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): November 17, 2017

DELMAR PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

Nevada	**000-54801**	**99-0360497**
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification Number)

Suite 720-999 West Broadway
Vancouver, British Columbia
Canada V5Z 1K5
(Address of principal executive offices) (zip code)

(604) 629-5989
(Registrant's telephone number, including area code)

(Former address, if changed since last report)

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))

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 7.01 Regulation FD Disclosure.

On November 21, 2017, DelMar Pharmaceuticals, Inc. (the "Company") issued a press release announcing its presentation of positive interim results from a study of VAL-083 in MGMT-unmethylated Recurrent GBM at the conference described below. A copy of the press release is attached hereto as Exhibit 99.1.

The information in this Current Report on Form 8-K under Item 7.01, including the information contained in Exhibit 99.1, is being furnished to the Securities and Exchange Commission, and shall not be deemed to be "filed" for the purposes of Section 18 of the Securities Exchange Act of 1934 or otherwise subject to the liabilities of that section, and shall not be deemed to be incorporated by reference into any filing under the Securities Act of 1933 or the Securities Exchange Act of 1934, except as shall be expressly set forth by a specific reference in such filing.

Item 8.01 Other Events.

On November 17 and November 18, 2017, the Company presented posters at the Annual Scientific Meeting and Education Day of the Society for Neuro-Oncology in San Francisco, California. Copies of the posters are attached as Exhibits 99.2, 99.3 and 99.4 hereto.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit Number	**Description**
99.1	Press Release dated November 21, 2017
99.2	Poster
99.3	Poster
99.4	Poster

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.

DELMAR PHARMACEUTICALS, INC.

Dated: November 22, 2017

By: /s/ Jeffrey Bacha
Name: Jeffrey Bacha
Title: President and Chief Operating Officer

Exhibit 99.1

DelMar Presents Positive Interim Results from VAL-083 Study in MGMT-unmethylated Recurrent GBM at The Society for NeuroOncology Annual Meeting

40% of recurrent GBM patients treated to date achieved stable disease as measured by magnetic resonance imaging (MRI)

VANCOUVER, British Columbia and MENLO PARK, Calif., November 21, 2017 /PRNewswire/ - - DelMar Pharmaceuticals, Inc. (NASDAQ: DMPI) ("DelMar" or the "Company"), a biopharmaceutical company focused on the development of new cancer therapies, today provided an overview of three scientific posters presented at the 22nd Annual Meeting and Education Day of the Society for Neuro-Oncology (SNO) held on November 16-19, 2017 in San Francisco, CA.

DelMar reported that 93% of patients enrolled were alive at the time of the analysis and 40% of patients enrolled were reported to have achieved stable disease as assessed by MRI following treatment with VAL-083 as a single agent. "While it is too early to interpret overall survival results from this study, the substantial disease control observed to date in the treatment recurrent GBM, an aggressive tumor that can double in size within 6-8 weeks, is an important and positive observation at this stage," said Mr. Saiid Zarrabian, DelMar's Interim Chief Executive Officer.

"The promising early observations from our ongoing Phase 2 clinical trial of VAL-083 as a potential new treatment option for MGMT-unmethylated GBM are also supported by extensive preclinical research into VAL-083's unique mechanism of action," added Mr. Zarrabian. "Based on these recent data, we believe VAL-083 represents a potential solution for some of the most important unmet medical needs in the treatment of GBM and other central nervous system tumors."

DelMar provided an update on the company's ongoing Phase 2 clinical studies in a poster entitled "*Clinical Trials with dianhydrogalactitol (VAL-083) in MGMT-unmethylated Glioblastoma*", which is being conducted in collaboration with The University of Texas MD Anderson Cancer Center. This trial is designed to enroll up to 48 patients to determine if VAL-083 treatment improves overall survival compared to historical reference control.

- DelMar reported that 27 subjects have been screened and 15 have been enrolled since the opening of recruitment in February 2017. To date, the trial has enrolled at a rate ahead of initial projections.

- All patients enrolled in the study have recurrent MGMT-unmethylated GBM with radiographic evidence of progression and were not surgically resected at the time of enrollment.

- DelMar reported that 93% of patients enrolled were alive at the time of the analysis and 40% of patients enrolled were reported to have achieved stable disease following treatment with VAL-083 as a single agent, as assessed by MRI.

- Enrollment is ongoing and median survival has not yet been reached in the trial.

- In general, VAL-083 treatment was well tolerated by patients with observed side effects (myelosuppression) similar to prior clinical experience.

The Company also provided an overview of the design a separate Phase 2 clinical trial of VAL-083 for newly diagnosed MGMT-unmethylated GBM patients on this poster. In this trial, which was recently initiated at Sun Yat-Sen University Cancer Center, patients will be treated with VAL-083 plus radiotherapy as an alternative to standard-of-care temozolomide plus radiation in the front-line setting. The trial is designed to enroll up to 30 patients with MGMT-unmethylated GBM to determine if VAL-083 treatment improves progression free survival (PFS) compared to a historical reference control. This trial is being supported though DelMar's collaboration with Guangxi Wuzhou Pharmaceutical (Group) Co., Ltd.

In addition, DelMar also presented two additional pre-clinical posters during the conference:

- *The Distinct Cytotoxic Mechanism of Dianhydrogalactitol (VAL-083) Overcomes Chemoresistance and Provides New Opportunities for Combination Therapy in the Treatment of Glioblastoma.*

  VAL-083 induces potent anti-cancer activity against treatment-resistant cells from glioblastoma, lung, prostate and ovarian tumors through a distinct mechanism of action. Cancer cells treated with VAL-083 exhibit persistent DNA double-strand breaks and activation of the homologous DNA repair (HR) system. Activation of the HR system is an indicator of VAL-083's unique anti-tumor activity.

  When combined with topoisomerase or PARP inhibitors, the treatment effect of VAL-083 is increased in a synergistic or super-additive manner. Taken together, these data support the broad potential of VAL-083 as a new treatment against a wide range of cancers both as a single agent and in combination with other established cancer therapies.

- *Dianhydrogalactitol (VAL-083) Overcomes Chemoresistance in Pediatric Malignant Brain Tumors and Displays Synergy with Topoisomerase Inhibitors*

  Pediatric high-grade glioma (HGG) and medulloblastoma are aggressive childhood brain tumors with a high incidence of recurrence and very few patients achieve long-term survival. VAL-083 demostrates potent activity as a single agent against both chemo-resistant pediatric HGG and medulloblastoma independent of p53 status. DelMar also reported that VAL-083 potentiates radiotherapy and exhibits synergy when used in combination with topoisomerase inhibitors, two regimens commonly used in the treatment of childhood brain tumors.

"We continue to be highly enthusiastic about the potential of VAL-083 as a novel treatment for cancer patients who have limited or no treatment options", added Mr. Zarrabian. "The excellent work performed by our world class academic research collaborators and our in-house team presented at the SNO meeting showcases VAL-083's potential both as a single agent and as a component of combination therapeutic regimens."

DelMar's poster presentations can be viewed in their entirety on DelMar's website at http://www.delmarpharma.com/scientific-publications.html

About VAL-083

VAL-083 (dianhydrogalactitol) is a "first-in-class", DNA-targeting agent that introduces interstrand DNA cross-links at the N7-position of guanine leading to DNA double-strand breaks and cancer cell death. VAL-083 has demonstrated clinical activity against a range of cancers including GBM and ovarian cancer in historical clinical trials sponsored by the U.S. National Cancer Institute (NCI). DelMar has demonstrated that VAL-083's anti-tumor activity is unaffected by common mechanisms of chemoresistance *in vitro*. Further details regarding these studies can be found at http://www.delmarpharma.com/scientific-publications.html.

VAL-083 has been granted an orphan drug designation by the U.S. FDA Office of Orphan Products for the treatment of glioma, medulloblastoma and ovarian cancer, and in Europe for the treatment of malignant gliomas.

About DelMar Pharmaceuticals, Inc.

DelMar Pharmaceuticals is focused on the development and commercialization of new therapies for cancer patients who have limited or no treatment options. By focusing on understanding tumor biology and mechanisms of treatment resistance, the Company identifies biomarkers to personalize new therapies in indications where patients are failing, or have become resistant to modern targeted or biologic treatments.

The Company's current pipeline is based around VAL-083, a "first-in-class," small-molecule chemotherapeutic with a novel mechanism of action that has demonstrated clinical activity against a range of cancers including central nervous system, ovarian and other solid tumors (e.g. NSCLC, bladder cancer, head & neck) in clinical trials sponsored by the NCI. Based on DelMar's internal research programs and these prior NCI-sponsored clinical studies, the Company is conducting clinical trials to support the development and commercialization of VAL-083 across multiple oncology indications to solve significant unmet medical needs.

VAL-083 is also being studied in two collaborator-supported, biomarker driven, Phase 2 clinical trials for MGMT-unmethylated GBM. Overcoming MGMT-mediated resistance represents a significant unmet medical need in the treatment of GBM. DelMar also recently announced the allowance of a separate IND for VAL-083 as a potential treatment for platinum-resistant ovarian cancer.

Further information on DelMar's clinical trials can be found on clinicaltrials.gov: https://www.clinicaltrials.gov/ct2/results?cond=&term=val-083&cntry1=&state1=&recrs

For further information, please visit http://delmarpharma.com/; or contact DelMar Pharmaceuticals Investor Relations: ir@delmarpharma.com / (604) 629-5989.

Connect with the Company on Twitter, LinkedIn, Facebook, and Google+.

Safe Harbor Statement

Any statements contained in this press release that do not describe historical facts may constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. Any forward-looking statements contained herein are based on current expectations, but are subject to a number of risks and uncertainties. The factors that could cause actual future results to differ materially from current expectations include, but are not limited to, risks and uncertainties relating to the Company's ability to develop, market and sell products based on its technology; the expected benefits and efficacy of the Company's products and technology; the availability of substantial additional funding for the Company to continue its operations and to conduct research and development, clinical studies and future product commercialization; and, the Company's business, research, product development, regulatory approval, marketing and distribution plans and strategies. These and other factors are identified and described in more detail in our filings with the SEC, including, our current reports on Form 8-K.

Dianhydrogalactitol (VAL-083) overcomes chemoresistance in pediatric malignant brain tumors and displays synergy with topoisomerase inhibitors

Beibei Zhai[1,2], Anne Steino[3], Jeffrey Bacha[3], Dennis M. Brown[3], Jie Zhang[5], Theodore Nicolaides[5], Mads Daugaard[1,2]

[1]Vancouver Prostate Centre, Vancouver, BC, Canada; [2]Department of Urologic Sciences, University of British Columbia, Vancouver, Canada; [3,4]DelMar Pharmaceuticals, Inc., Vancouver, BC and Menlo Park, CA; [5]Department of Pediatrics, University of California San Francisco, US

ABSTRACT #5248

More children die from brain cancer than from any other disease. Medulloblastoma (MB) and pediatric high-grade gliomas (pHGG) are the most common malignant brain cancers in children. Children with pHGG have few therapeutic options and 5-year survival is less than 20%. Treatment includes surgery, radiotherapy and various chemotherapeutic combinations often including topoisomerase inhibitors and/or temozolomide (TMZ). The expression of the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) is strongly correlated with TMZ-resistance and is highly expressed in many pHGG, and deficient DNA mismatch repair (MMR) (25% of pHGG) confers a secondary mechanism of TMZ-resistance.

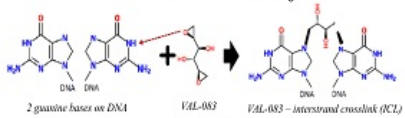
VAL-083 is a novel bi-functional DNA targeting agent that readily ***crosses the blood-brain barrier and accumulates in brain tumor tissue.*** In prior NCI-sponsored clinical trials, ***VAL-083 was well-tolerated*** and demonstrated activity against pediatric brain tumors, including pHGG and MB. VAL-083 overcomes MGMT-related resistance mechanisms and is equally active against HGG cancer stem cells and non-stem cells, *in vitro*. Here, we show that VAL-083 overcomes resistance to TMZ and is active against HGG and MB cell lines, independent of their MGMT, MMR and p53 status *in vitro*. We further show that VAL-083 displays synergy with topoisomerase I and II inhibitors *in vitro*.

BACKGROUND

VAL-083 overcomes MGMT-mediated chemoresistance

VAL-083 is a novel bi-functional DNA targeting agent that rapidly induces interstrand cross-links at N7-guanine, leading to DNA double-strand breaks (DSBs) and ultimately cell death. The N7-targeting mechanism differs from TMZ and nitrosoureas, enabling VAL-083 to overcome MGMT-mediated chemoresistance.

Mechanism of VAL-083 via crosslinks at N7 of guanine



Mechanism of temozolomide via alkylation at O6 of guanine

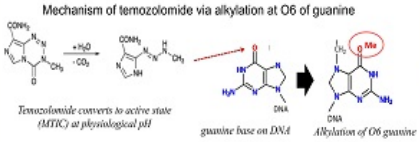


FIGURE 1. *The N7-targeting mechanism of action of VAL-083 differs from those of O6-alkylating agents like temozolomide and nitrosoureas.*

VAL-083 is a DNA-targeting agent with a unique mechanism of action

VAL-083 is a bifunctional DNA-targeting agent, with a mechanism of action that differs from other DNA-targeting agents.[1] VAL-083 rapidly introduces DNA interstrand crosslinks (ICLs) at the N7-position of guanine leading to persistent DNA DSBs, S/G2 phase cell cycle arrest and activation of the homologous recombination (HR) repair pathway. The DNA DSBs and HR activation persists for 24-72h after VAL-083 pulse treatment, ultimately ***leading to cell death through two parallel pathways: p53-dependent*** and ***p53-independent*** (Figure 2).[2]

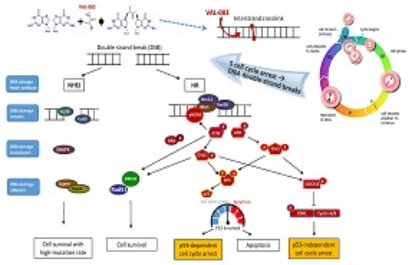


FIGURE 2. *Mechanisms of action of VAL-083 induced chemotherapeutic cytotoxicity. Apoptosis can be induced through either p53 dependent or p53 independent pathways. Red color signifies VAL-083-induced activation.*[1,2]

This distinct mechanism of action of VAL-083 suggests that VAL-083 may offer a treatment alternative against tumors with p53-, MMR-, or MGMT-mediated resistance to chemotherapeutic agents, including temozolomide and nitrosoureas.

VAL-083 ACTIVITY IS INDEPENDENT OF MGMT AND MMR DNA DAMAGE RESPONSE

The mechanism of action of VAL-083 differs from other alkylating agents and ***overcomes both MGMT- and MMR-related resistance to temozolomide, in vitro.***

VAL-083 cytotoxic activity overrides MGMT-mediated chemoresistance to TMZ and lomustine in pediatric (SF188) and adult (T98G) HGG and medulloblastoma (Med8a) cell lines, independent of p53-status (Figure 3).

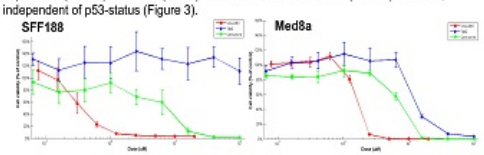


FIGURE 3. SF188 and Med8a tumor cells were treated for 3 days followed by 3 days in drug-free media with VAL-083, temozolomide or lomustine. Viable cells were quantified using CellTiterGlo. N=6.

TABLE 1: *IC_{50} values of VAL-083, TMZ and lomustine in pHGG SF188, MB Med8a and adult HGG T98G tumor cells. N=3*

Cell line		SF-188	Med8a	T98G[3]
MGMT expression		High	Low	High
p53 status		Mutant	Wild type	Mutant
IC_{50}	VAL-083	0.4 µM	1.6 µM	1.8 µM
	TMZ	>>100 µM	15.2 µM	>>100 µM
	lomustine	5.5 µM	6.8 µM	n/a

VAL-083 cytotoxic activity is independent of the cancer cell mismatch repair (MMR) status, suggesting that VAL-083 can overcome this secondary TMZ-resistance mechanism (Figure 4).

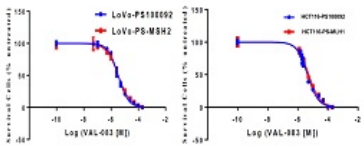


FIGURE 4. *Cytotoxicity of VAL-083 in isogenic human colorectal cancer cell lines using the crystal violet assay. MMR-proficient cell lines, HCT116-PS-MLH1 and LoVo-PS-MSH2, were established by lentiviral infection. HCT116-PS100092 is the MLH1-deficient cell line, HCT116-PS-MLH1 is the MLH1-proficient cell line; LoVo-PS-MSH2 is the MSH2-deficient cell line, and LoVo-PS-MSH2 is the MSH2-proficient cell line. N=3.*

VAL-083 POTENTIATES RADIATION AND IS ACTIVE AGAINST GBM CANCER STEM CELLS

VAL-083 (5 µM) overcame TMZ-resistance in both HGG tumor cells and HGG tumor stem cells (CSCs) independent of MGMT (Figure 5). In addition, when CSC cultures were treated with low dose VAL-083 (1µM) with or without 2Gy radiation, VAL-083 acted as a radio-potentiater against CSC's in all cultures tested (Figure 5C)[6].

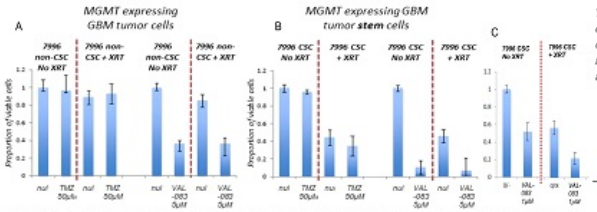


FIGURE 5. *Cell viability analysis at day 6 post treatment for the paired (A) non-CSC and (B,C) CSC MGMT-expressing 7996 cultures. MGMT expressing GBM tumor cells and GBM tumor stem cells were treated with TMZ (50 µM) or VAL-083 (1 or 5 µM) either with or without radiation (2Gy).*[6]

TABLE 2: *Historical data supporting radio-potentiating abilities of VAL-083. cReported median survival of VAL-083 in combination with radiotherapy, and the benefit versus radiotherapy alone is similar or superior to other alkylating agents.*

		Nitrosourea therapy			
XRT +	VAL-083 (Eagan 1979)[4]	TMZ (Stupp 2005)[5]	BCNU (Walker 1976)[4]	CCNU (Reagan 1976)[7]	ACNU (Takakura 1986)[8]
Median survival (months)	16.8	14.6	12.5	13.0	8.8
Benefit vs. XRT alone	**8.4**	2.5	2.5	1.2	n/a

VAL-083 DISPLAYS SYNERGY WITH TOPOISOMERASE INHIBITORS

The distinct mechanism of action of VAL-083 makes it a valuable partner for combination therapies with agents already used in the treatment of GBM and other CNS tumors.

- As VAL-083 induces cell cycle arrest initially in S- followed by G2/M-phase, we predicted synergy with agents that require cancer cells to be in S/G2-phase for maximum effect, including topoisomerase inhibitors. As expected, **VAL-083 demonstrated synergy with etoposide** *(TOP-2 inhibitor)* **and camptothecin** *(TOP-1 inhibitor)* (Table 3).

TABLE 3. *VAL-083 demonstrates synergy with etoposide (TOP2 inhibitor) and camptothecin (TOP1 inhibitor) in PC3 prostate and A549 NSCLC cancer cells. CI values for the cytotoxic effect (Fa). CI<1 shows synergy. N=4-5.*[6]

Cell line	Etoposide (topoisomerase II inhibitor)		Camptothecin (topoisomerase I inhibitor)	
	Cytotoxic effect (**Fa**)	Combination index (**CI**)	Cytotoxic effect (**Fa**)	Combination index (**CI**)
PC3	**ED50**	0.58	**ED75**	0.68
	ED75	0.48	**ED90**	0.59
	ED90	0.42	**ED95**	0.54
A549	**ED50**	0.72	**ED85**	0.94
	ED75	0.88	**ED90**	0.87
	ED80	0.94	**ED95**	0.77

Molar ratios: VAL-083:etoposide 5:1 in PC3 and 5:1 in A549; VAL-083:camptothecin 250:1 in PC3 and 212:1 in A549

Chemotherapy	Temozolomide[12]	Nitrosoureas[11,12]	VAL-083[9,10,11]
Cytotoxic target	O6-Guanine	O6-Guanine	N7-Guanine
DNA damage	Base mismatch Single-strand break	Interstrand crosslinks (G-C) Double-strand break	Interstrand crosslinks (G-G) Double-strand break
Cell cycle arrest	G2/M	G2/M	Late S/G2
ATM-Chk2	activated	activated	activated
MGMT	dependent	dependent	independent
MMR	dependent	independent	independent
p53	dependent	dependent	independent

CONCLUSIONS

- VAL-083 displays a distinct anti-cancer mechanism enabling it to overcome MGMT-mediated chemo-resistance to temozolomide and nitrosoureas
- VAL-083 is able to overcome MMR-mediated chemo-resistance, *in vitro*
- Low-dose VAL-083 potentiates radiation therapy
- VAL-083 displays synergy with topoisomerase inhibitors, *in vitro*
- VAL-083 is equally active against GBM cancer stem cells and non-cancer stem cells, *in vitro*

References:

1. ***Zhai B, et al.*** *Cancer Res: 77(13), abstract #2483 (2017)*
2. ***Peng C, et al.*** *Acta Pharmacol Sin: Apr;38(4):561-570 (2017)*
3. ***Hu et al.*** *Cancer Res: Volume 72, Issue 8, Supp 1 (2012)*
4. ***Eagan et al. JAMA:*** *241(19):2046-50 (1979)*
5. ***Stupp et al.*** *N Engl J Med 2005; 352(10):987-1003*
6. ***Walker et al.*** *Cancer Treat Rep 60:713-716 (1976)*
7. ***Reagan et al.*** *J. Neurosurg:44:186-190 (1976)*
8. ***Takakura et al.*** *J Neurosurg:64:53-7 (1986)*
9. ***Fouse et al.*** *Neuro Oncol:16 (suppl 5):v83 (2014)*
10. ***Steino et al.*** *AACR meeting 2017, Abstr. #1429*
11. ***Iraolfarla et al.*** *Cancer Chemother Pharm:24(5):311-3 (1989)*
12. ***Ramirez et al.*** *Pharmaceuticals;6(12):1476-1506 (2013)*

Clinical Trials with dianhydrogalactitol (VAL-083) in MGMT-unmethylated Glioblastoma

Jeffrey Bacha[1], Anne Steino[1], John Langlands[1], Sarath Kanekal[1], Richard Schwartz[1], Lorena M. Lopez[1], Barbara O'Brien[2], Zhong-ping Chen[3], Marta Penas-Prado[2], Dennis M. Brown[1]

[1]DelMar Pharmaceuticals, Inc., Vancouver, Canada and Menlo Park, California, USA; [2]Department of Neuro-Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Sun Yat-Sen University Cancer Center, Guangzhou, China

ABSTRACT #5235

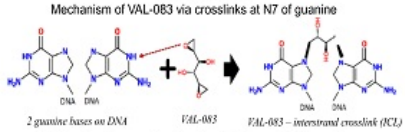
Glioblastoma (GBM) is the most common and aggressive primary brain cancer. Current standard-of-care includes surgery, radiation and treatment with temozolomide (TMZ), however nearly all tumors recur and the prognosis for recurrent GBM is dismal. Resistance to TMZ is correlated with expression of the DNA repair enzyme O6-methylguanine-DNA-methyltransferase (MGMT), which is highly expressed in a majority of GBM tumors. Deficiencies in the DNA mismatch repair (MMR) system is implicated in a secondary resistance mechanism to TMZ.

VAL-083

Dianhydrogalactitol (VAL-083) is a first-in-class bi-functional DNA-targeting agent that exhibited activity against GBM in NCI-sponsored clinical trials both as a single agent and in combination with radiotherapy. VAL-083 readily crosses the blood-brain barrier and accumulates in brain tumor tissue. We have demonstrated that VAL-083 targets N7-Guanine and rapidly induces interstrand DNA cross-links, leading to DNA double-strand breaks, S/G2 cell-cycle arrest and cell death in GBM cell lines and GBM cancer stem cells (CSCs) *in vitro*. This unique N7-guanine targeting mechanism not only circumvents MGMT-mediated chemo-resistance but also maintains cytotoxic activity in cancer cells deficient in mismatch repair (MMR). These data suggest VAL-083 may offer a superior chemotherapeutic alternative in the treatment of *MGMT*-unmethylated or MMR deficient GBM.

BACKGROUND

Mechanism of VAL-083 via crosslinks at N7 of guanine



Mechanism of temozolomide via alkylation at O6 of guanine

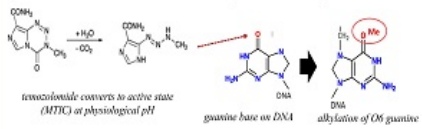


Figure 1. *The N7-targeting mechanism of action of VAL-083 differs from those of O6-alkylating agents like temozolomide and nitrosoureas.*

VAL-083 is a DNA-targeting agent with a unique mechanism of action

VAL-083 is a bifunctional DNA-targeting agent, with a mechanism of action that differs from other DNA-targeting agents.[1] VAL-083 introduces irreversible DNA interstrand crosslinks (ICLs) at the N7-position of guanine leading to persistent DNA DSBs and cancer cell death. The DNA DSBs persists for 24-72h after VAL-083 pulse treatment, ultimately leading to S/G2 phase cell cycle arrest and cell death through two parallel pathways: **p53-dependent** and **p53-independent (Figure 2).**[2]

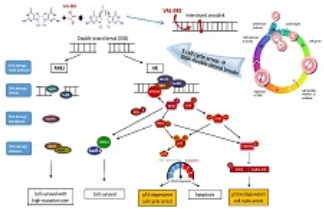


FIGURE 2. *Mechanisms of action of VAL-083 induced chemotherapeutic cytotoxicity. Apoptosis can be induced through either p53 dependent or p53 independent pathways. BRCA1 dysfunction, which is common in ovarian cancer, increases the cytotoxic potential of VAL-083.*

This distinct mechanism of action of VAL-083 suggests that VAL-083 may offer a treatment alternative against tumors with p53-, MMR-, or MGMT-mediated resistance to chemotherapeutic agents, including temozolomide and nitrosoureas.

VAL-083	MGMT		p53	
	high	low	proficient	defective
MMR+	sensitive	sensitive	sensitive	sensitive
MMR-	sensitive	sensitive	sensitive	sensitive
NHEJ+	sensitive	sensitive	sensitive	sensitive
NHEJ-	sensitive	sensitive	sensitive	sensitive

Temozo-lomide	MGMT		p53	
	high	low	proficient	defective
MMR+	resistant	sensitive	sensitive	sensitive
MMR-	resistant	resistant	resistant	resistant
NHEJ+	resistant	sensitive	sensitive	sensitive
NHEJ-	resistant	sensitive	sensitive	sensitive

VAL-083 ACTIVITY IS INDEPENDENT OF MGMT AND MMR DNA REPAIR SYSTEMS

The mechanism-of-action of VAL-083 differs from other alkylating agents and ***overcomes both MGMT- and MMR-related resistance to temozolomide, in vitro.***

VAL-083 was better than TMZ for inhibiting tumor growth in GBM cell lines SF188, U251, and T98G, and the activity of VAL-083 was independent of MGMT, suggesting VAL-083 can overcome the primary TMZ-resistance mechanism (Figure 3).

Table 1. TMZ resistance and MGMT status in GBM cell lines SF188, U251, and T98G

GBM cell line	SF188	U251	T98G
TMZ resistance	++	+	+++
MGMT status	Methylated	Methylated	Unmethylated

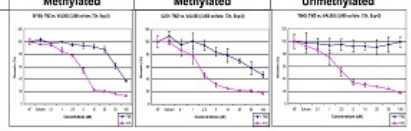


Figure 3. TMZ vs. VAL-083 in Adult GBM Cell Lines (3000 cells/well, 72-h exposure)

VAL-083 cytotoxic activity is independent of cancer cell's Mismatch Repair (MRR)-status, suggesting that VAL-083 can overcome the secondary TMZ-resistance mechanism (Figure 4).

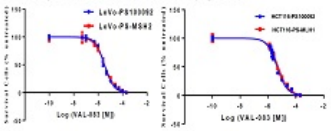


Figure 4. Cytotoxicity of VAL-083 in isogenic human colorectal cancer cell lines using the crystal violet assay. MMR-proficient cell lines, HCT116-PS-MLH1 and LoVo-PS-MSH2, were established by lentiviral infection. HCT116-PS100092 is the MLH1-deficient cell line, HCT116-PS-MLH1 is the MLH1-proficient cell line; LoVo-PS100092 is the MSH2-deficient cell line, and LoVo-PS-MSH2 is the MSH2-proficient cell line. N=3.

VAL-083 POTENTIATES RADIATION AND IS ACTIVE AGAINST GBM CANCER STEM CELLS

VAL-083 (5 µM) overcame TMZ-resistance in both GBM tumor cells and GBM tumor stem cells independent of MGMT (Figure 5). In addition, when VAL-083 was added to CSC cultures at low micromolar doses (1µM) with or without 2Gy radiation, VAL-083 acted as a radio-sensitizer against CSC's in all cultures tested (Figure 5C)[3].

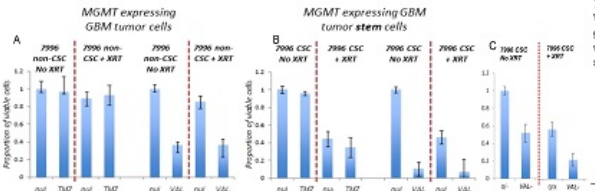


FIGURE 5. Cell viability analysis at day 6 post treatment for the paired (A) non-CSC and (B,C) CSC MGMT-expressing 7996 cultures. MGMT expressing GBM tumor cells and GBM tumor stem cells were treated with TMZ (50 µM) or VAL-083 (1 or 5 µM) either with or without radiation (2Gy).

TABLE 2: Historical data comparing randomized clinical trials of VAL-083 versus other chemotherapies used in the treatment of high grade gliomas. Reported median survival of VAL-083 in combination with radiotherapy, and the benefit versus radiotherapy alone is similar or superior to other alkylating agents.

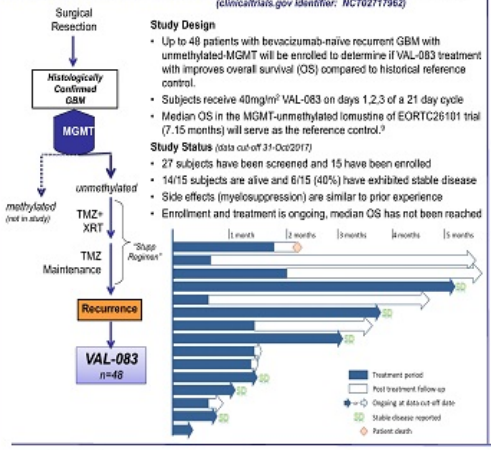
			Nitrosourea therapy		
XRT +	VAL-083 (Eagan 1979)[3]	TMZ (Stupp 2005)[4]	BCNU (Walker 1976)[5]	CCNU (Reagan 1976)[6]	ACNU (Takakura 1986)[7]
Median survival (months)	16.8	14.6	12.5	13.0	8.8
Benefit vs. XRT alone	8.4	2.5	2.5	1.2	*NS*

PHASE II TRIAL IN MGMT-UNMETHYLATED BEVACIZUMAB-NAÏVE RECURRENT GBM

An open label, single-arm, biomarker-driven, Phase 2 study of VAL-083 in patients with MGMT-unmethylated, bevacizumab-naïve recurrent GBM. Currently enrolling at University of Texas MD Anderson Cancer Center

(clinicaltrials.gov identifier: NCT02717962)

Link to trial on clinicaltrials.gov



Study Design

- Up to 48 patients with bevacizumab-naïve recurrent GBM with unmethylated-MGMT will be enrolled to determine if VAL-083 treatment with improves overall survival (OS) compared to historical reference control.
- Subjects receive 40mg/m² VAL-083 on days 1,2,3 of a 21 day cycle
- Median OS in the MGMT-unmethylated lomustine of EORTC26101 trial (7.15 months) will serve as the reference control.[9]

Study Status *(data cut-off 31-Oct-2017)*

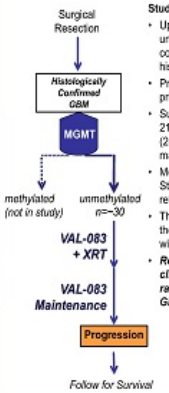
- 27 subjects have been screened and 15 have been enrolled
- 14/15 subjects are alive and 6/15 (40%) have exhibited stable disease
- Side effects (myelosuppression) are similar to prior experience
- Enrollment and treatment is ongoing, median OS has not been reached

PHASE II TRIAL IN MGMT-UNMETHYLATED NEWLY DIAGNOSED GBM

An open label, single-arm, biomarker-driven, Phase 2 study of VAL-083 and radiation therapy in patients with newly diagnosed MGMT-unmethylated GBM. Currently enrolling at Sun Yat-sen University Cancer Center

(clinicaltrials.gov identifier: NCT03050736)

Link to trial on clinicaltrials.gov



Study Design

- Up to 30 patients with newly diagnosed GBM with unmethylated-MGMT will be treated with VAL-083 in combination with standard radiation and compared to historical reference control.
- Progression free survival (PFS) will serve as the primary endpoint.
- Subjects receive 40mg/m² VAL-083 on days 1,2,3 of a 21 day cycle combined with standard radiotherapy (2Gy/day x 5 days) for six weeks followed by VAL-083 maintenance therapy.
- Median PFS in the MGMT-unmethylated arm of the Stupp 2005 trial (5.3 months) will serve as the reference control.
- The study will also assess overall survival (OS) and the safety and tolerability of VAL-083 in combination with a standard-of-care radiation regimen.
- ***Results will support a design of a Phase I/II clinical trial evaluating VAL-083 efficacy with radiation in newly diagnosed MGMT-unmethylated GBM.***

STATUS:
This study is open for enrollment

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1. **Zhai B, et al.** Cancer Res. July 2017; 77(13), abstract #2483.
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7. **Takakura et al.** *J Neurosurg*; 64:53-7 (1986)
8. **Fouse et al.** *Neuro Oncol.* 16 (suppl 5): v83 (2014)
9. **Weathers et al.** *J Neurooncol* 129(3): 487-94 (2016)

The distinct cytotoxic mechanism of dianhydrogalactitol (VAL-083) overcomes chemoresistance and provides new opportunities for combination therapy in the treatment of glioblastoma

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ABSTRACT #5264

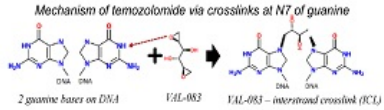
Treatment of glioblastoma (GBM) includes surgery and chemoradiation with temozolomide. Due to chemoresistance, nearly all tumors recur and 5-year survival is less than 3%. Various treatments, including anti-angiogenic treatment with bevacizumab, nitrosoureas and topoisomerase inhibitors, have failed to improve overall survival in recurrent GBM (rGBM). GBM tumors expressing O^6-methylguanine-DNA-methyltransferase (MGMT) are resistant to temozolomide and nitrosourea, and deficient DNA mismatch repair (MMR) confers secondary resistance to temozolomide. Our recent phase I/II trial in rGBM patients previously treated with temozolomide and bevacizumab, suggested that VAL-083 may offer a clinically meaningful survival benefit for rGBM patients. VAL-083 is a first-in-class bi-functional DNA-targeting agent that ***readily crosses the blood-brain barrier*** and accumulates in brain tumor tissue. The mechanism of action of VAL-083 differs from other alkylating agents ***and overcomes both MGMT- and MMR-related resistance to temozolomide***, *in vitro*. VAL-083 rapidly induces interstrand cross-links at N7-guanine, causing DNA double-strand breaks and persistent activation of the homologous recombination (HR) DNA repair pathway. Furthermore, VAL-083 potency is increased in HR-deficient cancer cells, suggesting increased cytotoxicity in HR-impaired tumors. Hypoxic GBM cells downregulate HR activity, thus proposing increased VAL-083 potency in hypoxic tumors. We demonstrated that VAL-083 induces irreversible S/G2-phase cell cycle arrest, thus proposing synergy with S-phase specific chemotherapeutics, including topoisomerase and PARP inhibitors. Our results support the potential of VAL-083 to i) overcome resistance to temozolomide, and ii) display synergy as part of combinatory therapies with topoisomerase or PARP inhibitors.

BACKGROUND

VAL-083 OVERCOMES MGMT-MEDIATED CHEMORESISTANCE

VAL-083 is a novel bi-functional DNA targeting agent that rapidly induces interstrand cross-links at N7-guanine, leading to DNA double-strand breaks (DSBs) and ultimately cell death. The N7-targeting mechanism differs from TMZ and nitrosoureas, enabling VAL-083 to overcome MGMT-mediated chemoresistance.

Mechanism of temozolomide via crosslinks at N7 of guanine



Mechanism of temozolomide via alkylation at O6 of guanine

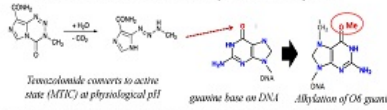


FIGURE 1. *The N7-targeting mechanism of action of VAL-083 differs from those of O6-alkylating agents like temozolomide and nitrosoureas.*

VAL-083 IS A DNA-TARGETING AGENT WITH A UNIQUE MECHANISM

VAL-083 is a bifunctional DNA-targeting agent, with a mechanism of action that differs from other DNA-targeting agents.[1] VAL-083 rapidly introduces DNA interstrand crosslinks (ICLs) at the N^7-position of guanine leading to persistent DNA DSBs, S/G2 phase cell cycle arrest and activation of the homologous recombination (HR) repair pathway. The DNA DSBs ad HR activation persists for 24-72h after VAL-083 pulse treatment, ultimately ***leading to cell death through two parallel pathways: p53-dependent and p53-Independent*** (Figure 2).[2]

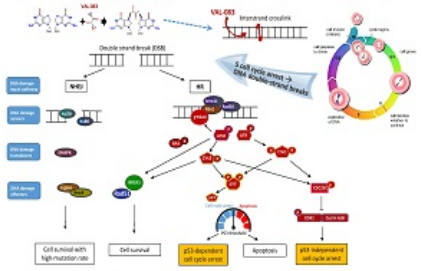


FIGURE 2. *Mechanisms of action of VAL-083 induced chemotherapeutic cytotoxicity. Apoptosis can be induced through either p53 dependent or p53 independent pathways. Red color signifies VAL-083-induced activation.*[1,2]

This distinct mechanism of action of VAL-083 suggests that VAL-083 may offer a treatment alternative against GBM tumors with MMR-, or MGMT-mediated resistance to chemotherapeutic agents, including temozolomide and nitrosoureas.

VAL-083 MEDIATES DNA DOUBLE STRAND BREAKS, S/G2 PHASE CELL CYCLE ARREST AND ACTIVATES THE HOMOLOGOUS RECOMBINATION (HR) DNA REPAIR SYSTEM

VAL-083 pulse treatment led to increased Rad51, BRCA1, RPA32 and γH2A.X foci formation in A549 lung cancer cells (Figure 3) and increased γH2A.X and ATM activation and S/G2 cell cycle arrest U251 GBM cancer cells for up to 72 hours (Figure 4), suggesting ***VAL-083-mediated DNA double strand breaks and persistent activation of the HR DNA damage repair system***

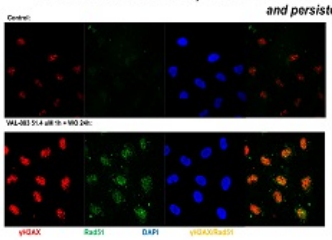


FIGURE 3. Serum-starved A549 lung cancer cells were treated with 51.4 μM VAL-083 for 1h, followed by washout for 24h. Cells were pre-extracted in CSK buffer for 5 min at 4°C, fixed in 4 % paraformaldehyde, washed in PBS and stained with corresponding antibodies.

A549 cells	γH2A.X +	BRCA1 +	Double positive
Control	21.59 %	10.23 %	10.23 %
VAL 1h + WO 24h	81.72 %	72.04 %	67.74 %

A549 cells	γH2A.X +	Rad51 +	Double positive
Control	23.73 %	1.69 %	0
VAL 1h + WO 24h	87.18 %	74.36 %	67.95 %

A549 cells	γH2A.X +	RPA32 +	Double positive
Control	16.26 %	1.63 %	0.81 %
VAL 1h + WO 24h	87.06 %	83.53 %	80 %

VAL-083 TREATMENT MEDIATES PERSISTENT DSBs, HR ACTIVATION AND S/G2 PHASE CELL CYCLE ARREST

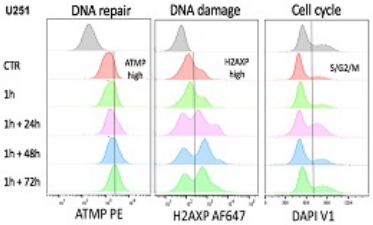


FIGURE 4. VAL-083 pulse treatment led to phosphorylation of DNA DSB marker H2AX, HR component ATM and mediates cell cycle arrest at S/G2 phase in U251 GBM cells (50 μM VAL-083 pulse treatment for 1 hr)

VAL-083 DISPLAYS SYNERGY WITH TOPOISOMERASE INHIBITORS

As VAL-083 induce cell cycle arrest in S/G2-phase, we predicted synergy with agents that require cancer cells to be in S/G2-phase for maximum effect, including topoisomerase inhibitors. As expected, **VAL-083 demonstrated synergy with etoposide** *(TOP-2 inhibitor)* **and camptothecin** *(TOP-1 inhibitor)* (Table 1).

TABLE 1. *VAL-083 demonstrates synergy with etoposide (TOP2 inhibitor) and camptothecin (TOP1 inhibitor) in PC3 prostate and A549 NSCLC cancer cells. CI values for the cytotoxic effect (Fa). CI<1 shows synergy. N=4-5.*

Cell line	Etoposide *(topoisomerase II inhibitor)*		Camptothecin *(topoisomerase I inhibitor)*	
	Cytotoxic effect (Fa)	Combination index (CI)	Cytotoxic effect (Fa)	Combination index (CI)
PC3	ED50	0.58	ED75	0.68
	ED75	0.48	ED90	0.59
	ED90	0.42	ED95	0.54
A549	ED50	0.72	ED85	0.94
	ED75	0.88	ED90	0.87
	ED80	0.94	ED95	0.77

Molar ratios: VAL-083:etoposide 5:1 in PC3 and 5:1 in A549; VAL-083:camptothecin 250:1 in PC3 and 212:1 in A549

VAL-083 CYTOTOXICITY IS INCREASED IN HR-IMPAIRED CANCER CELLS AND DISPLAYS SUPERADDITIVITY WITH PARP INHIBITORS (PARPi)

VAL-083 cytotoxicity against ovarian cancer A2780 cells was increased (IC50 decreased) when BRCA1 was impaired (HR impaired) (Figure 5A). This suggests ***increased activity in ovarian cancer with dysfunctional BRCA1*** and further suggests the potential for synergy with PARPi. ***VAL-083 in combination with PARPi olaparib, talazoparib or veliparib was superadditive*** in BRCA1-proficient ovarian cancer cells (Figure 5).

Studies of VAL-083 in combination with PARPis in BRCA1-deficient ovarian cancer cells are ongoing.

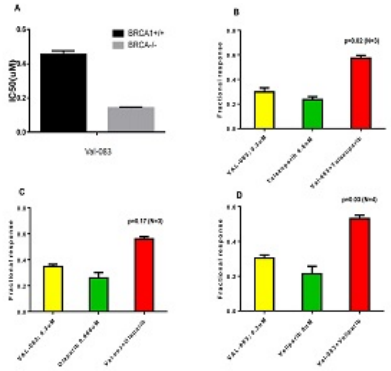
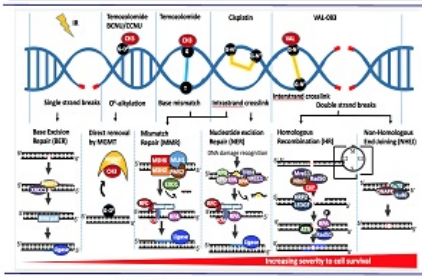


FIGURE 5. VAL-083 cytotoxicity against BRCA1-proficient (BRCA1+/+) and -deficient (BRCA1-/-) ovarian cancer cells A2780 (A). VAL-083 cytotoxicity in combination with PARPi talazoparib (B), olaparib (C) or veliparib (D) in BRCA1-proficient ovarian cancer cells A2780 .



CONCLUSIONS

- VAL-083 mediates persistent DNA double strand breaks, activates the HR repair system and mediates S/G2 cell cycle arrest
- VAL-083 displays synergy with topoisomerase I and II inhibitors
- Val-083 activity is increased in HR (BRCA1) impaired ovarian cancer cells
- VAL-083 displays superadditivity with PARPis talazoparib, olaparib and veliparib

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