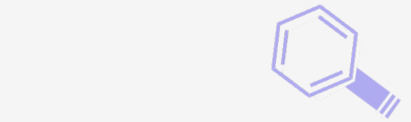
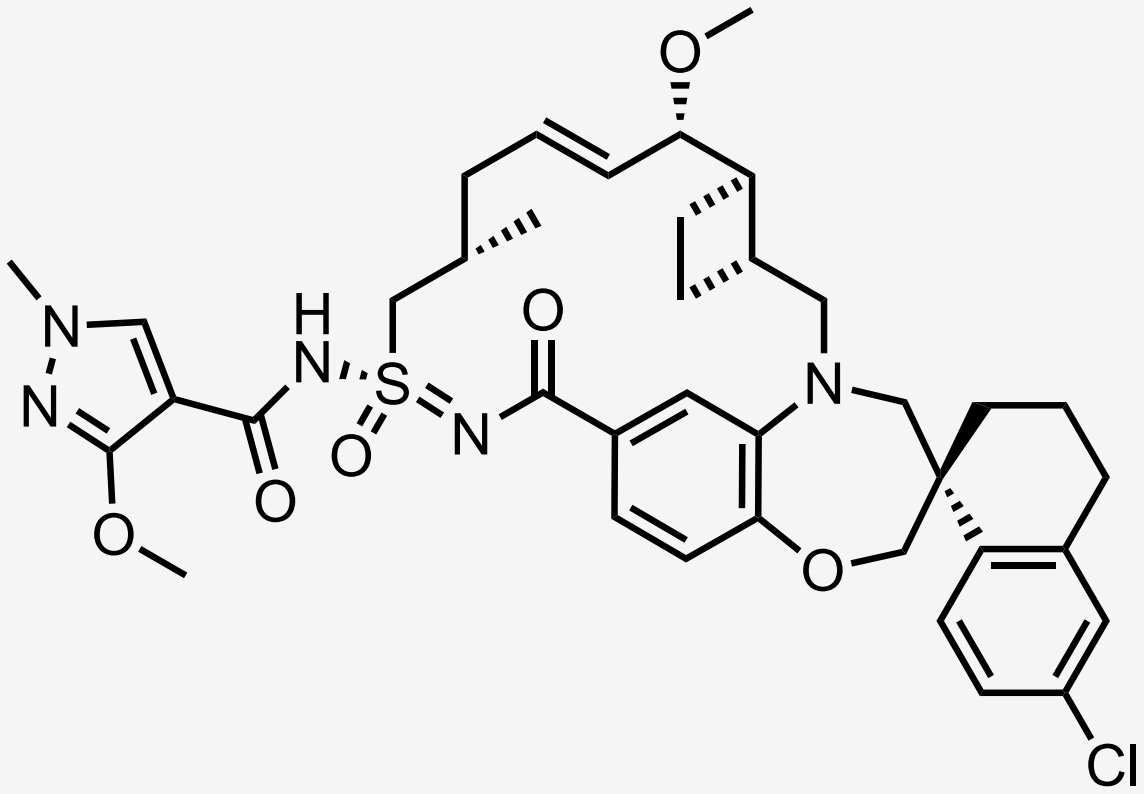
GS-9716 (MCL-1 inhibitor)

Gilead Sciences





GS-9176

GS-9716 is currently in phase 1 trials

NCT05006794

ClinicalTrials.gov

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Trial record **1 of 1** for: GS-9716

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Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of GS-9716 as Monotherapy and in Combination With Anticancer Therapies in Adults With Solid Malignancies

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT05006794

Recruitment Status : Recruiting
First Posted : August 16, 2021
Last Update Posted : January 11, 2023

See Contacts and Locations

View this study on Beta.ClinicalTrials.gov

Sponsor:
Gilead Sciences

Information provided by (Responsible Party):
Gilead Sciences

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Go to

Brief Summary:

The primary objective of Part A of this study is to define the maximum tolerated dose (MTD) or maximum administered dose of **GS-9716** as monotherapy in advanced solid malignancies and to characterize the safety, and tolerability of **GS-9716** monotherapy.

The primary objectives of Parts B and C of this study are: To characterize the safety, tolerability, and to define MTD and/or recommended Phase 2 dose (RP2D) of **GS-9716** in combination with either docetaxel or sacituzumab govitecan-hziy in adults with metastatic non-squamous non-small cell lung cancer (NSCLC) following treatment for metastatic disease, including an immune checkpoint inhibitor and a single line of platinum containing chemotherapy (for Cohorts B1, B2, C1, and C2) and in adults with metastatic triple-negative breast cancer (TNBC) following a single line of therapy for metastatic disease (for Cohorts B3, B4, C3, and C4); To characterize the safety, tolerability, and to define MTD and/or the RP2D of **GS-9716** in combination with gemcitabine and docetaxel in metastatic soft tissue sarcomas (mSTS) with nonspecific histologies previously untreated for metastatic disease (for Cohorts B5 and C5).

Condition or disease	Intervention/treatment	Phase
Solid Malignancies	Drug: **GS-9716** Drug: Docetaxel Drug: Sacituzumab Govitecan-hziy Drug: Gemcitabine	Phase 1

There are 2 sources of published information on this compound: company slides & an AACR abstract

Early Clinical Development

GS-9716: A Potent, Selective, Orally Bioavailable MCL1 Inhibitor for Solid Tumors and Heme Malignancies

Program Rationale

- Superior potency/PK relative to known competitors- picomolar binding affinity to human MCL1
- Broadly combinable: Strong preclinical combination activity with chemotherapy (e.g. taxanes, SN-38), targeted agents and IO agents (e.g. magrolimab, PD(L)1 Abs)
- Potential **first-in-class** in solid tumors and potential **best-in-class** in heme malignancies

- Ph1 study in solid tumors underway, includes combo with Trodelvy
- Ph1 study in heme moving forward ★ New

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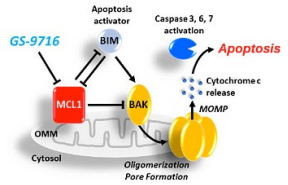
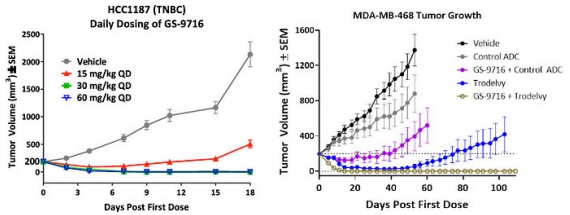
Mechanism of action



Preclinical activity as monotherapy and Trodelvy combo



AACR 2022

Oncology Deep Dive (April 14, 2022)

CANCER RESEARCH

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS COVID-19 WEBINARS

Volume 82, Issue 12_Supplement
15 June 2022

Article Contents

Abstract

POSTER PRESENTATIONS - PROFFERED ABSTRACTS | JUNE 15 2022

Abstract 3696: GS-9716: A potent, selective and orally bioavailable small molecule inhibitor of MCL1 for the treatment of cancer

Clinton K. Matson; Thomas Kenney; Bart H. Steiner; Chloe R. Deodato; Anella Yahiaoui; Claudia A. Rubio; Julie T. Chan; Nevena Mollova; Kathleen S. Keegan; Chandrasekar Venkataramani

Check for updates

Author & Article Information

Cancer Res (2022) 82 (12_Supplement): 3696.
https://doi.org/10.1158/1538-7445.AM2022-3696

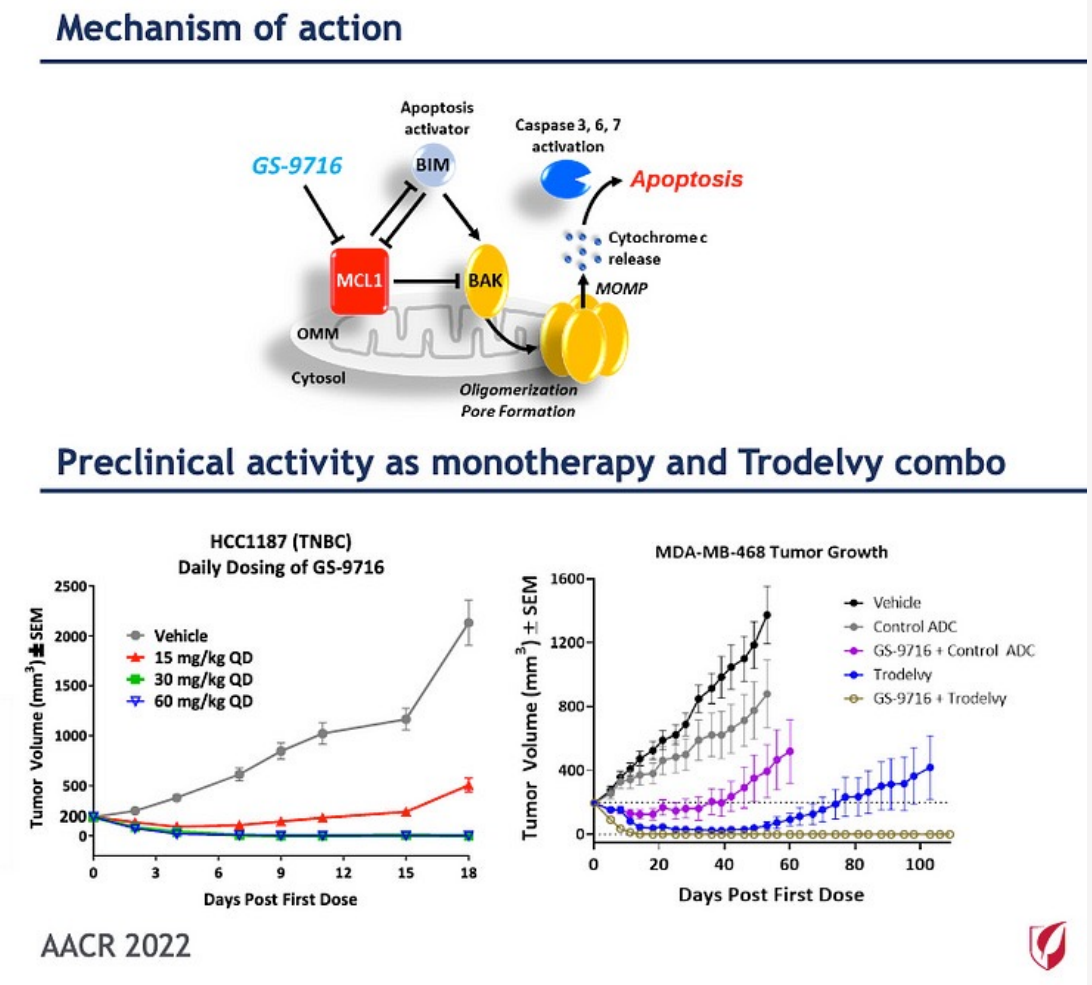
Split-Screen Share Tools Versions

Abstract

MCL1 is an anti-apoptotic member of the BCL2 family of proteins. These anti-apoptotic proteins prevent caspase-mediated cell apoptosis by binding to the pro-apoptotic proteins BIM, BAK and BAX, thereby inhibiting the formation of pores on the outer mitochondrial membrane. In cancer, MCL1 is upregulated to overcome such stress-induced effects, promoting cell survival, therapy resistance, and tumor progression. Here, we describe the in vitro and in vivo activity of GS-9716, a potent and selective MCL1 small molecule inhibitor that binds directly to MCL1 and induces rapid apoptosis in cancer cells by activating the mitochondrial apoptotic pathway. GS-9716 displayed potent and selective disruption of human MCL1-BIM protein dimer in vitro. In hematological and solid tumor cell line models, GS-9716 led to dose dependent reduction of MCL1-BIM and MCL1-BAK protein dimers. MCL1 protein dimer (BAK and BIM) reduction correlated with dose-dependent increases in cleaved caspase (apoptosis marker). GS-9716 potently reduced cellular viability across panels of hematological (Median GI_{50} = 30 nM) and breast cancer cell lines (Median GI_{50} = 470 nM). GS-9716 exhibits favorable pharmacokinetics properties with good oral bioavailability across species. GS-9716 dosed daily, once per week, or 7-day cycles of 2 days on/5 days off, resulted in significant tumor growth inhibition against models of multiple myeloma (H929), several TNBC cell line xenografts (HCC1187 and HCC70) and patient-derived xenografts. Also, in these models, GS-9716 demonstrated dose-dependent MCL1 protein dimer (BIM and BAK) reduction and activation of apoptosis in tumors. In addition to single agent activity, GS-9716 showed strong synergy with multiple anti-cancer therapies; robust in vitro synergy was observed with venetoclax in the AML models and as well as with paclitaxel in the TNBC models. The combination treatment of paclitaxel (dosed IV, QW) with GS-9716 (dosed orally, 2 days on/5 days off) in the TNBC HCC1187 xenograft model achieved complete tumor regression. Similar responses were also observed when GS-9716 was dosed with paclitaxel in the TNBC PDX models. GS-9716 is currently in Phase 1 clinical trial evaluating safety, tolerability and pharmacokinetics as monotherapy and in combination with anticancer therapies in adults with advanced solid tumors (NCT05006794).

Citation Format: Clinton K. Matson, Thomas Kenney, Bart H. Steiner, Chloe R. Deodato, Anella Yahiaoui, Claudia A. Rubio, Julie T. Chan, Nevena Mollova, Kathleen S. Keegan, Chandrasekar Venkataramani. GS-9716: A potent, selective and orally bioavailable small molecule inhibitor of MCL1 for the treatment of cancer [abstract]. In: Proceedings of the American Association for Cancer Research Annual Meeting 2022; 2022 Apr 8-13. Philadelphia (PA): AACR; Cancer Res 2022;82(12_Suppl):Abstract nr 3696.

Let's take a closer look at the company slide. Importantly, it has in vivo data, which offers many clues



Key items to note as clues:

- **What xenograft models are used?**
  - HCC1187 & MDA-MB-468 = triple negative breast cancer models
- **What treatments are involved?**
  - For MDA-MB-468: Vehicle, "Control ADC," GS-9716, and Trodelvy
- What are the axes boundaries?
  - Also note starting tumor volumes for each group.

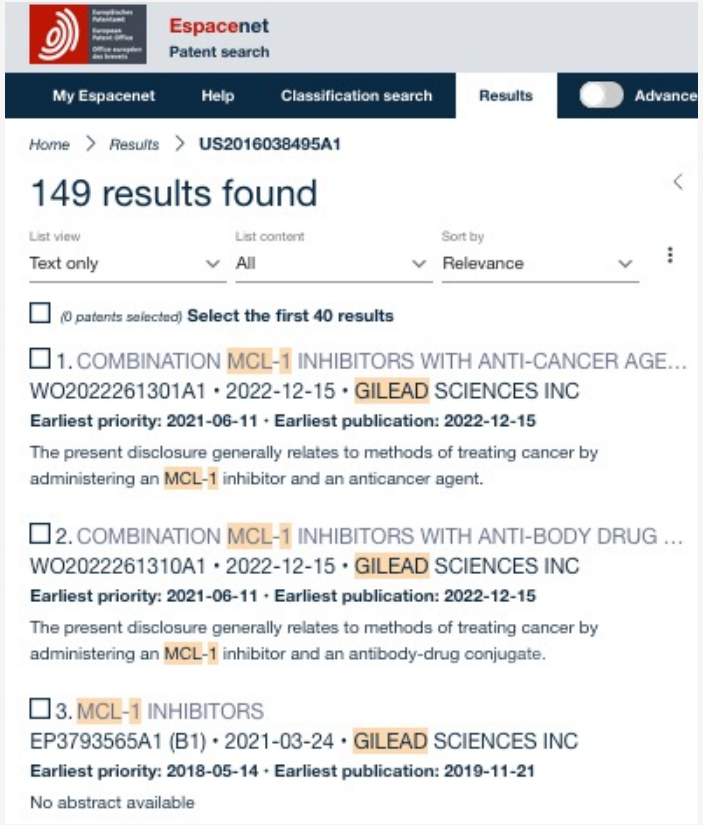
Also, keep in mind the general shape of the graphs.

This is a good start.

But to get an idea on what an MCL-1 inhibitor might look like, we got to turn to the patents.

Gilead’s patent space for MCL-1 inhibitors

Search “gilead, mcl-1” in the EPO database



No.	Title	Publication No.	Priority	Filing	Publication
1	MCL-1 Inhibitors	WO 2019/222112	May 14, 2018	May 13, 2018	November 21, 2019
2	Combination MCL-1 inhibitors with anti-body drug conjugates	WO 2022/261310	June 11, 2021	June 9, 2022	December 15, 2022
3	Combination MCL-1 inhibitors with anti-cancer agents	WO 2022/261301	June 11, 2021	June 9, 2022	December 15, 2022

‘310 catches my eye. It describes MCL-1 inhibitors combined with antibody drug conjugates (ADCs).

Recall: the in vivo data presented in the company slide described GS-9716 combined with ADCs.

We're in luck!

The front page figure looks remarkably familiar…

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63/322,509 22 March 2022 (22.03.2022) US

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(74) Agent: **YANG, Liuchun** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404 (US).

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

(54) **Title:** COMBINATION MCL-1 INHIBITORS WITH ANTI-BODY DRUG CONJUGATES

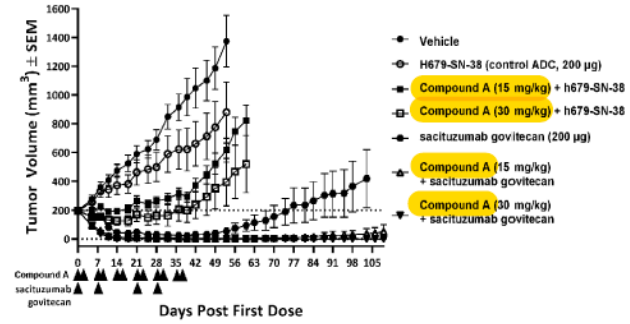


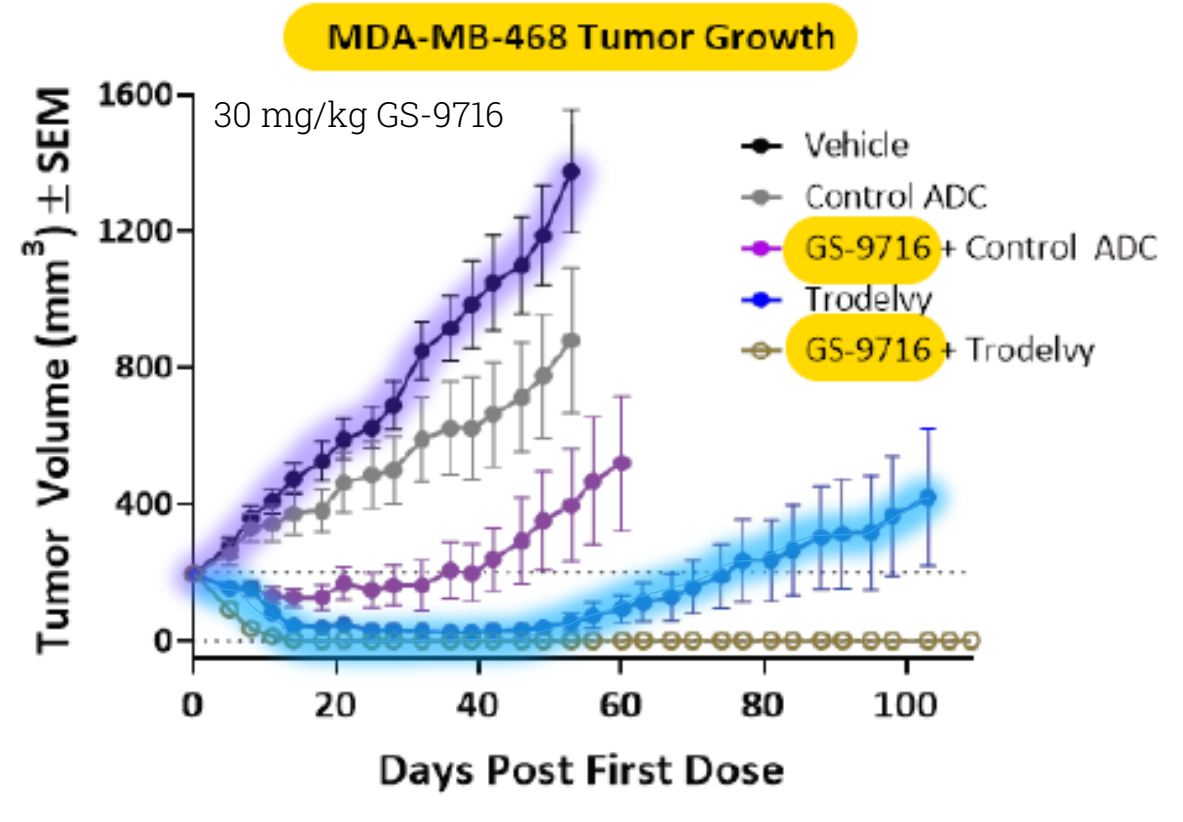
Figure 7

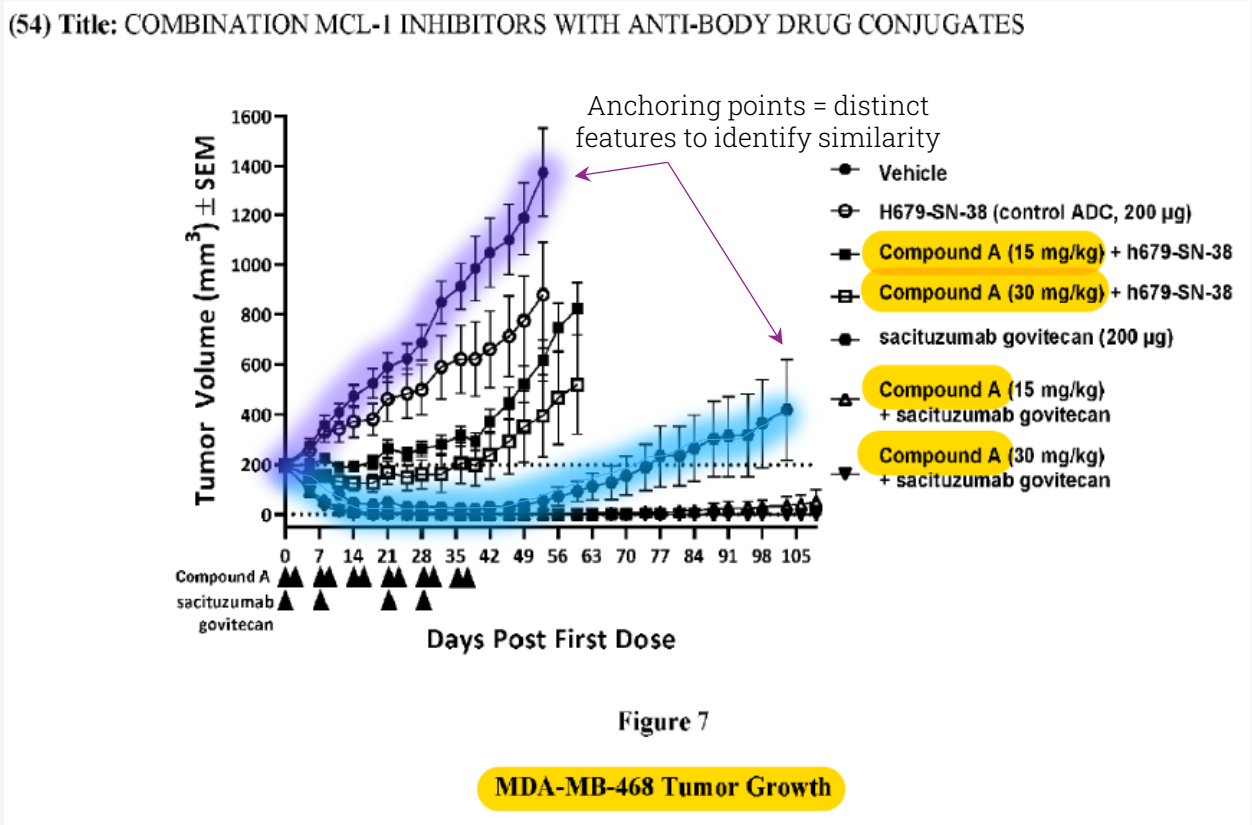
MDA-MB-468 Tumor Growth

(57) **Abstract:** The present disclosure generally relates to methods of treating cancer by administering an MCL-1 inhibitor and an antibody-drug conjugate.

WO 2022/261310 A1

Company slide vs. ‘310 patent



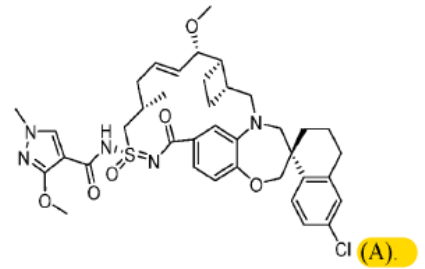


Control ADC = H679-SN-38 GS-9716 = Compound A Trodelvy = sacituzumab govitecan

Digging farther in the ‘310 patent reveals the structure of “Compound A”

Note the reference to the COM patent (Example 154 in ‘112)

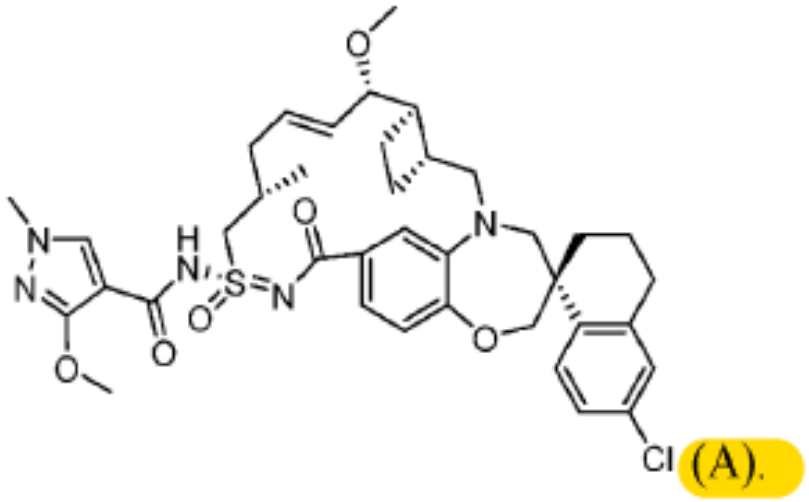
[0049] In some embodiments, the MCL-1 inhibitor is compound A, N-[(4*S*,7a*R*,9a*R*,10*S*,11*E*,14*S*)-6'-chloro-10-methoxy-14-methyl-16-oxido-18-oxo-3',4',7,7a,8,9,9a,10,13,14,15,18-dodecahydro-2'*H*-spiro[1,19-(ethanediylidene)-16λ^4-cyclobuta[*i*][1,4]oxazepino[3,4-*f*][1,2,7]thiadiazacyclohexadecine-4,1'-naphthalen]-16-yl]-3-methoxy-1-methyl-1H-pyrazole-4-carboxamide, and has the following structure:



(A).

compound A is described in Example 154 of USPN 10,703,733 and WO 2019/222112, which are incorporated herein by reference.

2. The method of claim 1, wherein the MCL-1 inhibitor is compound (A), or a pharmaceutically acceptable salt thereof.



(A).

Checking the other combination patent (‘301) also reveals the same structure of “Compound A”

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A61K 31/52 (2006.01) *A61K 45/06* (2006.01)
A61K 31/522 (2006.01) *A61P 35/00* (2006.01)
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(71) Applicant: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

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(74) Agent: **YANG, Liuchun** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

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(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) **Title:** COMBINATION MCL-1 INHIBITORS WITH ANTI-CANCER AGENTS

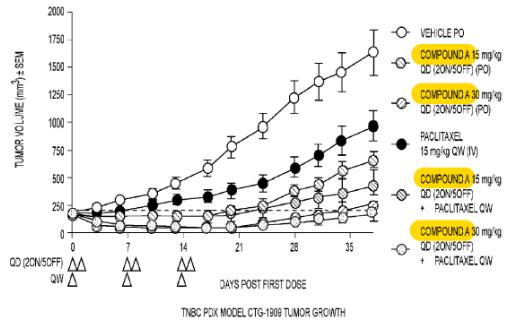
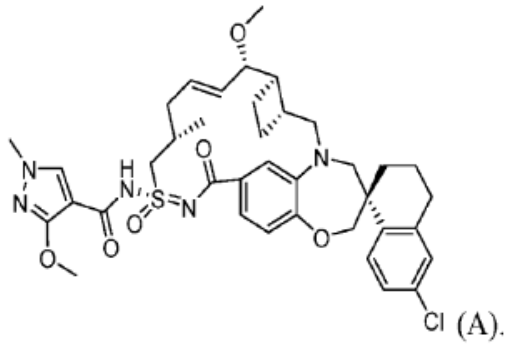


FIG. 5

(57) **Abstract:** The present disclosure generally relates to methods of treating cancer by administering an MCL-1 inhibitor and an anticancer agent.

WO 2022/261301 A1

[0053] In some embodiments, the MCL-1 inhibitor is compound A, N-[(4*S*,7a*R*,9a*R*,10*S*,11*E*,14*S*)-6'-chloro-10-methoxy-14-methyl-16-oxido-18-oxo-3',4',7,7a,8,9,9a,10,13,14,15,18-dodecahydro-2'*H*-spiro[1,19-(ethanediylidene)-16λ^4-cyclobuta[*i*][1,4]oxazepino[3,4-*f*][1,2,7]thiadiazacyclohexadecine-4,1'-naphthalen]-16-yl]-3-methoxy-1-methyl-1H-pyrazole-4-carboxamide, and has the following structure:



(A).

compound A is described in Example 154 of USPN 10,703,733 and WO 2019/222112, which are incorporated herein by reference.

Note ‘301 also references Example 154 in the 2019 COM patent (‘112).

Checking the 2019 COM patent (‘112) likewise shows the same structure.

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(71) Applicant: **GILEAD SCIENCES, INC.** [US/US]; 333 Lakeside Drive, Foster City, CA 94404 (US).

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(74) Agent: **YANG, Liuchun** et al.; Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *with international search report (Art. 21(3))*

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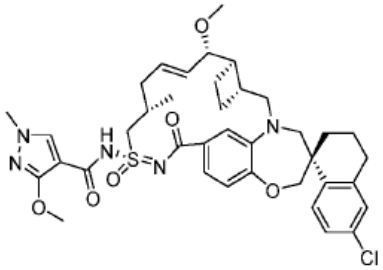
(54) Title: MCL-1 INHIBITORS

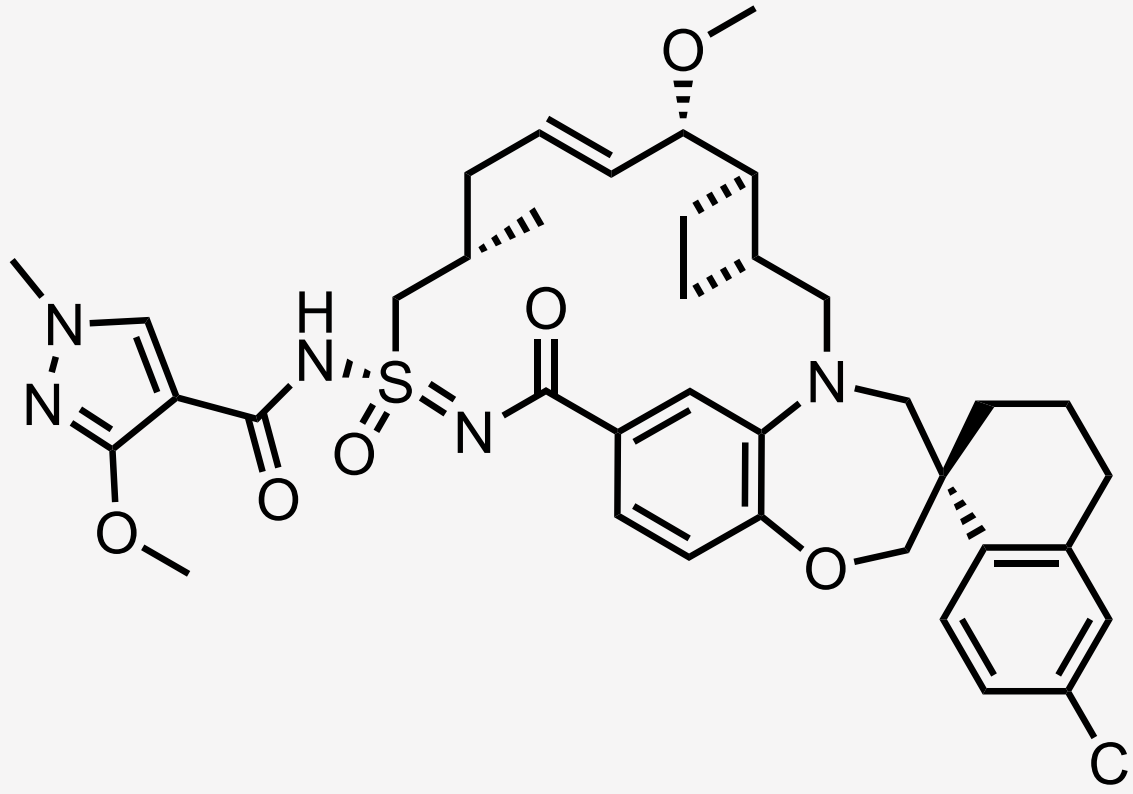
(57) Abstract: The present disclosure generally relates to compounds and pharmaceutical compositions that may be used in methods of treating cancer.

Example 154



[0447] **Example 154** was synthesized in the same manner as **Example 18** using 3-methoxy-1-methyl-1H-pyrazole-4-carboxylic acid and **Example 109**. **Example 109** (620 mg, 1.04 mmol) was dissolved in dichloromethane (12 mL). 3-Methoxy-1-methyl-1H-pyrazole-4-carboxylic acid (324 mg, 2.08 mmol, 2 equiv.) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (400 mg, 2.08 mmol, 2 equiv.) were added. The reaction mixture was stirred for 5 minutes at room temperature before DMAP (253 mg, 2.08 mmol, 2 equiv.) was added in a single portion. The reaction mixture was stirred overnight at room temperature and the progress of the reaction was monitored by LCMS. Upon completion, the reaction mixture was concentrated under reduced pressure, and the residue was purified by Gilson reverse phase prep HPLC (60-100% ACN/H_2O with 0.1% TFA) to give **Example 154**. ^{1}H NMR (400 MHz, methanol-d_4) δ 8.07 (s, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.22 – 7.10 (m, 3H), 6.92 (d, J = 8.2 Hz, 1H), 6.20 – 6.05 (m, 1H), 5.63 (dd, J = 15.5, 8.0 Hz, 1H), 4.10 (d, J = 12.0 Hz, 1H), 4.06 (s, 4H), 3.91 – 3.83 (m, 1H), 3.82 (s, 3H), 3.79 (s, 1H), 3.72 (d, J = 14.4 Hz, 1H), 3.38 (d, J = 14.5 Hz, 1H), 3.30 (s, 3H), 3.09 (dd, J = 15.1, 10.0 Hz, 1H), 2.89 – 2.72 (m, 2H), 2.51 (d, J = 26.7 Hz, 2H), 2.24 (dd, J = 10.9, 6.0 Hz, 2H), 2.12 (d, J = 13.7 Hz, 1H), 2.02 – 1.70 (m, 4H), 1.54 – 1.40 (m, 1H), 1.14 (d, J = 6.1 Hz, 3H). LCMS-ESI+ (m/z): calcd for $C_{38}H_{46}ClN_5O_6S$: 735.28; found: 735.94.

Therefore



GS-9716 = Compound A = Example 154 in ‘112

Questions?

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