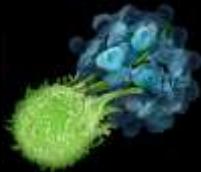


Radiation plus Immunotherapy to improve systemic immune response



MDAnderson
Cancer Center

James Welsh, MD
Associate Professor
Thoracic Radiation Oncology
Head of Immuno Radiation

Disclosures

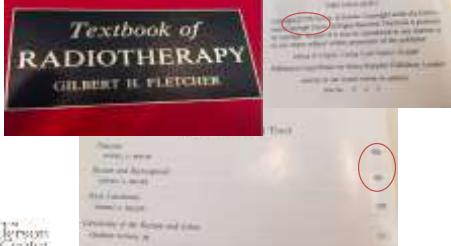
- Employment:
 - University of Texas MD Anderson
- Founder:
 - Healios Oncology, MolecularMatch.com, OncoResponse
- Research Support:
 - **BMS**, Incyte, **GSK**, **Merck**, Nanobiotics, Mavu, CheckMate
- Patents:
 - MP470 (amuvatinib), MRX34 regulation of PDL1
- Scientific Advisor Board:
 - **ReflexXion Medical**, MolecularMatch, OncoResponse, CheckMate, Mavu, Alpine

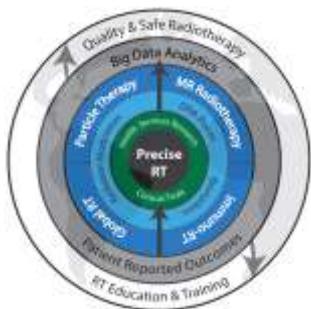


XRT as systemic therapy

- 1) XRT ability to turn tumor into “in-Situ” vaccine
- 2) Ways of using XRT to address the inhibitory stroma
- 3) How automation of XRT can further improve immune response



Perspective

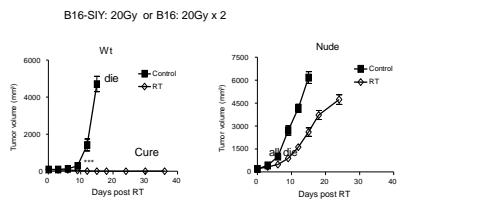
MDA Radiation
Strategic Vision



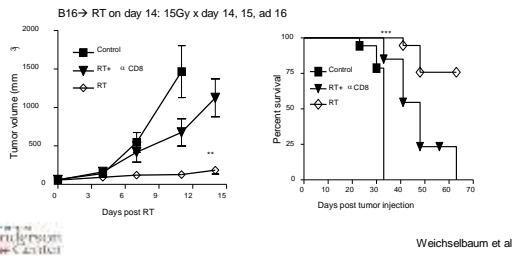




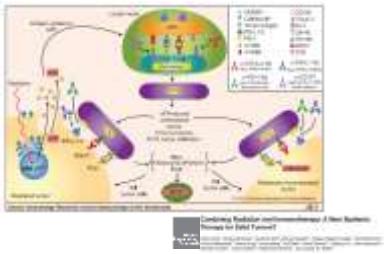
Radiation needs an immune response



Radiation needs CD8+ cells



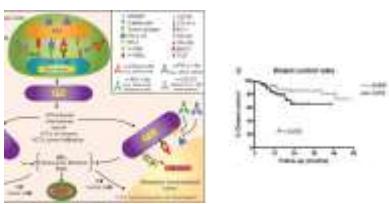
Why XRT needs an Immune Response



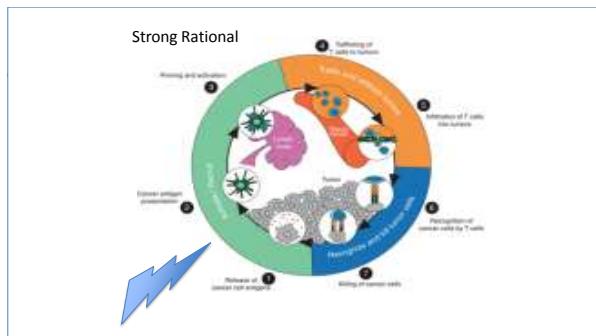
© 2012 by the American Association for Cancer Research.

Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis

AKKUTLU, G., ET AL. JOURNAL OF CLINICAL ONCOLOGY, 2012



© 2012 by the American Association for Cancer Research.







A Historic Academic Battle

Ewing believed Radiation
Would be the future

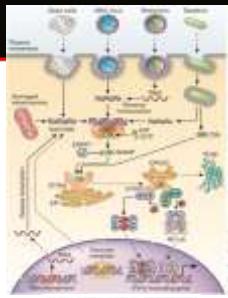


VS

Coley believed Immunology
would be the future



- Ironically XRT is an immuno agent
- DNA → cGAS → STING → type I IFN



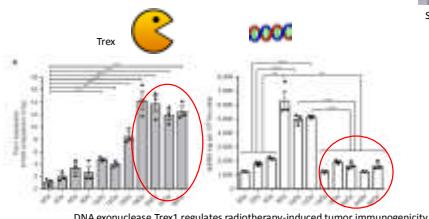
What Dose of XRT?



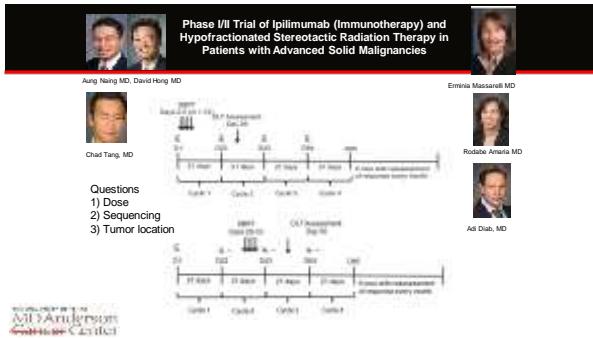
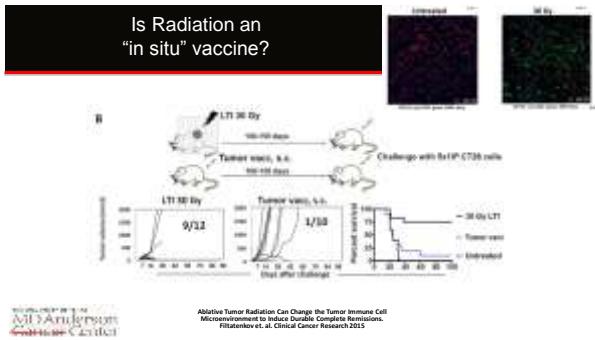
Silvia Formenti



Sandra Demaria

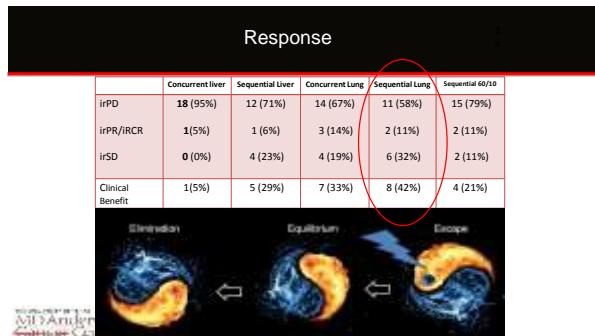
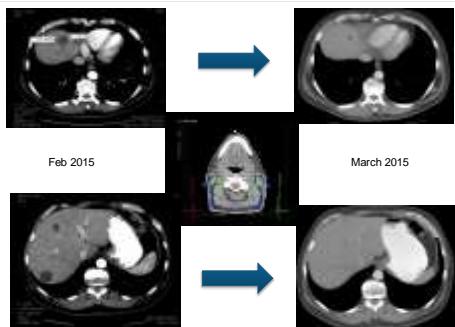
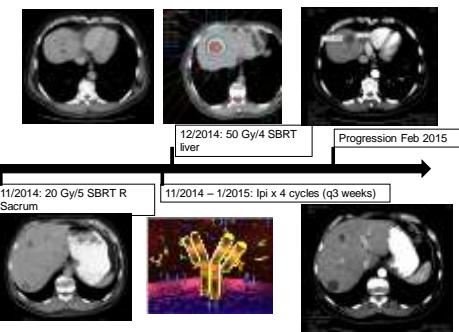


DNA exonuclease Trex1 regulates radiotherapy-induced tumor immunogenicity
Silvia C. Formenti & Sandra Demaria
Nature Communication Jun 9, 2017

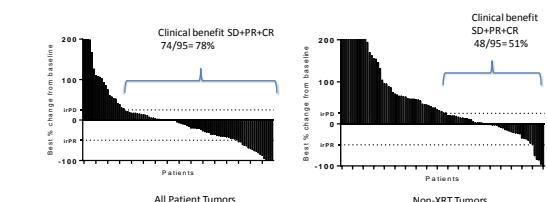


Adverse Events (G3, no G4-5) (n=100)

AE	Conc Lung	Conc Liver	Seq Lung	Seq Liver	Seq 60/10
GIT: Colitis Obstruction Abdominal Pain Diarrhea	4 (4%) 1 (1%) 1 (1%)			2 (2%) 1 (1%)	2 (2%) 1 (1%)
AST/ALT Increase Lipase Increase Bilirubin Increase		2 (2%) 1 (1%)	1 (1%)	2 (2%) 1 (1%) 1 (1%)	5 (5%) 1 (1%)
Endocrine: Hypophysis TSI Increase			1 (1%) 1 (1%)	1 (1%)	1 (1%)
Chest: Pneumonitis Chest Pain Dyspnea	1 (1%)		2 (2%) 1 (1%)	1 (1%)	
Rash maculo- papular	2 (2%)			2 (2%)	



Response rate



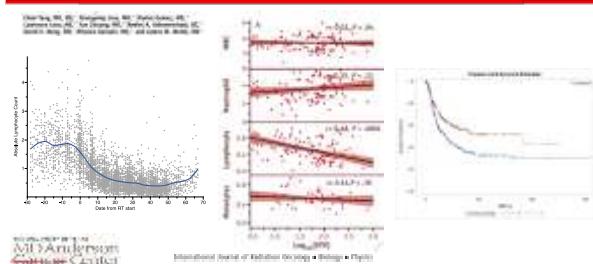
© 2014 Mayo Foundation for Medical Education and Research. All rights reserved.

Complete Leukotrichia in 3 days



© 2014 Mayo Foundation for Medical Education and Research. All rights reserved.

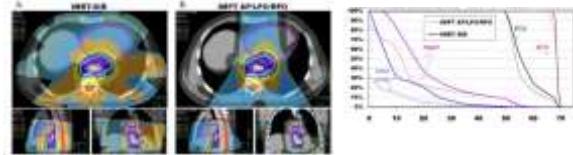
Lymphopenia Association With Gross Tumor Volume and Lung VS and Its Effects on Non-Small Cell Lung Cancer Patient Outcomes



© 2014 Mayo Foundation for Medical Education and Research. All rights reserved.

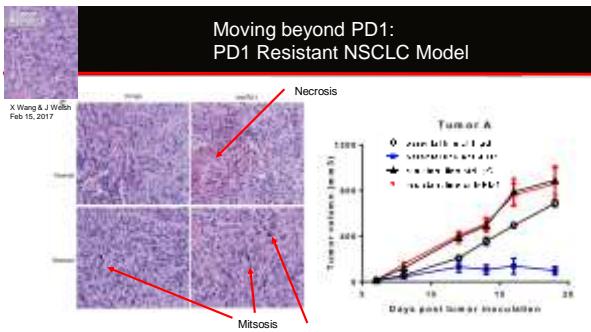
INTERSTITIAL RADIOTHERAPY FOR EARLY STAGED NORMAL TISSUE EXPOSURE IN RING DEFINITIVE THERAPY FOR LOCALLY ADVANCED ORGANOGRAPHIC TUMORS: A DOSIMETRIC STUDY

Jesse Wilson, M.D.,* Daniel Miniaci, M.D.,† Michael P. Parsons, M.R.E.,‡,§,¶,||,** Mark J. Bernstein, D. Bryan Cheadle,† Alan V. Mehta, M.D.,** CMCU Radiation Oncology, MD,|| The University of Texas MD Anderson Cancer Center, Houston, TX, USA, †The University of Texas MD Anderson Cancer Center, Houston, TX, USA, ‡The University of Texas MD Anderson Cancer Center, Houston, TX, USA, §The University of Texas MD Anderson Cancer Center, Houston, TX, USA, ¶The University of Texas MD Anderson Cancer Center, Houston, TX, USA, ||The University of Texas MD Anderson Cancer Center, Houston, TX, USA

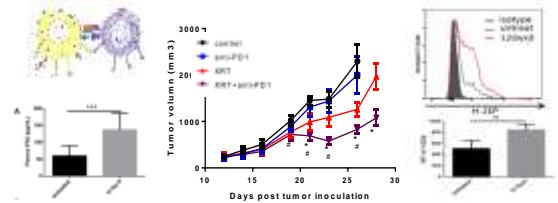


WILLIAMS
ANDERSON
CANCER CENTER

Int. J. Radiation oncology Biol. Phys. Vol 81, 2011

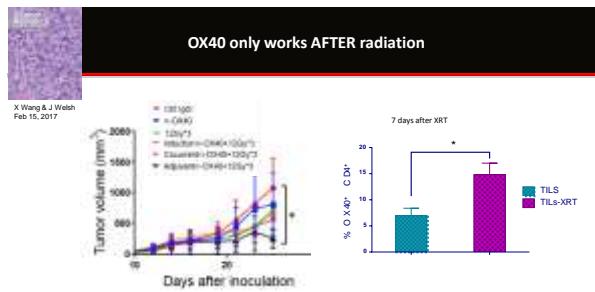


**XRT Increases IFN β → MHC-I
XRT Overcomes PD1 Resistance**

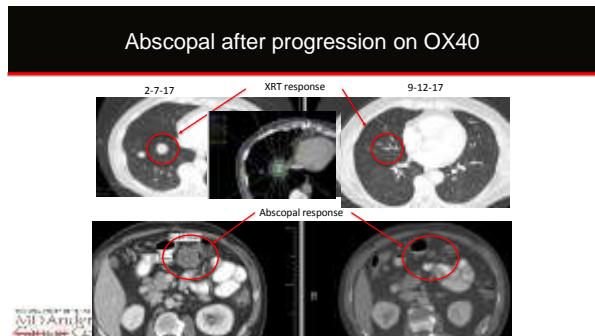


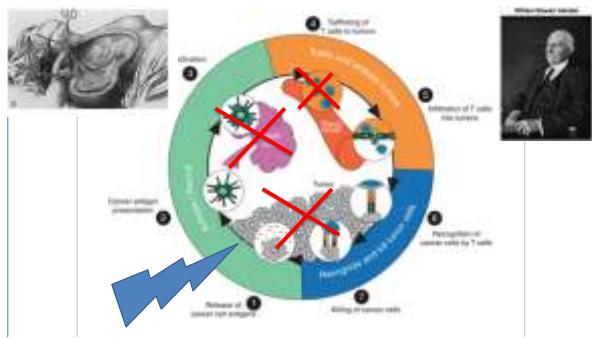
WILLIAMS
ANDERSON
CANCER CENTER

Wang, Welsh et al, Cancer Research, 2016



Niknam and Barsoumian et al., 2017





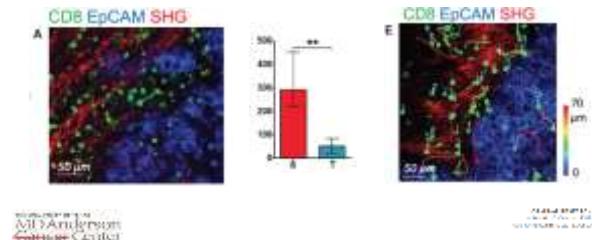
PRECISE: Preoperative Radiotherapy to Elicit Critical Immune Stimulating Effects



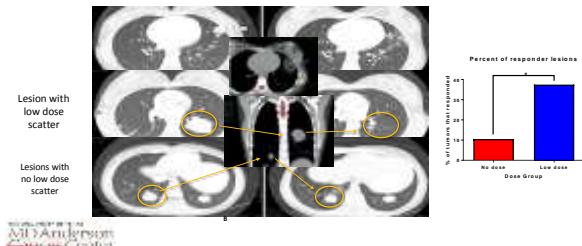
Figure 1. Protocol schema.

Co-PI: S. Shaitelman & E. Mittendorf

Stroma Blocks T cells

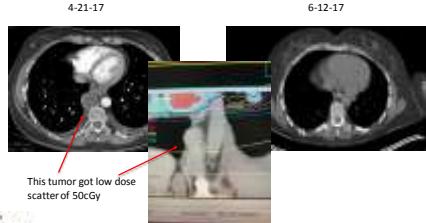


Using low dose scatter XRT to “Pull” in T cells



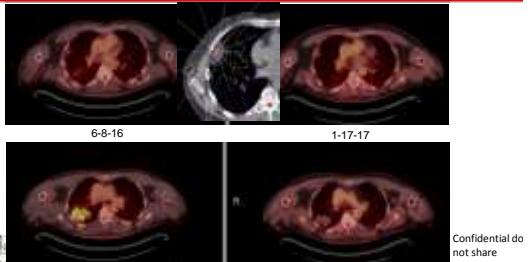
© 2016 Massachusetts General Hospital

Melanoma resistant to anti-PD1



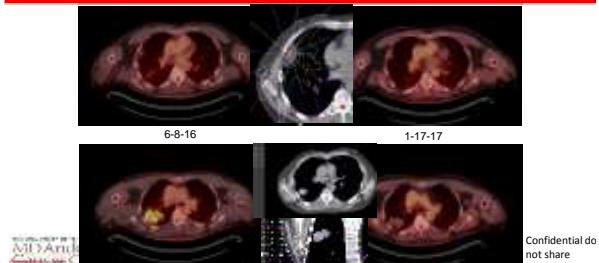
© 2016 Massachusetts General Hospital

Melanoma resistant to anti-PD1

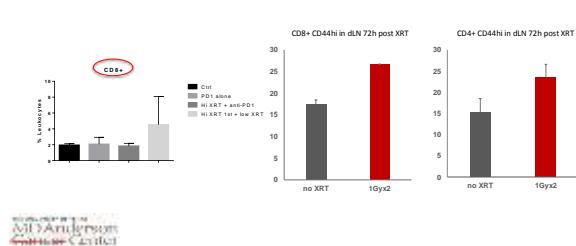


© 2016 Massachusetts General Hospital

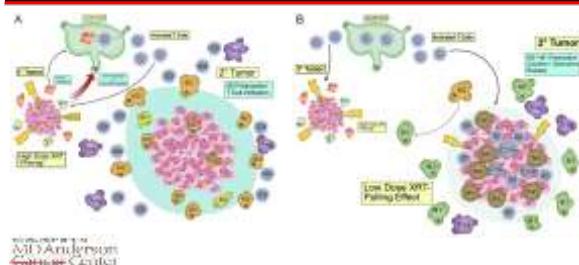
Low dose scatter XRT



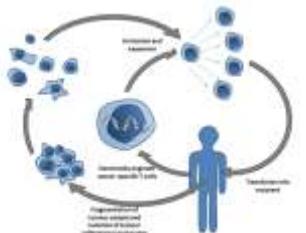
Low dose XRT "Pulls" and activates CD4+ and CD8+



RadScopal



Adoptive T cell Therapy

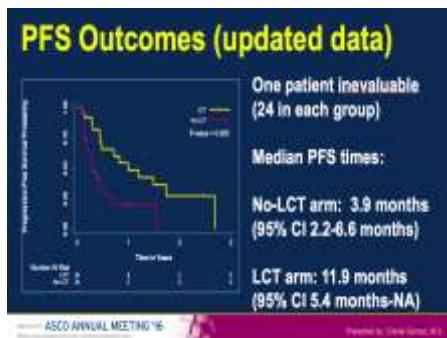
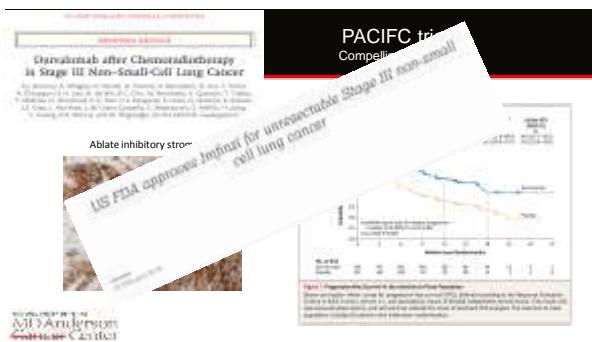


WILLIAMS
ANDERSON
ONCOLOGY CENTER

First Clinical of RadScopal in PD1 resistant melanoma

(RadScopal= high dose XRT to prime and low dose XRT to pull in T cells)







My Car can drive itself why not my Linac?



© 2018 William J. Anderson
RefleXion Cancer

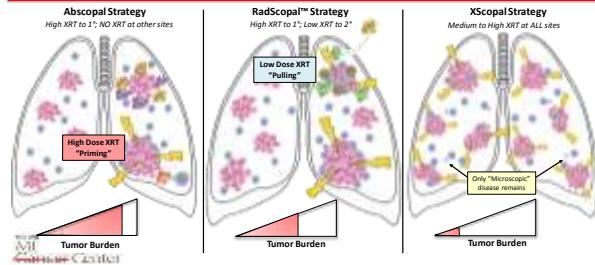
BGRT: Biologically Guided Radiation Therapy



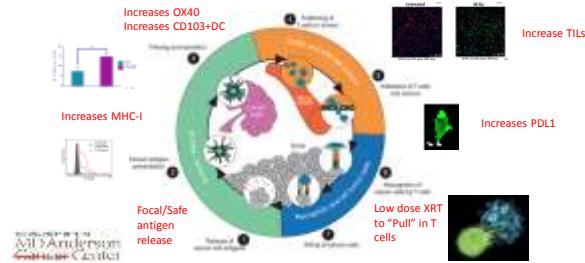
RefleXion is developing a novel radiation therapy system that harnesses signals originating from tumors continuously to guide the treatment beam

refleXion

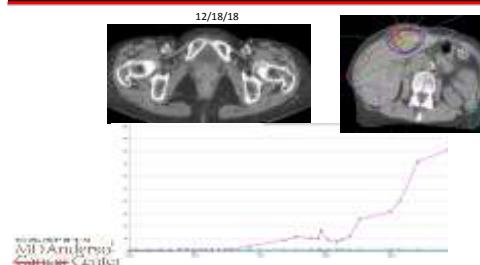
Abscopal, RadScopal™ & XScopal strategies



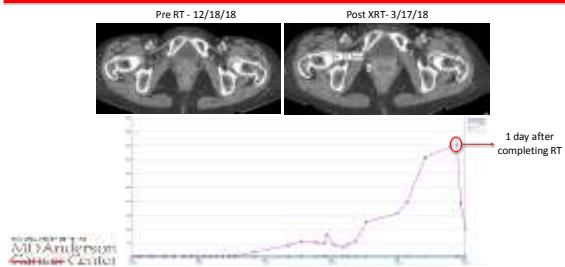
Conclusion: Potential Immunologic Benefits of XRT:



Metastatic Pancreatic cancer progressing on immunotherapy



Vaginal metastatic abscopal after liver XRT



Acknowledgment!

Welsh Lab

Grant Support:
K-12 (NIH)
Knowledge Gap Award
Lung Cancer Research Society
Doctor Cancer foundation
GSK, BMS, Merck
Mirum Biosciences
Hamed Foundation
Orr Family Foundation
Susan And Peter Goodwin Foundation
Mabuchi Foundation
VanSteklenburg Family

Radiologist:
Patricia de Grot, MD
Jeremy Erasmus, MD

Welsh Lab

Angelica Cortez, PhD
David Hwang, PhD
Hampartsoum, PhD
Mina Maserpour, Master
Taylor Cushman, MD
Alex Cadena, BS
Ahmed Younes, MD

Huiying Ye, MD, Wanqin Sheng, PhD
Jon Schreiber, BS (UT Southwest)
El Tsakos, PhD, Sheila Niknam, MS
Alin Li, MD, David Wesseler

Prior
Phase I:
Mina Maserpour, Master
Taylor Cushman, MD
Alex Cadena, BS
Ahmed Younes, MD

Huiying Ye, MD, Wanqin Sheng, PhD
Jon Schreiber, BS (UT Southwest)
El Tsakos, PhD, Sheila Niknam, MS
Alin Li, MD, David Wesseler

Immuno:
Adi Diab, MD
Pam Sharma, MD
James Allison, PhD
Patrick Hwu, MD



Radiation Oncology:
Christopher, MD
Steven Hahn, MD
Ritsuko Komaki, MD
Joe Chang, MD, PhD
Dan Gomez, MD
Zhongxing Liao, MD

John Heymach, MD PhD, Bonnie
Glosson, MD, Ferdinand
Skoulidis, MD, Lauren Byers, MD,
Don Gibbons, MD, Frank Fossella,
MD, Anne Taso, MD
Vassil Papadimitriopoulou, MD,
Frank Mott, MD
George Simon, MD