SITC 2018

NOVEMBER 7-11
WASHINGTON, D.C.
Walter E. Washington
Convention Center

sitc

Society for Immunotherapy of Cancer

SITC 2018 NOVEMBER 7–11 • WASHINGTON, D.C.

First-in-human phase 1 dose-escalation trial of the potent and selective next generation transforming growth factor-β receptor type 1 (TGF-βR1) inhibitor LY3200882 in patients with advanced cancer

Timothy A. Yap[1], Capucine Baldini[2], Christophe Massard[2], Ivelina Gueorguieva[3], Yumin Zhao[4], Shelly L. Schmidt[4], Michael Man[4], Shawn T. Estrem[4], Karim A. Benhadji[5], Maria Vieito[6]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Gustave Roussy Cancer Campus, Villejuif, France; [3]Eli Lilly and Company, Windlesham, UK; [4]Oncology, Eli Lilly and Company, Indianapolis, IN, USA; [5]Oncology, Eli Lilly and Company, New York, NY, USA; [6]Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain

Presented by: Timothy A. Yap, MD PhD

Society for Immunotherapy of Cancer
#SITC2018

Presenter Disclosure Information

The following relationships exist related to this presentation:

Timothy Yap:

1. *Employment: Medical Director of the Institute for Applied Cancer Science and Associate Director for Translational Research of the Institute for Personalized Cancer Therapy at the University of Texas MD Anderson Cancer Center. Previous employee of the Institute of Cancer Research, London, England.*
2. *Research support: AstraZeneca, Bayer, Pfizer, Tesaro, Jounce, Eli Lilly, Seattle Genetics, Kyowa, Constellation, and Vertex Pharmaceuticals.*
3. *Consultancies: Aduro, Almac, AstraZeneca, Atrin, Bayer, Bristol-Myers Squibb, Calithera, Clovis, Cybrexa, EMD Serono, Ignyta, Jansen, Merck, Pfizer, Roche, Seattle Genetics, and Vertex Pharmaceuticals.*
4. *Speaker bureau: AstraZeneca, Merck, Pfizer, and Tesaro.*

- **There will be a discussion about the use of an investigational product for non-FDA approved indications in this presentation.**

Additional Author Disclosure Information:

The following relationships exist related to this presentation:

1. ***Capucine Baldini:***
   a. *Travel and accommodation expenses: Roche, Amgen, Pfizer*
   b. *Paid expert testimony: Abbvie, BMS*
   c. *Principal/sub-Investigator of Clinical Trials: Abbvie, Aduro, Agios, Amgen, Argen-x, Astex, AstraZeneca, Aveo pharmaceuticals, Bayer, Beigene, Blueprint, BMS, Boeringer Ingelheim, Celgene, Chugai, Clovis, Daiichi Sankyo, Debiopharm, Eisai, Eos, Exelixis, Forma, Gamamabs, Genentech, Gortec, GSK, H3 biomedecine, Incyte, Innate Pharma, Janssen, Kura Oncology, Kyowa, Lilly, Loxo, Lysarc, Lytix Biopharma, Medimmune, Menarini, Merus, MSD, Nanobiotix, Nektar Therapeutics, Novartis, Octimet, Oncoethix, Oncopeptides AB, Orion, Pfizer, Pharmamar, Pierre Fabre, Roche, Sanofi, Servier, Sierra Oncology, Taiho, Takeda, Tesaro, Xencor*

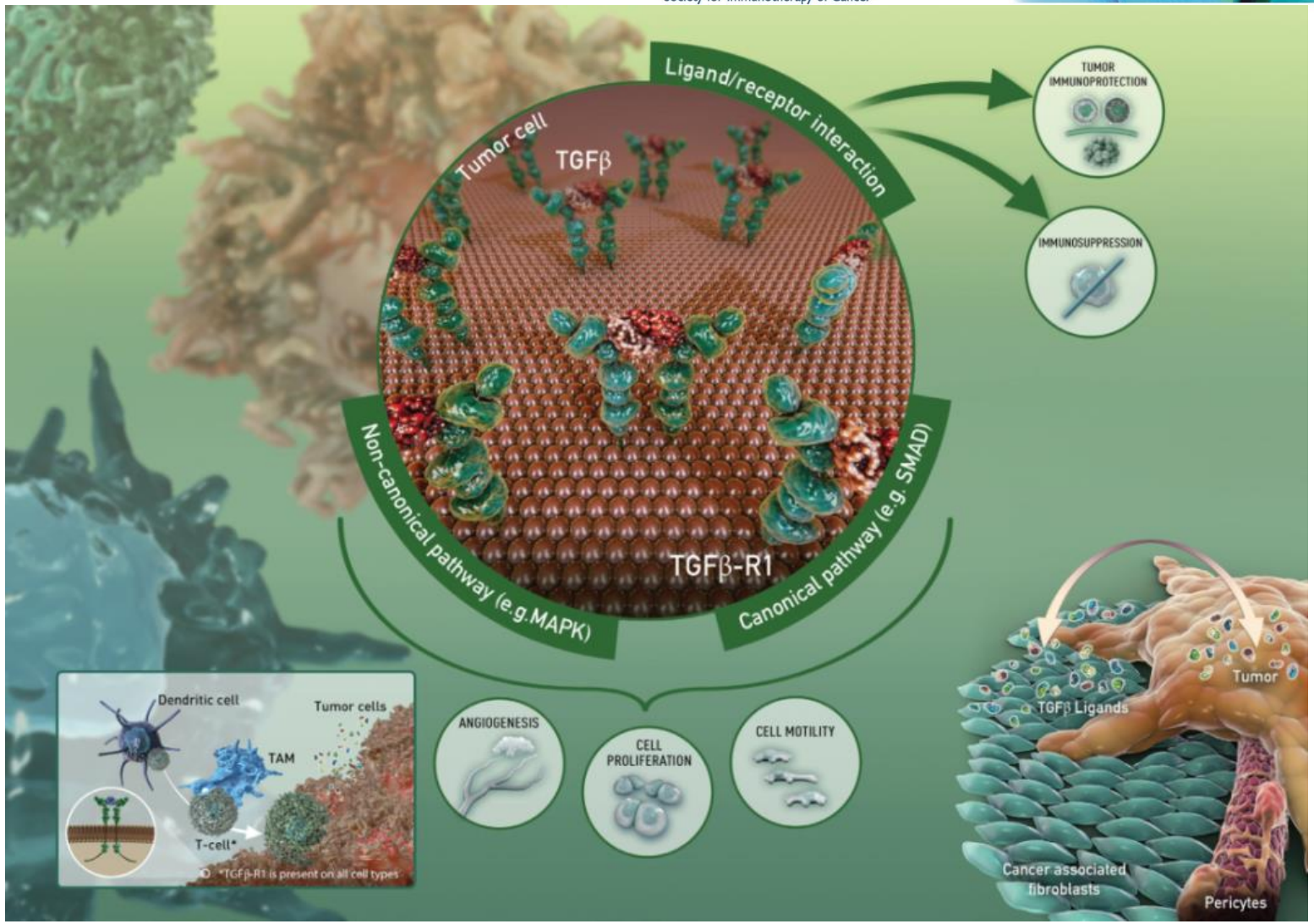
2. ***Christophe Massard****: No disclosures reported*

3. ***Maria Vieito****: Travel and accommodation expenses: Roche*

4. ***Ivelina Gueorguieva, Yumin Zhao, Shelly L. Schmidt, Michael Man, Shawn T. Estrem, & Karim A. Benhadji*** *are all employees and stock holders of Eli Lilly and Company*

Background

- Transforming growth factor- β (TGFβ) is a pleiotropic cytokine[1]
- Tumorigenesis converts TGFβ from a tumor suppressor to a tumor promoter[1-3]
- TGFβ induces angiogenesis and epithelial–mesenchymal transition[1], inhibits immune surveillance[2], promotes tumor proliferation[3]

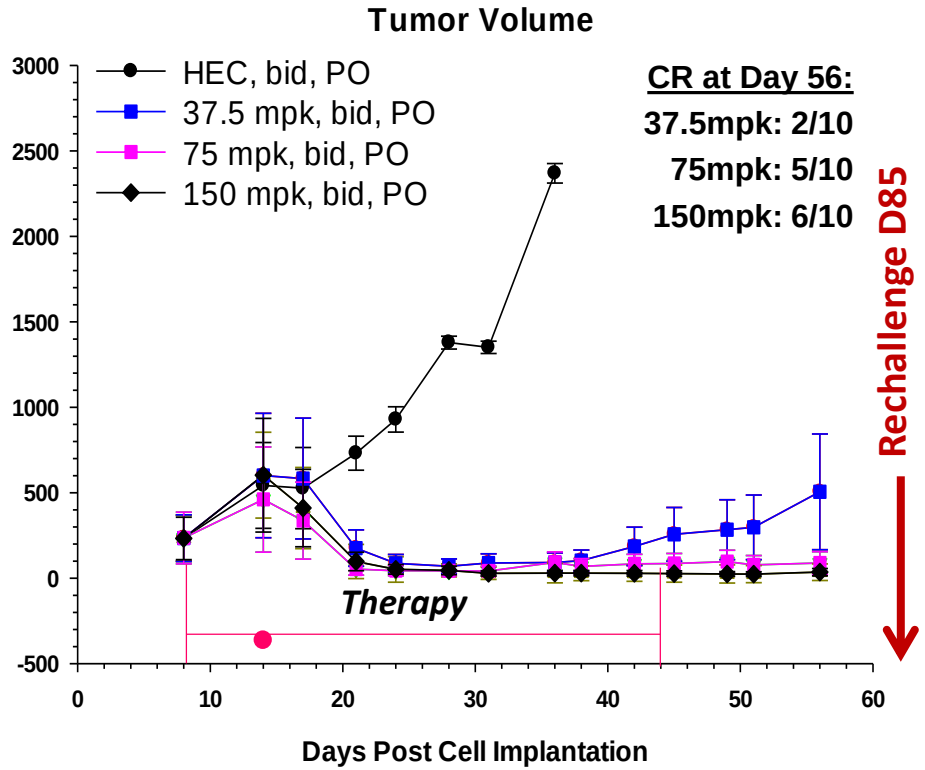


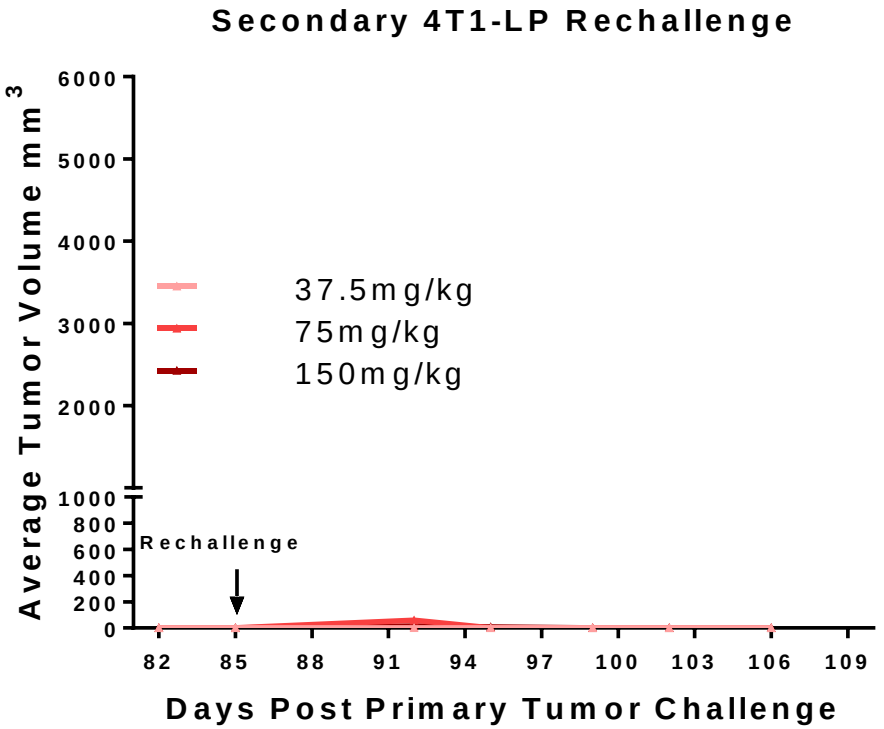
Data from: Poster presented at AACR Annual Meeting 2017[4]; and, http://www.lillyoncologypipeline.com/molecule/tgf-beta-r-1-kinase-inhibitor-ii/overview

[1]Prud'homme GJ. Lab Invest. 2007;87(11):1077-1091; [2]Flavell RA, et al. Nat Rev Immunol. 2010;10(8):554-567; [3]Ikushima H, Miyazono K. Nat Rev Cancer. 2010;10(6):415-424; [4]Pei et al. Cancer Res. 2017;77(13 Suppl): Abstract nr 955.

Background

- LY3200882 is a next generation small-molecule TGF-β receptor 1 (TGF-βR1) inhibitor shown to have high potency and is highly selective[4]





Abbreviations: BID, Twice Daily; CR, Complete Response; D, Day; HEC, Hydroxyethyl Cellulose (vehicle control); mpk, mg/kg; PO, Orally

Data from: Poster presented at AACR Annual Meeting 2017; [4]Pei et al. Cancer Res. 2017;77(13 Suppl): Abstract nr 955.

- LY3200882 treatment in a pre-clinical model of orthotopic 4T1-LP triple negative breast cancer in mice has demonstrated[4]:
  - Durable tumor regression with initial therapy (left panel)
  - Compete rejection during rechallenge with congenic tumors (right panel)

Study Design: NCT02937272 Part A, Schedule A

Patient Population:
Advanced / metastatic cancer pts after progression on standard therapy

Dose Escalation - guided by safety assessment of previous cohort

Cohort 1:	Cohort 2:	Cohort 3:	Cohort 4:	Cohort 5:
Monotherapy 5 mg Oral, BID	Monotherapy 10 mg Oral, BID	Monotherapy 20 mg Oral, BID	Monotherapy 35 mg Oral, BID	Monotherapy 50 mg Oral, BID

Recommended Dose:
Maximum safe dose is the MTD and highest allowable dose

- 1 cycle is 28 days, with 2 wks on / 2 wks off treatment
- DLT observation period lasts to the completion of Cycle 1
- n=3 to assess DLTs in each cohort
- n=3 – 12 additional pts to confirm recommended dose = BED

Abbreviations: BED, Biologically Effective Dose; BID, Twice Daily; DLT, Dose-Limiting Toxicity; MTD, Maximum Tolerated Dose; pts, patients; wks, weeks

- LY3200882 tosylate salt (hereafter referred to as LY3200882) was given twice daily to 5 cohorts of patients at increasing doses (5 to 50 mg) for 14 days in a 28 day cycle
- Primary endpoint was to determine the recommended phase 2 dose
- Secondary objectives included safety, response assessments and pharmacokinetics (PK), and exploratory objectives included pharmacodynamics (PD)

Key Inclusion and Exclusion Criteria

- **Inclusion:**
  - Histological/cytological evidence of an advanced/metastatic solid tumor or lymphoma that is refractory to available standard therapy
  - Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1
  - Adequate organ function
  - Estimated life expectancy of ≥12 weeks
  - Able to swallow tablets or capsules

- **Exclusion:**
  - Have moderate or severe cardiovascular disease
  - Have serious concomitant systemic disorder
  - Concomitant use of strong P450 (CYP) 3A4 inhibitor

Baseline Characteristics

Safety population	Cohort 1, 5 mg, BID (*n*=4)	Cohort 2, 10 mg, BID (*n*=3)	Cohort 3, 20 mg, BID (*n*=3)	Cohort 4, 35 mg, BID (*n*=3)	Cohort 5, 50 mg, BID (*n*=17)	Total (*N*=30)
Age, median, years (range)	58.5 (52 – 66)	58.0 (44 – 73)	46 (37 – 53)	44 (41 – 74)	46 (32 – 69)	47 (32 – 74)
< 65 years, *n* (%)	3 (75.0)	2 (66.7)	3 (100.0)	2 (66.7)	16 (94.1)	26 (86.7)
≥ 65 years, *n* (%)	1 (25.0)	1 (33.3)	-	1 (33.3)	1 (5.9)	4 (13.3)
Sex, *n* (%)						
Male	2 (50.0)	2 (66.7)	1 (33.3)	3 (100.0)	11 (64.7)	19 (63.3)
Female	2 (50.0)	1 (33.3)	2 (66.7)	-	6 (35.3)	11 (36.7)
Race, *n* (%)						
White	4 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	16 (94.1)	29 (96.7)
African American	-	-	-	-	1 (5.9)	1 (3.3)
Baseline ECOG PS, *n* (%)						
0	-	1 (33.3)	1 (33.3)	-	6 (35.3)	8 (26.7)
1	4 (100.0)	2 (66.7)	2 (66.7)	3 (100.0)	11 (64.7)	22 (73.3)
Initial Pathological Diagnosis, *n* (%)						
Glioma[a]	1 (25.0)	1 (33.3)	2 (66.7)	1 (33.3)	10 (58.8)	15 (50.0)
Glioblastoma	2 (50.0)	-	-	-	3 (17.6)	5 (16.7)
Pancreatic cancer	-	1 (33.3)	-	1 (33.3)	1 (5.9)	3 (10.0)
Cervical cancer	1 (25.0)	1 (33.3)	-	-	1 (5.9)	3 (10.0)
Chondrosarcoma	-	-	1 (33.3)	-	1 (5.9)	2 (6.7)
Appendix carcinoma	-	-	-	1 (33.3)	-	1 (3.3)
Colorectal adenocarcinoma	-	-	-	-	1 (5.9)	1 (3.3)

[a]***Glioma*** *includes: anaplastic astrocytoma, astrocytoma, glioma, oligoastrocytoma, and oligodendroglioma*

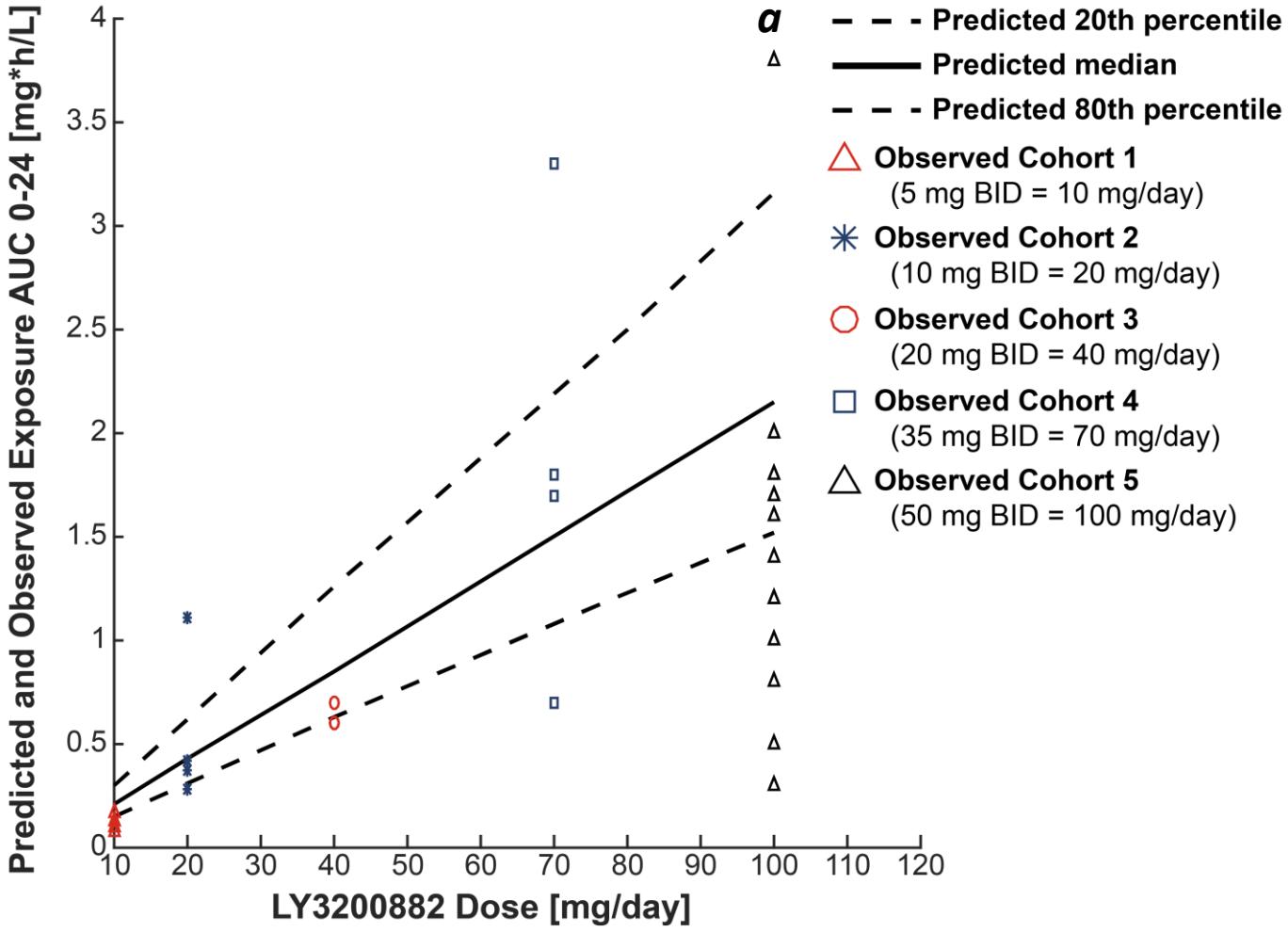
Safety: Treatment-Related Adverse Events in All Treated Patients

Safety Population	Cohort 1, 5 mg, BID (*n*=4)		Cohort 2, 10 mg, BID (*n*=3)		Cohort 3, 20 mg, BID (*n*=3)		Cohort 4, 35 mg, BID (*n*=3)		Cohort 5, 50 mg, BID (*n*=17)	
TRAE Terms, *n* (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Patients with DLT	-		-		-		-		-	
Patients with ≥1 TRAE	1 (25.0)	-	2 (66.7)	-	1 (33.3)	-	2 (66.7)	-	4 (23.5)	-
Anemia	1 (25.0)	-	-	-	-	-	-	-	-	-
Thrombocytopenia (or platelet count decreased)	-	-	1 (33.3)	-	-	-	1 (33.3)	-	-	-
Troponin I increased	-	-	-	-	-	-	-	-	1 (5.9)	-
Edema peripheral	-	-	1 (33.3)	-	-	-	-	-	-	-
Dry mouth	-	-	-	-	-	-	-	-	1 (5.9)	-
Constipation	-	-	-	-	-	-	1 (33.3)	-	1 (5.9)	-
Nausea	-	-	-	-	-	-	-	-	1 (5.9)	-
Vomiting	-	-	1 (33.3)	-	-	-	-	-	-	-
Dermatitis acneiform	-	-	-	-	1 (33.3)	-	1 (33.3)	-	-	-
Rash maculo-papular	-	-	-	-	-	-	1 (33.3)	-	-	-
Rash pustular	-	-	-	-	1 (33.3)	-	-	-	-	-
Dry Skin	-	-	-	-	-	-	-	-	1 (5.9)	-

- No Dose Limiting Toxicities (DLTs) Observed

Pharmacokinetics (PK)

Increased Exposure with Increased Dose

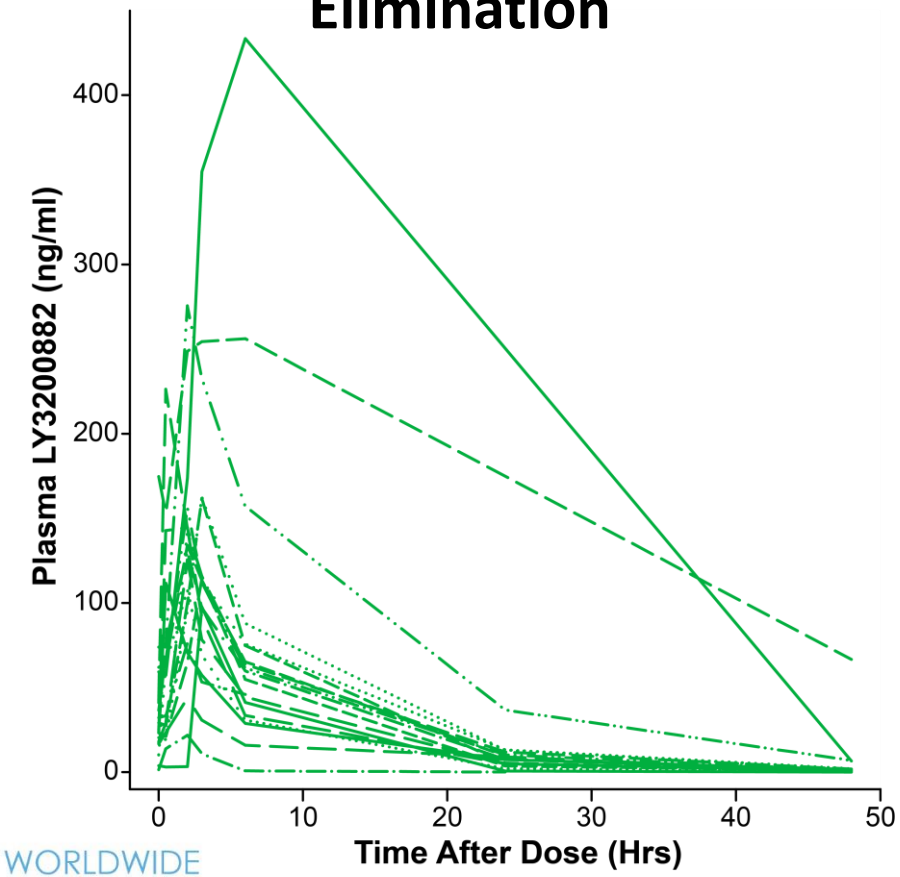


[a]In the 100 mg/day cohort, 2 additional samples were measured at 5.6 & 7.2 mg*h/L

PK Summary Table:

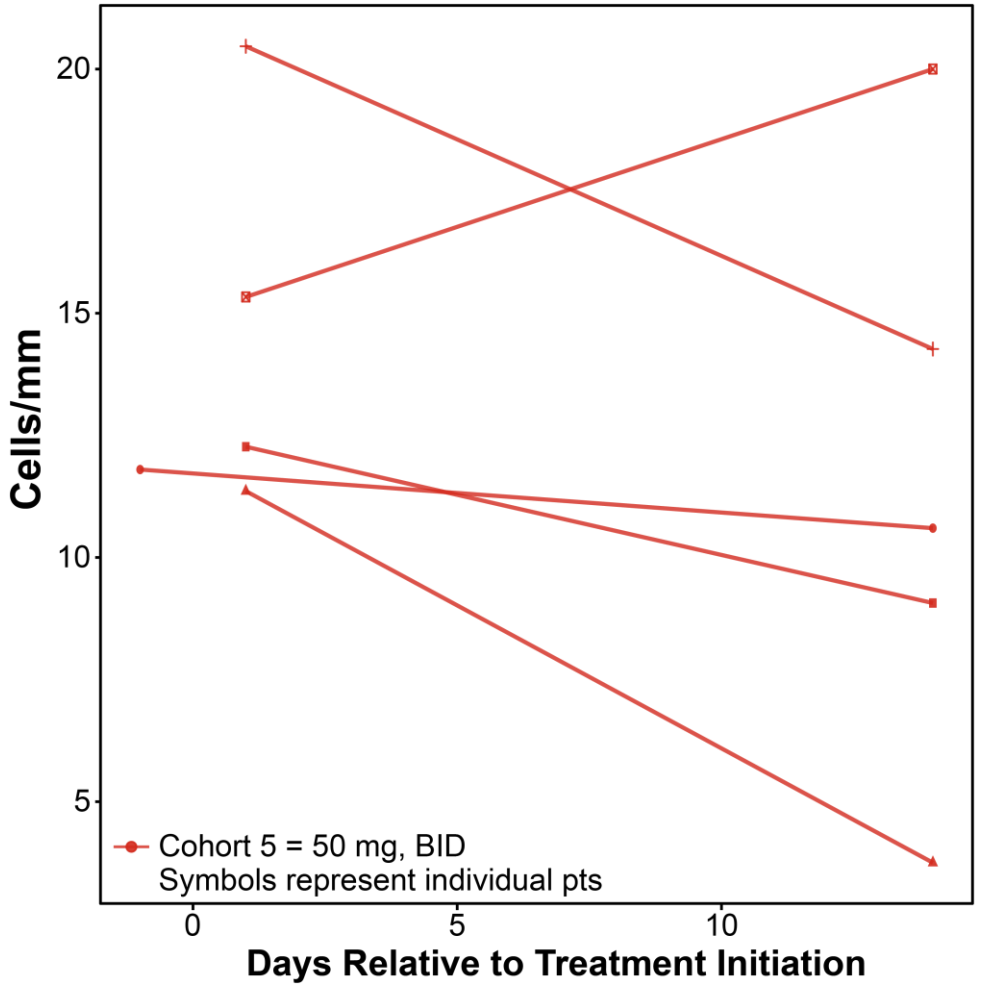
50 mg, BID Dose (*n*=15 patients)	Absorption (Tmax, h)	Half-Life (T1/2, h)	Exposure (AUC_tau, h*mg/L)
Mean	2.16	7.44	1.5

Elimination



Skin Langerhans Cell (LC) Density Trends Down Post-Treatment

- Maintenance of LCs in skin epidermis requires active TGFβ[5]
- TGFβ inhibits *in vivo* LC maturation and migration in mouse[6]
- TGFβ is required to maintain LCs in epidermis, and interruption leads to LC migration in mouse[7]
- These data suggest that TGFβ is modulated in some patients



[5]*Mohammed, J. et al. Nat Immunol. 2016;* [6]*Kel, J.M. et al. J Immunol. 2010;* [7]*Bobr, A., et al., Proc Natl Acad Sci USA. 2012.*

Best Overall Response

Best Overall Response in all treated patients, *n* (%)	Cohort 1, 5 mg, BID (*n*=4)	Cohort 2, 10 mg, BID (*n*=3)	Cohort 3, 20 mg, BID (*n*=3)	Cohort 4, 35 mg, BID (*n*=3)	Cohort 5, 50 mg, BID (*n*=17)	Total (*N*=30)
Complete Response (CR)	-	-	-	-	-	-
Partial Response (PR)	-	-	-	-	1 (5.9)	1 (3.3)
Stable Disease (SD)	1 (25.0)	-	1 (33.3)	2 (66.7)	2 (11.8)	6 (20.0)
Progressive Disease (PD)	1 (25.0)	1 (33.3)	2 (66.7)	1 (33.3)	6 (35.5)	11 (36.7)
Non Evaluable	2 (50.0)	2 (66.7)	-	-	8 (47.1)	12 (40.0)
Overall Response Rate (CR/PR)	-	-	-	-	1 (5.9)	1 (3.3)
Disease Control Rate (CR/PR/SD)	1 (25.0)	-	1 (33.3)	2 (66.7)	3 (17.6)	7 (23.3)

Response criteria used was RANO for glioma and RECIST v1.1 for other solid tumors

Preliminary Antitumor Activity

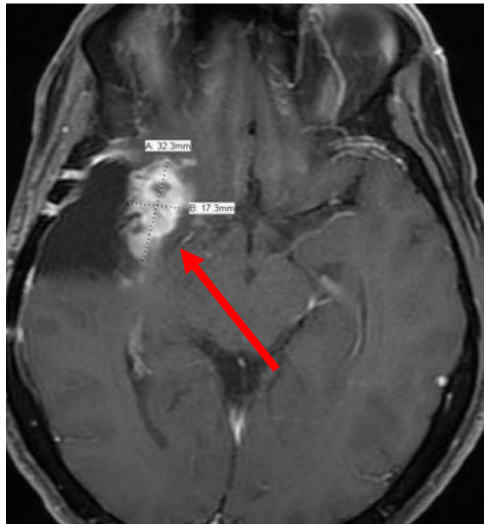
Summary of Tumor Reductions:

Type of Cancer Patient	(%) Change from Baseline
Glioblastoma	-94.00
Glioma	-37.65
Astrocytoma	-18.75
Glioma	-8.33
Oligoastrocytoma	-1.32

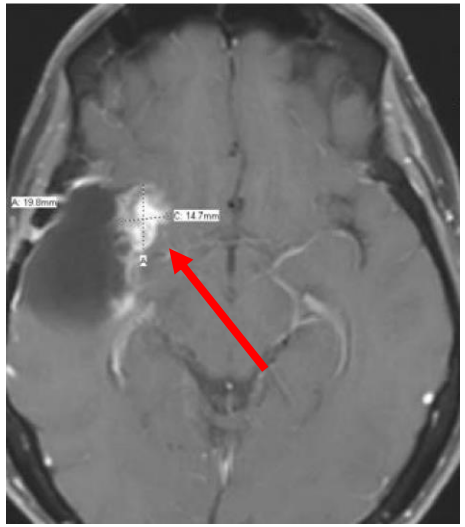
53y male. GBM on LY3200882 monotherapy 50mg BID 2-wk-on, 2-wk-off

Molecular profiling: *EGFR* P772_V774dupPHV mutation; *CDK4* amplification; *IDH1/2* WT, *MGMT* methylated

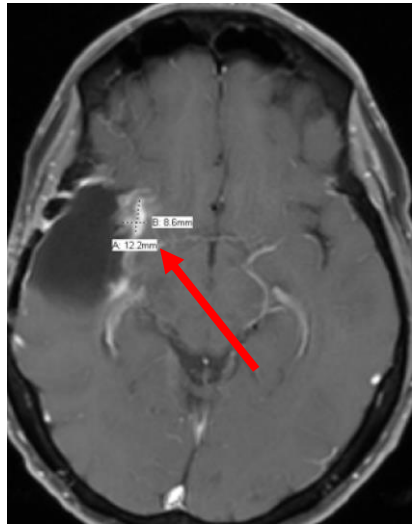
Oct 2016: Tumor resection; **Nov-Dec 2016:** Radiotherapy (60Gy); **Feb 2017:** Temodar (2 cycles); **Apr 2017:** Tumor resection; **May-Jun 2017:** Lomustine



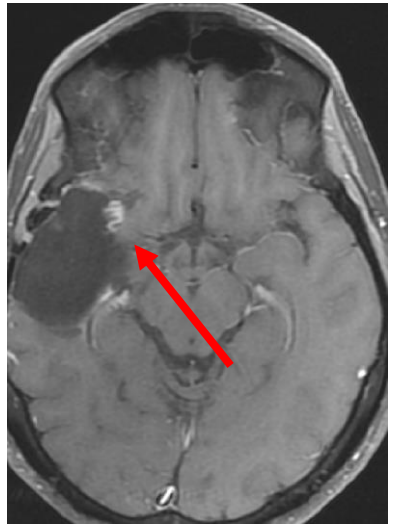
Aug 2017 (baseline)



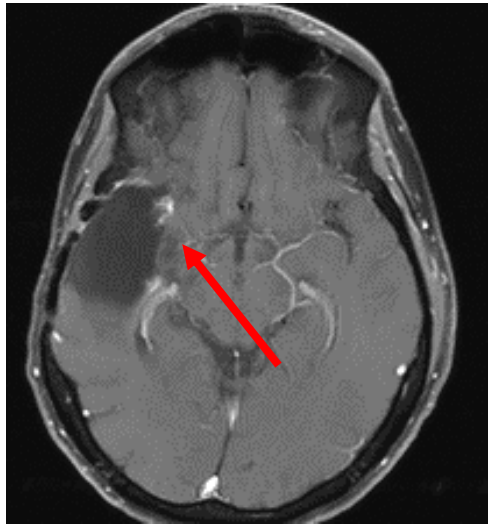
Oct 2017 (-39%)



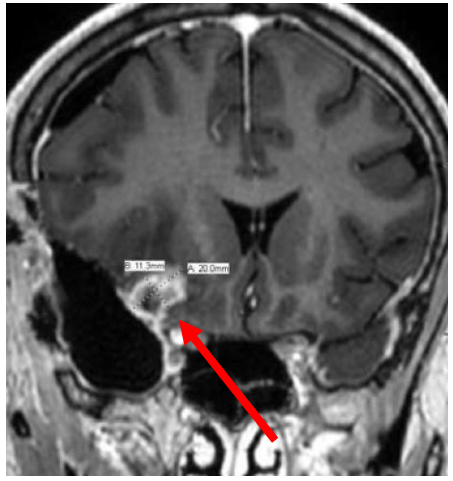
Dec 2017 (-69%)

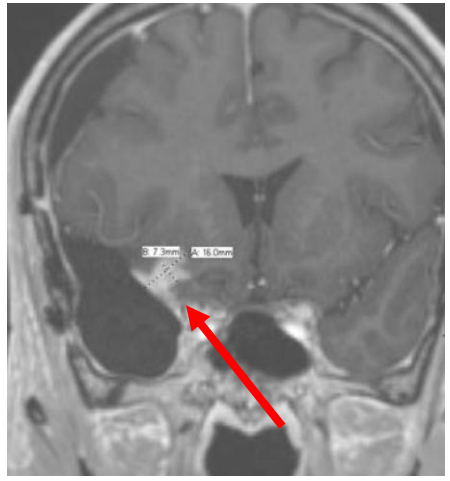


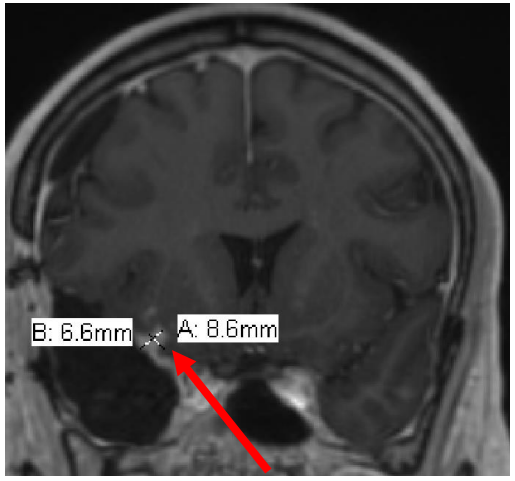
Jan 2018 (-86%)

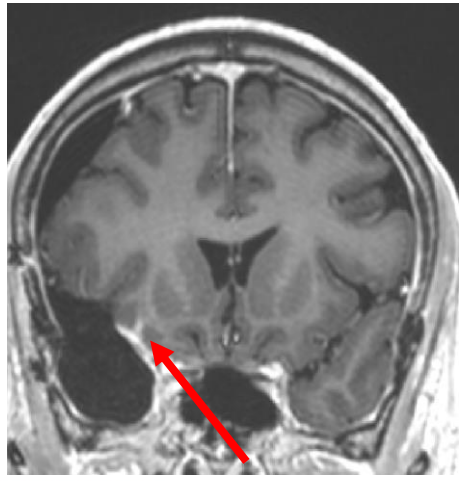


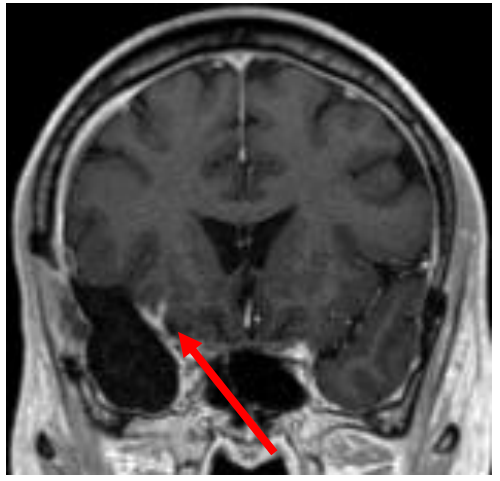
Sep 2018 (-94%)











Conclusions:

In this dose-escalation study of LY3200882 monotherapy:

- The recommended phase 2 dose (RP2D) of 50mg BID at 2 weeks on / 2 weeks off:
  - Safe and well tolerated
  - Appropriate plasma PK exposures
  - Pharmacodynamic target modulation
  - Preliminary antitumor activity

An expansion cohort assessing patients with glioblastoma is ongoing

Acknowledgements:

- We thank all of the patients and their caregivers for participation in this trial
- We thank all of the investigators and their support staff who generously participated in this work
- Medical writing support was provided by Matthew DiStasi, an employee at Eli Lilly and Company