and Kyowa Kirin Announce Completion of Patient Enrollment in Follicular Lymphoma Primary Efficacy Population of Global Phase 2 TIDAL Study Intended to Support Potential Accelerated Approval Application from U.S. Food and Drug Administration (FDA)

Topline TIDAL Study Data on Track to be Reported in the Fourth Quarter

SAN DIEGO, April 13, 2021 — MEI Pharma, Inc. (NASDAQ: MEIP), a late-stage pharmaceutical company focused on advancing potential new therapies for cancer, and Kyowa Kirin Co., Ltd. (TSE:4151, Kyowa Kirin), a global specialty pharmaceutical company that strives to create new value through the pursuit of advances in life sciences and technologies, today announced completion of enrollment in the follicular lymphoma primary efficacy population of the global Phase 2 TIDAL study. Topline data from the study is on track to be reported in the fourth quarter. If successful, the complete Phase 2 TIDAL study data are intended to be submitted to FDA to support accelerated approval applications under 21 CFR Part 314.500, Subpart H.

Following discussions with FDA, MEI finalized the sample size to evaluate zandelisib in patients with follicular and marginal zone lymphomas in the global Phase 2 TIDAL study. The primary efficacy population sample size for follicular lymphoma is 91 patients and the primary efficacy population sample size for marginal zone lymphoma is 64 patients. To provide a robust safety database, MEI will maintain the total study enrollment of approximately 120 follicular lymphoma patients and 64 marginal zone lymphoma patients.

“The completion of enrollment in the follicular lymphoma efficacy population arm of the TIDAL study is an important milestone for the zandelisib program, and we are grateful to the patients and healthcare providers that are participating in the TIDAL study as we diligently work to advance the program towards potential U.S. marketing authorization,” said Daniel P. Gold, Ph.D., president and chief executive officer of MEI Pharma. “In collaboration with our partner, Kyowa Kirin, we are committed to exploring zandelisib’s full potential, both as a monotherapy and in combination with other agents, for patients with B-cell malignancies.”

“I am truly pleased with this news that the enrollment for the patients with the follicular lymphoma has been successfully completed,” said Yoshifumi Torii, Ph.D., Executive Officer, Vice President, Head of Global R&D Division of Kyowa Kirin. “One of our big missions is to steadily advance this drug, which we believe has the potential to provide new value to patient suffering from the follicular lymphoma. We are looking forward to working closely with MEI Pharma to ensure that we fulfill that mission and our responsibilities.”

About Zandelisib

Zandelisib (formerly called ME-401), a selective PI3Kd inhibitor, is an investigational cancer treatment being developed as an oral, once-daily, treatment for patients with B-cell malignancies. In March 2020 the U.S. FDA granted zandelisib Fast Track designation for treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least 2 prior systemic therapies.

In April 2020, MEI and Kyowa Kirin entered a global license, development, and commercialization agreement to further develop and commercialize zandelisib. MEI and Kyowa Kirin will co-develop and

co-promote zandelisib in the U.S., with MEI booking all revenue from the U.S. sales. Kyowa Kirin has exclusive commercialization rights outside of the U.S. and will pay MEI escalating tiered royalties on ex-U.S. sales.

Ongoing zandelisib studies include a Phase 2 pivotal study in Japan in patients with indolent B-cell non-Hodgkin's lymphoma (iNHL) without small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPL), and Waldenström's macroglobulinemia (WM) conducted by Kyowa Kirin.

About the TIDAL Phase 2 Study

The TIDAL study (**T**rials of P**I**3K **D**elt**A** in Non-Hodgkin's **L**ymphoma) is a global Phase 2 study evaluating zandelisib as a monotherapy across two study arms: the first study arm for the treatment of adults with relapsed and refractory follicular lymphoma and the second study arm for marginal zone lymphomas, in both cases after failure of at least two prior systemic therapies including chemotherapy and an anti-CD20 antibody. The primary endpoints of the study are the objective response rate and the tolerability of zandelisib.

Subject to the results and discussions with FDA, data from each study arm are intended to be submitted to FDA to support separate accelerated approval marketing applications under 21 CFR Part 314.500, Subpart H.

The study is evaluating zandelisib administered once daily at 60 mg for two 28-day cycles and then on an intermittent schedule (IS) of once daily dosing for the first seven days of each subsequent 28-day cycle. Approximately 120 follicular lymphoma and 60 marginal zone lymphoma patients will be enrolled and treated with the IS regimen. The primary efficacy endpoint will be the rate of objective responses to therapy and other endpoints will include duration of response and tolerability of zandelisib.

More information about this trial is available at ClinicalTrials.gov.

About Follicular and Marginal Lymphomas

Follicular lymphoma (FL) is the most common indolent lymphoma, comprising about 20-30% of all non-Hodgkin lymphomas. The disease also forms on B cells, is chronic in most cases and tends to progress slowly. Most people diagnosed with FL are over 65 years of age. Sometimes follicular lymphomas can change into diffuse large B-cell lymphoma, a fast-growing (aggressive) type of NHL.

Marginal zone lymphoma (MZL) is a group of indolent, or slow growing, lymphomas. The disease forms on B-cells, a type of white blood cell called a lymphocyte. MZL accounts for approximately eight percent of all non-Hodgkin lymphoma cases; over 77,000 cases of non-Hodgkin lymphoma are diagnosed in the U.S. each year. The average age at diagnosis is 60 years, and it is slightly more common in women than in men.

About MEI Pharma

MEI Pharma, Inc. (Nasdaq: MEIP) is a late-stage pharmaceutical company focused on developing potential new therapies for cancer. MEI Pharma's portfolio of drug candidates contains four clinical-stage assets, including zandelisib, currently in an ongoing Phase 2 clinical trial which may support an accelerated approval marketing application with the U.S. Food and Drug Administration. Each of MEI Pharma's pipeline candidates leverages a different mechanism of action with the objective of developing therapeutic options that are:
(1) differentiated, (2) address unmet medical needs and (3) deliver

improved benefit to patients either as standalone treatments or in combination with other therapeutic options. For more information, please visit www.meipharma.com.

About Kyowa Kirin

Kyowa Kirin strives to create and deliver novel medicines with life-changing value. As a Japan-based Global Specialty Pharmaceutical Company with a heritage of 70+ -years, we apply cutting-edge science including an expertise in antibody research and engineering, to address the needs of patients and society across multiple therapeutic areas including Nephrology, Oncology, Immunology/Allergy and Neurology. Across our four regions – Japan, Asia Pacific, North America and EMEA/International – we focus on our purpose, to make people smile, and are united by our shared values of commitment to life, teamwork/Wa, innovation, and integrity. You can learn more about the business of Kyowa Kirin at: https://www.kyowakirin.com.

Forward-Looking Statements

Under U.S. law, a new drug cannot be marketed until it has been investigated in clinical studies and approved by the FDA as being safe and effective for the intended use. Statements included in this press release that are not historical in nature are "forward-looking statements" within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. You should be aware that our actual results could differ materially from those contained in the forward-looking statements, which are based on management's current expectations and are subject to a number of risks and uncertainties, including, but not limited to, our failure to successfully commercialize our product candidates; costs and delays in the development and or FDA approval, or the failure to obtain such approval, of our product candidates; uncertainties or differences in interpretation in clinical trial results; the impact of the COVID-19 pandemic on our industry and individual companies, including on our counterparties, the supply chain, the execution of our clinical development programs, our access to financing and the allocation of government resources; our inability to maintain or enter into, and the risks resulting from our dependence upon, collaboration or contractual arrangements necessary for the development, manufacture, commercialization, marketing, sales and distribution of any products; competitive factors; our inability to protect our patents or proprietary rights and obtain necessary rights to third party patents and intellectual property to operate our business; our inability to operate our business without infringing the patents and proprietary rights of others; general economic conditions; the failure of any products to gain market acceptance; our inability to obtain any additional required financing; technological changes; government regulation; changes in industry practice; and one-time events. We do not intend to update any of these factors or to publicly announce the results of any revisions to these forward-looking statements.

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Voruciclib, a CDK9 inhibitor, downregulates MYC and inhibits proliferation of *KRAS* mutant cancers in preclinical models

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ABSTRACT

Mutations in *KRAS* at G12, G13, and Q61 are oncogenic drivers in many cancers, including lung, colorectal, pancreatic, bone marrow, and endometrial carcinomas.[1] *KRAS* mutations are frequently accompanied by stabilization of the MYC oncoprotein through increased *MYC* transcription and decreased protein degradation that is mediated by phosphorylation of MYC on Ser 62 by ERK and CDK9 kinases.[2,3] Voruciclib is a novel oral inhibitor of CDKs 9, 4, 6, and 1 that is currently being tested in Phase 1B clinical trials (NCT03547115) for B-cell malignancies and acute myeloid leukemia.[4] Voruciclib inhibition of CDK9 leads to decreased expression of transcriptional targets of RNA Pol II, such as *MCL1* and *MYC*.[5] Phosphoproteomics analysis revealed that voruciclib treatment resulted in a reduction in phosphorylation of proteins that regulate Pol II. To investigate MYC protein stability, MIA PaCa-2 (*KRAS* G12C) cells were treated with voruciclib, followed by Western Blot analysis with α-MYC and α-pSer62-MYC antibodies. Voruciclib treatment resulted in a reduction in phosphorylation of MYC on Ser 62. A 60% decrease in pSer62 was observed after 5 min that reached 80% by 60 min. In contrast, there was no decrease in total MYC protein at either 5 or 15 min. A 10% reduction in total MYC was observed at 60 min that reached 50% at 240 min. To test if voruciclib could be effective in cancers driven by dysregulated KRAS-MYC signaling, 22 cancer cell lines with *KRAS* mutations (G12A, G12C, G12D, G12S, G12V, G13C, G13D, Q61H) were treated in preclinical studies with voruciclib *in vitro*. Voruciclib decreased viability in all cell lines tested and inhibited tumor growth *in vivo* in murine xenograft models using *KRAS* mutant human cancer cells: HCT-116 (CRC, *KRAS* G13D), SW-480 (CRC, *KRAS* G12V), and H-460 (NSCLC, *KRAS* Q61H). Voruciclib also demonstrated synergy *in vitro* with the KRAS G12C inhibitors sotorasib (AMG 510) and adagrasib (MRTX849) in cell lines from multiple indications and *in vivo* within a MIA PaCa-2 murine xenograft model. Collectively, these data demonstrate that voruciclib inhibition of CDK9 leads to reduced phosphorylation of MYC on Ser62 followed by a decrease in total MYC protein in MIA PaCa-2 cells, and inhibition of growth in multiple *KRAS* mutant cancer cell lines *in vivo* and *in vitro*. This suggests that voruciclib could be an attractive therapeutic option for cancers driven by KRAS-MYC, possibly in combination with KRAS G12C inhibitors.

CDK9 REGULATES TRANSCRIPTION OF *MYC* BY RNA POL II AND MYC PROTEIN STABILITY

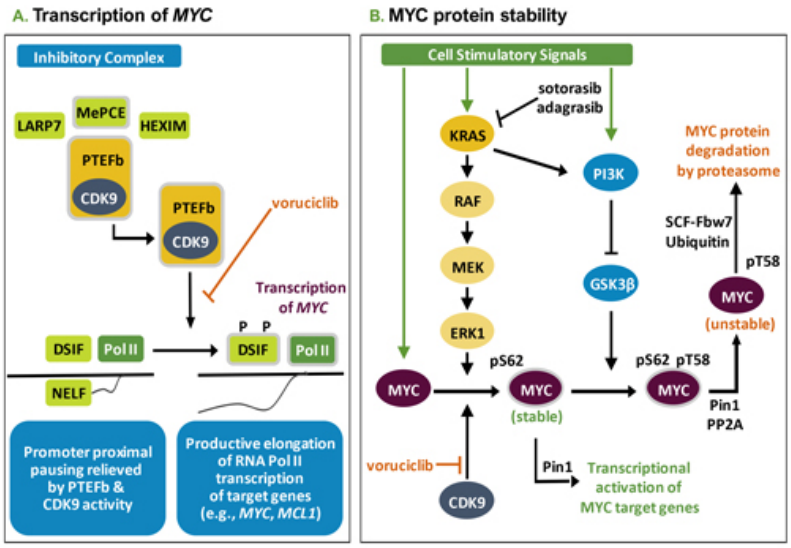

Figure 1. Schematic illustrating (A) P-TEFb regulation of RNA Pol II driven transcription of *MYC* and (B) KRAS-ERK1 signaling pathway and regulation of MYC protein stability by phosphorylation of Ser 62. Proteins with decreased phosphorylation after voruciclib treatment are circled in light gray. Points of CDK9 inhibition by voruciclib are noted.

Poster # 1962

Voruciclib, a CDK9 inhibitor, downregulates MYC and inhibits proliferation of *KRAS* mutant cancers in preclinical models

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VORUCICLIB INDUCES RAPID DOWN REGULATION OF RNA POL II ASSOCIATED PROTEINS THAT CONTROL *MYC* TRANSCRIPTION

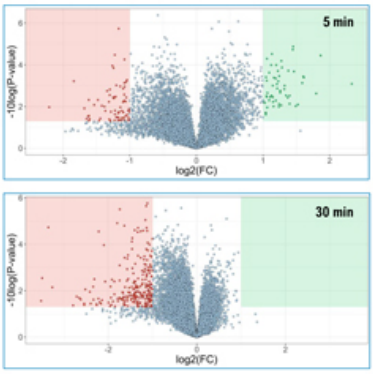
A.

Summary of Phosphoproteomics Analysis	
Total Peptides	98,140
Total Proteins	5,753
Phosphoproteins (n)	4,806
Phosphosites (n)	21,384

C.

Voruciclib (min)	Downreg Phospho-peptides (n)	Downreg Phospho-proteins (n)
5	72	67
15	33	28
30	237	174
60	159	117

B.



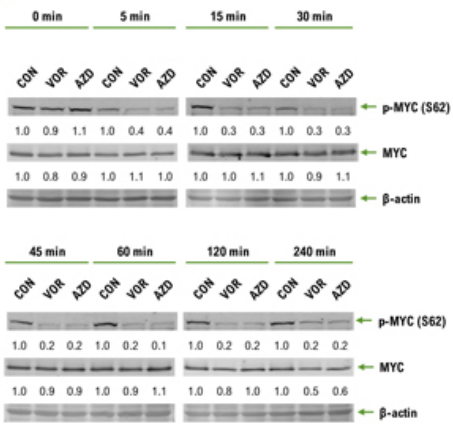
D.

Database ID	Gene Symbol	Role in RNA Pol II Regulation
P24928	POLR2A	RNA Pol II complex
Q96ST2	IWS1	
O60885	BRD4	pTEFb complex
Q03111	MLLT1	
Q7L2J0	MEPCE	pTEFb regulation
O00267-2	SUPT5H	RNA Pol II regulation
Q15648	MED1	
P23193	TCEA1	
Q9UHB7	AFF4	

Figure 2. Landscape of the voruciclib-sensitive phosphoproteome in MIA Paca-2 cells reveals rapid downregulation of phosphoproteins controlling transcription of *MYC*. Cells were treated with voruciclib (4 μM) for 5, 15, 30, 60 min, followed by lysis, 16-plex TMT labelling, IMAC phosphopeptide enrichment, and analysis by LC-MS/MS. (A) Summary of total and phosphopeptide quantification for combined samples after MS. (B) Volcano plots of phosphosites (log2 fold change vs –log10 p-value). Significantly downregulated phosphosites are shown in red. Significantly upregulated phosphosites are shown in green ($p \leq 0.05$. Fold change ≥2.0). (C) Summary of significantly down-regulated phosphoproteins and phosphopeptides over time. (D) Downregulated phosphoproteins with a role in regulation of RNA Pol II activity. UniProt database ID and gene symbols noted.

VORUCICLIB CAUSES RAPID INHIBITION OF MYC pSer62 PHOSPHORYLATION AND REDUCES MYC PROTEIN LEVELS

A.



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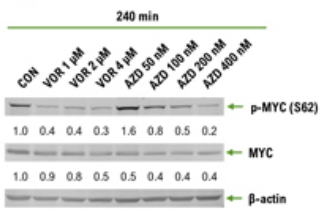

Figure 3. Immunoblot analyses of c-MYC, phospho-c-MYC (Ser62), and actin in MIA Paca-2 *KRAS* G12C mutant PDAC cells. (A) Cells were treated with vehicle control, voruciclib (VOR, 4 μM), or AZD4573 (AZD, a CDK9 inhibitor, 400 nM) for the indicated times. (B) Cells were treated with various concentrations of voruciclib or AZD4573 for 4 hours. Relative densitometry values are indicated.

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VORUCICLIB INHIBITS PROLIFERATION OF *KRAS* MUTANT CANCER CELL LINES *IN VITRO* AND *IN VIVO*

A.

Cell Line	Indication	*KRAS* Mut	IC_{50} (μM)
Gp2D	CRC	G12D	0.8
HCT-116	CRC	G13D	1.8
LS-513	CRC	G12D	0.6
SW-480	CRC	G12V	3.9
SW837	CRC	G12C	2.1
KYSE-410	Esoph	G12C	1.9
RPMI-8226	MM	G12A	2.4
A-549	NSCLC	G12S	1.5
Calu-1	NSCLC	G12C	2.0
HCC1171	NSCLC	G12C	3.0
HCC44	NSCLC	G12C	0.8
NCI-H460	NSCLC	Q61H	3.1
NCI-H1373	NSCLC	G12C	1.2
NCI-H1792	NSCLC	G12C	1.4
NCI-H2030	NSCLC	G12C	1.1
NCI-H23	NSCLC	G12C	1.2
NCI-H358	NSCLC	G12C	0.6
TOV-21G	Ovarian	G13C	1.7
AsPC-1	PDAC	G12D	2.3
HPAF-II	PDAC	G12D	1.9
MIA PaCa-2	PDAC	G12C	1.1
Panc 04.03	PDAC	G12D	1.4

B.

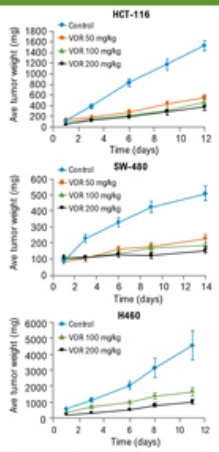

Figure 4. (A) Voruciclib IC_{50} values in multiple cell lines with *KRAS* mutations. (B) Murine xenograft experiment showing tumor growth over time in mice bearing HCT-116 (CRC, *KRAS* G13D), SW-480 (CRC, *KRAS* G12V) or H-460 (NSCLC, *KRAS* Q61H) tumors after treatment with voruciclib (VOR) at various doses (QD, p.o.) for 11-14 days.

VORUCICLIB SYNERGIZES WITH *KRAS* G12C INHIBITORS *IN VITRO*

Cell Line	*KRAS* mut	Sensitivity to G12C Inhibitors	Synergy Scores: Voruciclib + Sotorasib	Synergy Scores: Voruciclib + Adagrasib
NCI-H23	G12C	High		
HCC1171	G12C	High		
MIA Paca-2	G12C	High		
SW837	G12C	Moderate - High		
NCI-H2030	G12C	High		
Calu-1	G12C	Moderate - High		
HCC-44	G12C	Moderate - High		
NCI-H1373	G12C	Moderate - High		
NCI-H358	G12C	High		
NCI-H1792	G12C	Moderate - High		
KYSE-410	G12C	Low - High		
Panc 04.03	G12D	Low		
Gp2D	G12D	Low		
LS-513	G12D	Low - Moderate		
AsPC-1	G12D	Low		
HPAF-II	G12D	Low		
TOV-21G	G13C	Low		

Non-small cell lung cancer cell lines
Esophageal cell line
Pancreatic adenocarcinoma cell lines
Ovarian cell line
Colorectal cancer cell lines
low Moderate high

Figure 5. Heatmap of combination activity of voruciclib with KRAS G12C inhibitors in cancer cell lines after 72 hours. Cell lines are ranked by synergy score of voruciclib in combination with either sotorasib or adagrasib. HSA, Bliss, and Loewe analyses were performed to generate the synergy scores using Chalice Analyzer. High synergy scores are represented as dark green. Moderate synergy scores are represented in shades of green. Low to moderate synergy scores are represented in white. Cell sensitivity to KRAS G12C inhibitors are ranked by EC_{50} scores. High (<0.1 μM), Moderate (> 0.1 μM), low (>1 μM). Where sensitivities to the two inhibitors differ, a range of responses is given.

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VORUCICLIB SYNERGIZES WITH SOTORASIB IN AN *IN VIVO* MIA PaCa-2 TUMOR MODEL

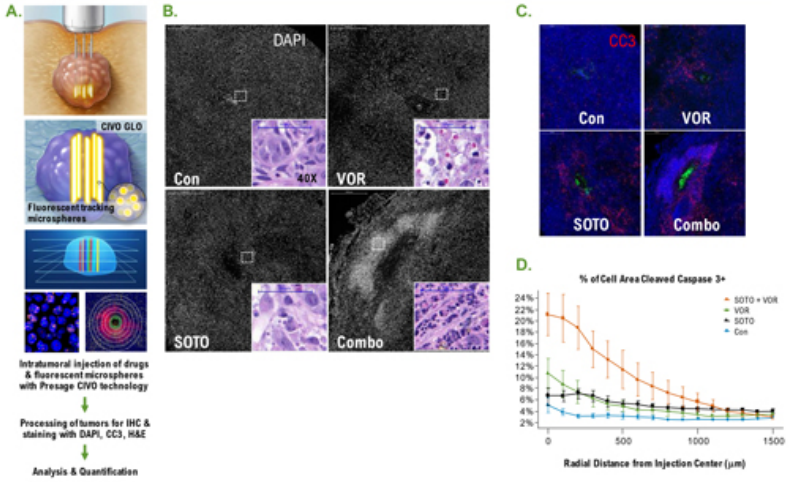

Figure 6. Voruciclib synergizes with sotorasib *in vivo*. (**A**) Presage CIVO technology[4,6] was used to inject MIA PaCa-2 cell tumors *in vivo* in a murine xenograft model. Tumors were injected with either vehicle (Con), voruciclib (VOR), sotorasib (SOTO), or voruciclib + sotorasib (Combo). Tumors were harvested and processed for IHC 24 hr after drug injection. (**B**) Representative IHC images of DAPI and H&E staining. (**C**) Representative IHC images of cleaved caspase-3 staining (CC3). (**D**) Analysis of cell area with cleaved caspase-3 staining for each treatment. (Mean ± SEM) (**C, E**) Data represents 5 tumors with duplicate combination and SOTO injection sites per tumor, single injection sites other conditions; 4 sections imaged per tumor. Similar results were obtained for VOR + adagrasib combination (data not shown).

CONCLUSIONS

- MYC is implicated in *KRAS* mutant tumors. CDK9 is a known regulator of *MYC* transcription and a modulator of MYC protein phosphorylation at Ser62. Treatment of *KRAS* G12C mutant MIA PaCa-2 pancreatic cancer cells with voruciclib, a potent inhibitor of CDKs 9/4/6/1, resulted in a rapid decrease in both phosphorylation of proteins that regulate transcription of *MYC*, and in phosphorylation of MYC protein on Ser62 that was followed by a reduction in total MYC protein.
- In *in vitro* and *in vivo* preclinical models, voruciclib demonstrated single agent efficacy against multiple *KRAS* mutant cancer cell lines harboring various G12, G13, and Q61 mutations.
- Voruciclib acted synergistically with KRAS G12C inhibitors in killing *KRAS* G12C mutant cancer cell lines, both *in vitro* and *in vivo*.
- Collectively, these experiments suggest that voruciclib could be an attractive therapeutic option for cancers driven by KRAS-MYC.

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ACKNOWLEDGMENTS AND DISCLOSURES

SW – employee of MEI Pharma, Inc.
YS – nothing to disclose.
YG – research grant received from MEI Pharma, Inc.
This study was funded by MEI Pharma, Inc. Editorial support provided by BluPrint Oncology Concepts, LLC.

Presented at American Association for Cancer Research (AACR) 10 – 15 Apr 2021.