National Cancer Institute

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MOLECULAR RADIATION THERAPEUTICS BRANCH

A branch of RADIATION RESEARCH PROGRAM

Clinical Working Groups

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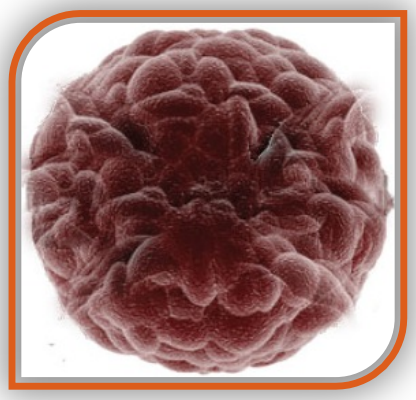
Executive Summary



The Molecular Radiation Therapeutics Branch (MRTB) is a Radiation Research Program (RRP) in-house branch activity that serves as a focal point for collaborations with: the Developmental Therapeutics Program (DTP) and Cancer Therapy Evaluation Program (CTEP) in DCTD, investigators in the Radiation Biology and Radiation Oncology Branches in the Center for Cancer Research (CCR), and academia and industry collaborators specifically addressing research and development needs in combined modality therapy using radiation. The MRTB participates as a major role in developing radiosensitizers as part of the recently initiated NCI Experimental Therapeutics (NExT) Program.

The primary mission of the MRTB is to facilitate the generation of preclinical data that will support new clinical trials with radiation modifiers. The program that was first initiated was called the Radiation Modifiers Evaluation Module (RAMEM) that was a unique national and international resource to assist a wide range of potential collaborators in providing preclinical data to support the safe conduct of drug approval for clinical trials involving radiation modifiers. Adopting such concepts, currently MRTB plays a central role developing the overall design for clinical implementation of radiation modifiers coupled with updates on advances in approaches, particularly, in molecular targeted therapy.

Through these efforts, the MRTB stimulates discussion among various disease-site / biology working groups that interact periodically to bring in new agents as radiation modifiers from either the CTEP portfolio or company interactions. There are currently five active working groups that include: (1) Brain metastasis in breast cancer, (2) Colorectal cancer, (3) Sarcoma, (4) Lung cancer and (5) Radiation and immune modulation. In addition to these five groups, three more additional groups including (1) Upper gastro-intestinal cancer, (2) Gliobastoma multiforme and (3) Head and neck cancer. These three groups will conduct their first meeting in March 2015.

This booklet will highlight the mission of each working group along with member list as well as key initiatives taken since its inception. Please feel free to contact us if you want to be a part of any of this working group or require expertise of members of in the working group for future project team formation for new incoming agents in CTEP. You can contact us if you are aware of an agent that is a potential radiation sensitizer developed in either academia or industry that needs attention to these working groups. In addition, if you have any new clinical concepts that needs advise, you can contact us for setting up such discussions.

This pamphlet will be updated every two months and will be available on the website URL: http://rrp.cancer.gov/aboutRRP/mrtb.htm.

Staff

Mansoor M. Ahmed, Ph.D.
Acting Chief

Dr. Mansoor M. Ahmed received his Ph.D. from the University of Madras in Environmental Toxicology studying the cytogenetics and molecular biology of pesticide-induced myelodysplastic syndrome in farmers from South India. He then had 18 months of training as a Monbusho Scholar at the Hiroshima University, Research Institute for Radiation Biology and Medicine in Japan, where he studied molecular biology of Non-Hodgkin's lymphoma and T-cell leukemia in A-bomb survivors. During his post-doctoral training at Thomas Jefferson University in Pennsylvania and the University of Kentucky, he studied micro-dissection of chromosomes in solid tumors and radiation-induced signal transduction respectively.

He held his first faculty position at the University of Kentucky, Department of Radiation Medicine, where he established a Molecular Radiation Biology Program. After his full-tenure at the University of Kentucky, he then later joined Weis Center for Research at Geisinger Clinic and later University of Miami, Department of Radiation Oncology, whereby he established programs in Molecular Radiation Biology. At all three centers, including Fox Chase Cancer Center, he taught Mammalian Radiation Biology.

His major research focuses involved employing various novel strategies with the goal of increasing the therapeutic ratio through two broad areas: (1) the manipulation of tumor control by modulating the processes that control cell cycle and apoptosis; and (2) the reduction of normal tissue morbidity by applying the emerging information on the molecular mechanistic basis of radiation or chemotherapeutic sensitivity. His seminal contributions include: (1) Identification of EGR-1 as a marker of radiation resistance in prostate tumors; (2) Identification of TGF-beta signaling for radiation response in pancreatic cancer; (3) Utilizing low-dose radiation as a chemo-potentiator; and (4) Identification of abscopal factors in high-dose hypofractionated radiation therapy.

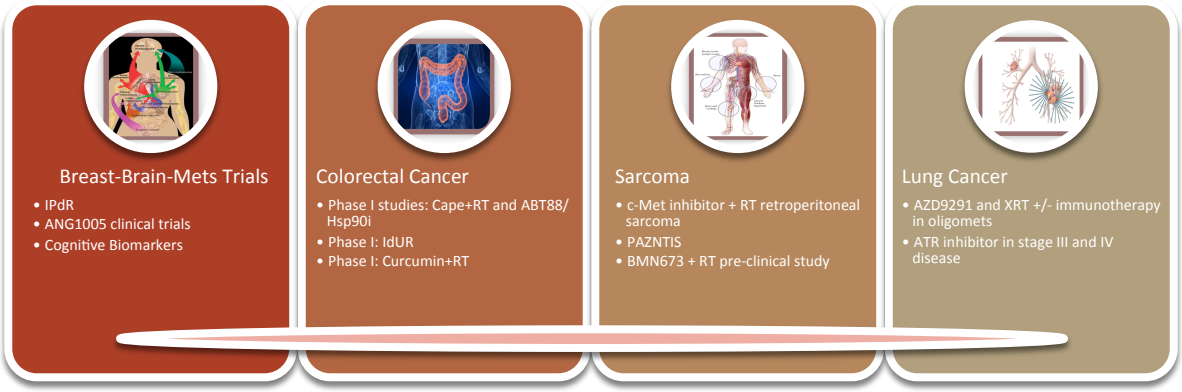
His major interest is in the best way to apply fractionation schemes from a mechanistic standpoint. His translational, pre-clinical research on low-dose radiation as a chemo-potentiator resulted in the development of novel clinical protocols for: head and neck, lung, ovarian, and pancreatic cancers. More recently, his group has described seminal mechanistic findings on bystander signal transduction pathways in response to high-dose ablative radiotherapy. This was translated into clinics that were using Lattice radiotherapy in prostate and lung tumors.

During his career, he has totaled 65 peer-reviewed publications with 15 invited reviews and chapters. He recently co-authored a book titled: *Hypofractionation: Scientific Concepts and Clinical Experiences.* He joined RRP in March 2012 covering a portfolio of grants in signal transduction, bio-markers, cancer stem cells and in-vitro & in-vivo models in radiotherapy and currently acting Chief of MRTB since February 2014.

Erica Butler, M.S.
Program Specialist

Ms. Butler received her Bachelor's degree in Medical Technology from George Mason University of Fairfax, VA. She received her Masters in Bioscience Regulatory Affairs from Johns Hopkins University, Baltimore, MD. Ms. Butler has more than several years experience as a clinical laboratory professional in DC area hospitals, NIH's Clinical Center and as a faculty member with The George Washington University, Washington DC. She joined NCI in 2014 and works as a Program Specialist for the Radiation Research Program.

"HIGHLIGHTS OF KEY INITIATIVES"



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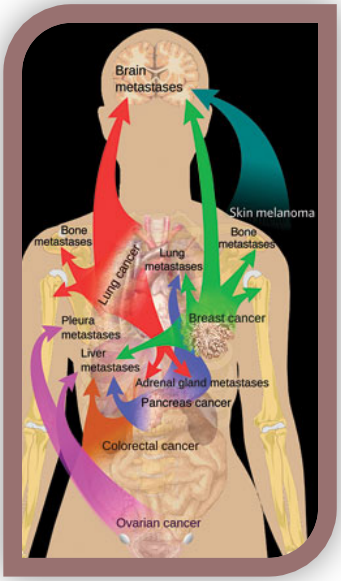
Brain Metastasis in Breast Cancer

Chair: Minesh Mehta, M.B.Ch.D., FASTRO



MISSION

The Brain Metastases in Breast Cancer Working Group is an ad-hoc, unfunded working group charged with stimulating translational research and assisting in the development of clinical trial ideas for breast cancer patients with brain metastases. The group meets through WebEx approximately once a month and includes diverse expertise from basic scientists to a variety of clinical disciplines involved in the management of brain metastases patients, or instrumental to the conduct of clinical trials in this arena. The primary objectives of this group therefore are to:

1. Serve as a common platform and forum for the discussion of various pre-clinical translational ideas with a high likelihood of being developed into clinical trial concepts, including evaluation of conventional Phase I-II endpoints, but also including development of novel endpoints, including compartmental disease control, novel imaging, and patient reported outcomes including quality of life, and neurocognitive function.

2. Collaborate with individual institutions, industry partners, consortia, and co-operative groups to help conduct clinical concepts.

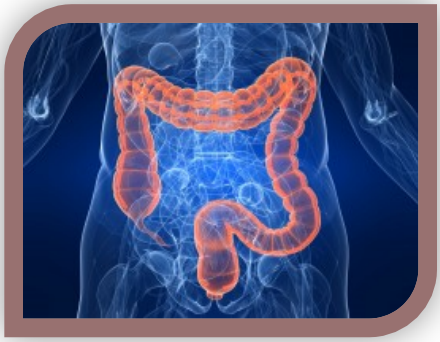
Assist the NCI disease-specific and other working groups specifically in terms of evaluating concepts for brain metastases from breast cancer. The group meets once a month through webinar.

MEMBERS

Members	Affiliations	Members	Affiliations
Minesh Mehta	*University of Maryland*	**Rakesh Jalali**	*Tata Memorial Hospital*
Nancy Lin	*Dana Farber Cancer Institute*	**Manmeet Ahluwalia**	*Cleveland Clinic*
Morris Groves	*US Oncology*	**Matthew Foote**	*Princess Alexandra Hospital Brisbane QLD Australia*
David Peereboom	*Cleveland Clinic Foundation*	**Erik Sulman, MD, PhD**	*MD Anderson Cancer Center*
Jeff Wefel	*MD Anderson Cancer Center*	**Bhadrasain (Vik) Vikram**	*NCI*
Christina Tsien	*Washington University*	**Mansoor Ahmed**	*NCI*
Carey Anders	*University of North Carolina*	**Jo Anne Zujewski**	*NCI*
Timothy Zagar	*University of North Carolina*	**Alice Chen**	*NCI*
John Suh	*Cleveland Clinic Foundation*	**Pamela Harris**	*NCI*
Julia White	*Ohio State University*	**Percy Ivy**	*NCI*
Arnab Chakravarti	*Ohio State University*	**Eric Bernhard**	*NCI*
Tim Lautenschlaeger	*Ohio State University*	**Susan Bates**	*NCI*
Andrew Seidman	*Memorial Sloan Kettering Cancer Center*	**Laleh Amiri-Kordestani**	*NCI*
Jacek Jassem	*Medical University of Gdansk, Poland*	**Patricia Steeg**	*NCI*
Fabiana Viola	*Brazil*	**Kevin Camphausen**	*NCI*
Anca Ligia Grosu	*University of Freiburg, Germany*	**Bhupinder Mann**	*NCI*
Oliver Oehlke	*University of Freiburg, Germany*	**Pat Prasanna**	*NCI*
Matthias Preusser	*University of Vienna, Austria*	**Rosemary Wong**	*NCI*
Anna Berghoff	*University of Vienna, Austria*	**Norman Coleman**	*NCI*
Quentin Smith	*Texas Tech University Health Sciences*	**Jacek Capala**	*NCI*
Renata Duchnowksa	*Military Institute of Medicine, Poland*	**Dee Dee Smart**	*NCI*
In Ah Kim	*Seoul National University Bundang Hospital*		

KEY INITIATIVES

1. Pharmacologic Study of Oral 5-Iodo-2-Pyrimidinone-2’ deoxyribose (IPdR)
2. Biomarkers for RTOG 0614 – Cognitive defects, disease progression and survivorship
3. ANG1005 clinical trials in breast cancer metastases Phase II were launched in December 2014
4. Phase IIR/III Trial of Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer



Colorectal Cancer

Chair: Thomas J. George, M.D., FACP

MISSION

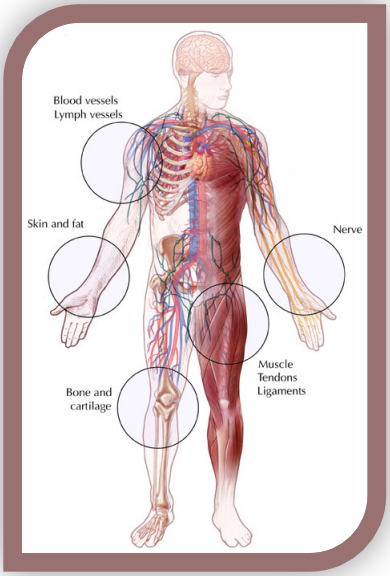
The Colorectal Working Group (WG) is an active committee with a goal of strategically fostering the rational development of novel radiation sensitizers to eradicate or palliate human colorectal cancer. The WG represents a multidisciplinary and diverse partnership between the NCI-sponsored National Clinical Trial Network (particularly NRG Oncology), the NCI Extramural Radiation Research Program, the Cancer Therapy Evaluation Program (CTEP), industry and global academic partners. Members participate in regular strategic planning meetings, collaborative projects and educational content aimed to link the pre-clinical scientific models with the clinical validation of enhanced agent activity in biomarker selected and non-selected colorectal cancer patient subgroups. Pragmatic interaction with other Working Groups ensures that common biologic principles and opportunities for synergistic collaboration are optimized. The group meets once a month through webinar.

MEMBERS

Members	Affiliations	Members	Affiliations
Thomas George	*Univ of Florida*	**Zhen Zhang**	*Fudan University*
Bruce Boman	*Christian Care Health Systems*	**Ann Ree**	*The Norwegian Radium Hospital*
Nicholas Petrelli	*Christian Care Health Systems*	**David Raben**	*UC Denver*
May Abdel-Wahab	*Cleveland Clinic*	**Joel Tepper**	*UNC*
Jerome Landry	*Emory*	**Andrew Wang**	*UNC*
Russell Schilder	*Jefferson University Hospitals*	**Michael Chuong**	*Univ. of MD*
Voichita Barad	*Jefferson University Hospitals*	**Bapsi Chakravarthy**	*Vanderbilt*
Howard Safran	*Lifespan Partners*	**Bhadrasain Vikram**	*NCI*
Timothy Kinsella	*Lifespan Partners*	**Mansoor Ahmed**	*NCI*
Theodore Hong	*Massachusetts General*	**Deborah Citrin**	*NCI*
Christopher Crane	*MD Anderson*	**Eric Bernhard**	*NCI*
Prajnan Das	*MD Anderson*	**Helen Stone**	*NCI*
Sunil Krishnan	*MD Anderson*	**Jacek Capala**	*NCI*
Javier Torres-Roca	*Moffitt Cancer Center*	**Pamela Harris**	*NCI*
Carol Aghajanian	*MSKCC*	**Pat Prasanna**	*NCI*
Samuel Jacobs	*Nat'l Surgical Adjuvant Breast and Bowel*	**Rosemary Wong**	*NCI*
Terence Williams	*Ohio State University*	**Jo Anne Zujewski**	*NCI*
Kjersti Flatmark	*Olso University Hospital Research*	**Norman Coleman**	*NCI*
Mo Mohiuddin	*Saudi Arabia*		

KEY INITIATIVES

1. Phase I studies using capecitabine, radiotherapy and either veliparib or ganetespib in neoadjuvant treatment of rectal cancer
2. Planning of phase I results of studies using veliparib and ganetespib in locally advanced rectal cancer
3. Phase I study of curcumin in combination with radiotherapy for rectal cancer
4. IdUR – Awaiting approval for phase I study through the Brown Group



Sarcoma

Chair: Dian Wang, M.D.

MISSION

The translational research program (TRP) in the Sarcoma Working Group is aimed at enhancing the translational aspect of research in sarcoma for which the current priority is to identify new agents that sensitize sarcoma to radiotherapy for clinical trials development. As sarcomas are histologically diverse and may originate from any anatomical site, the TRP team consists of fundamental scientists and clinicians specialized in different sites and disciplines involved in the management of sarcoma patients to optimize its ability to convert basic research to clinical trials in this arena. Meetings are held through WebEx approximately every other month, during which the primary objectives are the sarcoma working group TRP discussed:

1. To serve as a platform and forum for the discussion of various pre-clinical translational ideas with a high likelihood of being developed into clinical trial concepts.

2. Evaluation and development of clinically important endpoints for phase I-II trials, such as compartmental disease control, biomarker response and novel imaging surrogates signals of treatment response.

3. Facilitate the collaboration between individual institutions, industry partners, consortia, and co-operative groups in the development and design of clinical concepts.

Assist NCI disease-specific committees and other working groups in evaluating concepts related to sarcoma. The group meets once a month through webinar.

MEMBERS

Members	Affiliations	Members	Affiliations
Dian Wang	*Rush University*	**Adam Dicker**	*Jefferson Hospital*
Arta Monjazeb	*UC Davis University*	**Brian Van Tine**	*Washington University, St. Louis*
Meng Welliver	*Ohio State University*	**David G. Kirsch**	*Duke University*
Burton Eisenberg	*Univ. South California*	**Martee Hensley**	*MSKCC*
Sam Yoon	*Memorial Sloan-Kettering*	**Ping Chi**	*MSKCC*
John Kane	*Roswell Park Cancer Institute*	**Bhadrasain Vikram**	*NCI*
Philip Wong	*Princess Margaret Hospital*	**Mansoor Ahmed**	*NCI*
Zhenfeng Duan	*Harvard Cancer Center*	**Norman Coleman**	*NCI*
Steven Finkelstein	*21th Century Radiation Oncology*	**Pat Prasanna**	*NCI*
Sudha Amarnath	*Cleveland Clinic*	**Eric Bernhard**	*NCI*
Carl Maki	*Rush University*	**Beverly Teicher**	*NCI*
Robert Canter	*UC Davis University*	**Jacek Capala**	*NCI*
Peter Houghton	*Nationwide Children's*		

KEY INITIATIVES

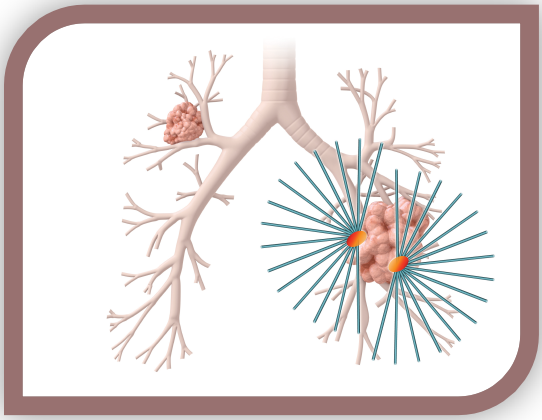
1. LOI "Phase IIR of neoadjuvant XL-184 combined with RT for retroperitoneal sarcoma"
2. miR-182 expression in RTOG 9415/MGH TMA
3. Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS): A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib (NSC# 737754, IND# 75648)
4. BMN673 and XRT pre-clinical study
5. Publication: Wong P1, Houghton P1, Kirsch DG1, Finkelstein SE1, Monjazeb AM1, Xu-Welliver M1, Dicker AP1, Ahmed M1, Vikram B1, Teicher BA1, Coleman CN1, Machtay M1, Curran WJ1, Wang D2. Combining targeted agents with modern radiotherapy in soft tissue sarcomas. J Natl Cancer Inst. 2014 Oct 18;106(11). pii: dju329. doi: 10.1093/jnci/dju329. Print 2014 Nov.

Lung Cancer

Chairs: Bo Lu, M.D.

Steven H. Lin, M.D., Ph.D.

MISSION



Lung Cancer Working Group is an ad-hoc, unfunded working group, which consists of NCI-funded researchers with expertise and interests in lung cancer research and assisting in the development of novel clinical trial for lung cancer patients. The group meets through WebEx approximately once a month and includes diverse expertise from basic scientists to a variety of clinical disciplines involved in the management of lung cancer patients, or instrumental to the conduct of clinical trials. The primary objectives of this group are to:

Serve as a common platform and forum for the discussion of various pre-clinical translational ideas with a high likelihood of being developed into clinical trial concepts. Emphasis will be placed upon novel biology, targets, imaging, biomarkers, physics, technology, QA and clinical trial design.

Collaborate among individual institutions, industry partners and co-operative groups to help to advance clinical trial concepts. The group meets once a month through webinar.

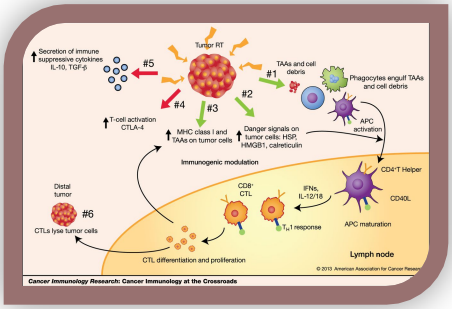
MEMBERS

Members	Affiliations	Members	Affiliations
Bo Lu	*Thomas Jefferson University Hospitals*	**Terence Williams**	*Ohio State University*
Steven Lin	*The University of Texas*	**Yang-Xin Fu**	*University of Chicago*
Marjan Boerma	*University of Arkansas for Medical Sciences*	**Christopher Bakkenist**	*University of Pittsburgh*
Max Diehn	*Stanford University*	**Phouc Tran**	*Johns Hopkins Medicine*
Dr. Xiaodong Wu	*Biophysics Research Institute of America*	**Russell Hales**	*Johns Hopkins Medicine*
Sandra Demaria	*NYU Langone Medical Center*	**Wannian Yang**	*Geisinger Health Systems*
Jeff Bradley	*Washington University, St. Louis*	**Ahmed Mansoor**	*NCI*
Martin Edelman	*University of Maryland*	**Bhadrasain Vikram**	*NCI*
Christine M. Lovly	*Vanderbilt University School of Medicine*	**Pat Prasanna**	*NCI*
Eric Deutsch	*Chair of Rad One at Gustave*	**Eric Bernhard**	*NCI*
David Raben	*University of Colorado Denver*	**Norman Coleman**	*NCI*
Marka Crittenden	*Providence Portland Medical Center*	**Jacek Capala**	*NCI*
Ralph Weichselbaum	*University of Chicago Medicine*		

KEY INITIATIVES

1. Clinical concepts of combining AZD9291 and XRT +/- immunotherapy in patients with oilgo metastases or brain metastases after they fail Tarceva are planned.

2. ATR Inhibitor in chemo-rad settings in stage III and IV NSCLC clinical concept is planned through NRG.



Radiation and Immune Modulation

Chair: Samir N. Khleif, M.D.

MISSION

Several studies have demonstrated that radiation can modulate and enhance immune responses to tumors. Hypofractionation or other modifications of standard fractionation may promote immune responses to tumors, but other novel delivery options may also affect several immune responses including T-cell activation and changes in tumor-antigen presentation. However, there is limited understanding of the immunologic impact of hypo- and special multi-fractionated radiotherapy, as these observations are relatively recent. This NCI working group will bring together clinicians and researchers with an interest in radiotherapy and/or immunology to open a dialogue on the potential for exploiting radiation-induced immune responses in the context of cancer therapy. The group meets once a month through webinar.

MEMBERS

Members	Affiliations	Members	Affiliations
Samir N. Khleif	*GRU Cancer Center*	**Paul T. Nghiem**	*UW Medicine, Seattle*
Marka Crittenden	*Providence Cancer Center*	**Lisa Lundgren**	*Cancer Immunotherapy Trials Network (CITN)*
Sandra Demaria	*NYU, Dept. of Pathology*	**Mansoor Ahmed**	*NCI*
Stephen Shiao	*Cedars-Sinai*	**Bhadrasain Vikram**	*NCI*
Ralph Weichselbaum	*Univ of Chicago Medicine*	**Elad Sharon**	*NCI*
Chandan Guha	*Montefiore Medical Center*	**Michael G. Espey**	*NCI*
Yang-Xin Fu	*University of Chicago*	**Eric Bernhard**	*NCI*
Bo Lu	*Jefferson Hospital*	**Norman Coleman**	*NCI*
Martin "Mac" Cheever	*UW Medicine, Seattle*	**Pat Prasanna**	*NCI*
Ramesh Rengan	*UW Medicine, Seattle*	**Eric Bernhard**	*NCI*

KEY INITIATIVES

1. NCI protocol: CITN-09: Merkel Cell Carcinoma- MK-3475
2. Pancreatic trial: anti-PDL1 + Radiation; the study is progressing and are working with Medimmune/Azteca
3. IDO inhibitor and XRT in sarcoma

AGENTS OF INTEREST

Working Groups	CTEP drugs	Non-CTEP drugs
Brain Mets Breast Cancer	ANG1005 Birinapant (TL32711) IPdR Pembrolizumab (MK-3475) VX-970 Veliparib	Memantin
Colorectal	AZD 6244 Bevacizumab/erlotinib Birinapant (TL32711) Cedirinib IPdR IUdR Oxaliplatin Regorafenib Trametinib Triapine Veliparib (ABT-888)	Capecitabine CRLX101 Curcumin Fluoropyrimidine Ganitespib Midostaurin Perifosine PKC412 Vorinostat
Lung	AZD9291 Birinapant (TL32711) Tarceva (Erlotinib) Pemrolizumab (MK-3475)	Anti-PDL1 Cisplatin CO-1686
Sarcoma	AMG-337 BMN-673 Pazopanib CMET inhibitors	HDM2 inhibitor PI3K inhibitor
Radiation Immune Modulation	Ipilimumab (anti-CTLA4) Pemrolizumab (MK-3475) IDO inhibitors	anti-OX40 anti-PDL1