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The 21st Century Handbook of Clinical Ovarian Cancer

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The 21st Century Handbook of Clinical Ovarian Cancer

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Author biographies

Krishnansu S Tewari, MD, is a Professor and Director of Research in the Division of gynecologic oncology at the University of California (UC) Irvine. He received his bachelor's degree in molecular biology at UC Berkeley, and went to medical school, completed his residency in obstetrics and gynecology, and fellowship in gynecologic oncology at the UC Irvine. He serves as the Principal Investigator of the National Cancer Institute's NRG-Oncology Cooperative Group and Gynecologic Oncology Group Partners at UC Irvine. At UC Irvine, Dr Tewari is the Chairman of the Clinical Trials Protocol Review and Monitoring Committee and the Director of the Women's Disease Oriented Team for the Chao Family National Cancer Institute Designated Comprehensive Cancer Center. He is also the Director of the Gynecologic Oncology Program at St Joseph's Center for Cancer Prevention and Treatment. Dr Tewari is a voting member of the NRG's Cervix Committee, Publications Committee, and Committee on Experimental Medicine, and Chairs the Society of Gynecologic Oncology's Publications Committee.

Dr Tewari has published over 100 peer-reviewed articles and written numerous book chapters. His research interests include novel targeted therapeutics in ovarian cancer and cervical cancer. Dr Tewari is funded by the National Institutes of Health to study surrogate markers of angiogenesis in cervical cancer and is the Study Chair/Principal Investigator for Gynecologic Oncology Group protocol 240, the practice-changing phase III randomized clinical trial, which demonstrated that compared with chemotherapy alone, the addition of the anti-angiogenesis drug, bevacizumab, significantly improved overall survival, progression-free survival, and response rate without a significant deterioration in health-related quality of life (Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med.* 2014;370:734-743). This pivotal trial led to US Food and Drug Administration approval of bevacizumab in advanced cervical cancer on August 14, 2014.

Dr Tewari has been listed for seven consecutive years as one of the Top Doctors in Orange County and has been listed in Best Doctors of

America for the past 4 years. An expert in robotic surgery, for the past 2 years Dr Tewari has been traveling every 8 months to conduct robotic surgery workshops in different cities in India for women diagnosed with early stage cervical and endometrial cancer.

Bradley J Monk, MD, received his medical degree from the University of Arizona in 1988 where he graduated at the top of his class. He then underwent training in obstetrics and gynecology at the University of California (UC) Los Angeles between 1988 and 1992, and gynecologic oncology at the UC Irvine between 1992 and 1995. In 1995, he was appointed the Director of gynecology oncology at Texas Tech University and Associate Director of the Southwest Cancer Center where he served until 1998. Since 1998, he has been a member of the faculty at UC Irvine where he currently is Associate Professor (with tenure). He is board certified in both obstetrics and gynecology and gynecologic oncology. He is a fellow of the American College of Surgeons and the American College of Obstetricians and Gynecologists. He is also an active full member of the Society of Gynecologic Oncologists, American Society of Clinical Oncology, and the American Association of Cancer Research.

Dr Monk has been an investigator for the Gynecologic Oncology Group since 1995 and is the Chair of the Cervical Committee along with serving on the tissue utilization and publications committees. He is the Co-Principal Investigator for the Gynecologic Oncology Group at UC Irvine and Study Chair for both group wide phase III trials in cervical carcinoma and also serves as the study chair or co-chair for seven other trials investigating new therapies in cervical and ovarian cancer. Dr Monk has received career development funding (K-23) from the National Cancer Institute to investigate new strategies against HPV-related illnesses and, in addition, is funded by the National Cancer Institute to study therapeutic HPV vaccines. Dr Monk has over 90 peer-review publications predominantly dealing with the areas of cervical and ovarian cancer prevention, therapeutics as well as issues related to quality of life. He has also published 15 book chapters and is on the Editorial Board for *Gynecologic Oncology* and *The American Journal of Hematology/Oncology* and is a past President of the Orange County OB/GYN Society.

Abbreviations

AACR	American Association for Cancer Research
ACOG	American College of Obstetricians and Gynecologists
ACS	American Cancer Society
ALDH1	Aldehyde dehydrogenase 1
Ang	Angiopoietin
APC	Antigen-presenting cell
ARID1A	<i>AT-rich interactive domain-containing gene 1A</i>
ASCO	American Society of Clinical Oncology
ATM	Ataxia telangiectasia mutated
BARD1	BRCA1-associated RING domain
BEP	Bleomycin, etoposide and cisplatinum
BH3	BCL2 homology 3 domain
BRAF	<i>B-Raf proto-oncogene, serine/threonine kinase</i>
BRCA1/2	<i>Breast cancer susceptibility gene 1/2</i>
BRCT	Breast cancer 1 carboxy-terminal
BRIP1	BRCA1-interacting protein 1
CA 125	Cancer antigen 125
CA4P	Combretastatin A4 phosphate
CCL2/4	Chemokine (C-C motif) ligand 2/4
CD4⁺/8⁺	Cluster of differentiation 4 ⁺ /8 ⁺
CDK2	Cyclin-dependent kinase 2
CDMRP	Congressionally Directed Medical Research Program
CEA	Carcinoembryonic antigen
CHK2	Checkpoint kinase 2
CHORUS	Chemotherapy or Upfront Surgery non-inferiority
CRADA	Cooperative Research and Development Agreement
CT	Computerized tomography
CTA	Clinical Trials Agreement
CTEP	Cancer Therapy Evaluation Program
CtIP	Carboxy-terminal binding protein interacting protein
CTL	Cytotoxic T lymphocyte

CTLA4	Cytotoxic T-lymphocyte antigen 4
DoD	Department of Defense
DSS1	Deleted in split hand/split foot protein 1
E-box	Enhancer box
ECOG	Eastern Cooperative Oncology Group
EDR	Extreme Drug Resistance
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ERK	Extracellular signal-regulated kinase
ESGO	European Society of Gynaecological Oncology
ESMO	European Society of Medical Oncology
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FIGO	International Federation of Gynecology and Obstetrics
GCSC	Gynecologic Cancer Steering Committee
G-CSF	Granulocyte-colony stimulating factor
GCT	Granulosa cell tumor
GOG	Gynecologic Oncology Group
HE4	Human epididymis protein 4
HER2	Human epidermal growth factor receptor 2
HGF	Hepatocyte growth factor
HIPAA	The Health Insurance Portability and Accountability Act
HIPEC	Hyperthermic intraperitoneal chemotherapy
HMO	Health maintenance organization
HPF	High-power field
Hsp90	Heat shock protein 90
JGCT	Juvenile granulosa cell tumor
JGOG	Japanese Gynecologic Oncology Group
KRAS	<i>Kirsten rat sarcoma viral oncogene homolog</i>
IGCS	International Gynecologic Cancer Society
INDs	Investigational New Drug Applications
IL-8/12	Interleukin 8/12

IP	Intraperitoneal
IVC	Inferior vena cava
MAPK	Mitogen-activated protein kinase
MDR1	<i>Multidrug resistant gene 1</i>
mDC	Myeloid dendritic cell
MHC	Major histocompatibility complex
MEK	MAPK/Erk kinase
MRC	Medical Research Council
MRI	Magnetic resonance imaging
mTOR	Mammalian target of rapamycin
mTORi	Mammalian target of rapamycin inhibitors
NCI	National Cancer Institute
NF1	Neurofibromin 1
NK	Natural killer
NLS	Nuclear localization signal
NSABP	National Surgical Adjuvant Breast and Bowel Project
OCRF	Ovarian Cancer Research Fund
OCRPR	Ovarian Cancer Research Program
OCNA	Ovarian Cancer National Alliance
OCP	Oral contraceptive pill
ONC	Oncogene
ORR	Objective response rate
OS	Overall survival
PALB2	Partner and localizer of BRCA2
PAR	Poly (ADP-ribose)
PARG	Poly (ADP-ribose) glycohydrolase
PARP	Poly (ADP-ribose) polymerase
PD1	Programmed death 1 receptor
PD-L1	PD-1 ligand
PDGF	Platelet-derived growth factor
PDGFR-β	Platelet-derived growth factor receptor β
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphoinositide 3 kinase
PI3KCA	Phosphoinositide 3 kinase catalytic alpha

PLD	Pegylated liposomal doxorubicin
PMP	Pseudomyxoma peritonei
PPE	palmar plantar erythrodysesthesia
PPO	Preferred provider organization
PS	Performance status
PTEN	Phosphatase and tensin homolog
RB1	Retinoblastoma 1
RING	<i>Really interesting new gene</i>
ROCA	Risk of Ovarian Cancer Algorithm
rrBSO	Risk-reducing bilateral salpingoophorectomy
RTOG	Radiation Therapy Oncology Group
SGO	Society of Gynecologic Oncology
siRNA	Small interfering RNA
SNP	Single nucleotide polymorphisms
SOX2	SRY(sex determining region Y)-box 2
SPOREs	Specialized Programs of Research Excellence
SSB	Single-strand breaks
STIC	Serous tubal intraepithelial carcinoma
SV40	Simian virus 40
SWI–SNF	Switch–sucrose non fermentable
TCR	T-cell receptor
TLR	Toll-like receptor
TNFα	Tumor necrosis factor α
T_{regs}	Regulatory T cells
TSG	Tumor suppressor gene
TVS	Transvaginal sonography
VDA	Vascular disrupting agent
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
WBC	White blood cell
WHO	World Health Organization

Foreword

Managing the Message

Welcome to *The 21st Century Handbook of Clinical Ovarian Cancer*. Like our companion piece, *The 21st Century Handbook for Clinical Cervical Cancer*, this handbook is unlike any other repository of clinical guidelines on the shelves. Whether you are a medical student, OB/GYN resident, oncology fellow, oncology nurse or Board Certified Gynecologic Oncologist or Medical Oncologist, this handbook is designed to actively engage you while in the operating room trenches and infusion centers caring for women struggling with this devastating disease. We continue to describe Gynecologic Oncology as the ‘crown jewel’ of all medicine, and which other disease but ovarian cancer does better justice to this claim? To succeed in the delivery of highly personalized and curative therapy, you must see all facets of this disease simultaneously. The epidemiologic aspects are just as important as the clinical management protocols; that which has gone before has as much value as the therapies coming down the drug discovery pipeline; pivotal phase III practice-changing trials must be challenged by the strongest translational science being done in the tumor microenvironment. All of these crucial building blocks are contained in this handbook. As the British literary giant Alan Moore once said, “Multi-screen viewing is seemingly anticipated by Burrough’s ‘cut-up’ technique. He suggested rearranging words and images to evade rational analysis, allowing subliminal hints of the future to leak through – an impending world of exotica, glimpsed only peripherally.”

Most importantly, *The 21st Century Handbook of Clinical Ovarian Cancer* will give you an insight into ‘The Message’. What is ‘The Message’ and why is it important? Back in the late 1980s, paclitaxel was only provided for compassionate use to the hospitalized patient. Phil DiSaia told one of the authors (BJM) that there will come a day when every gynecologic cancer patient would get this drug and that there would be different schedules, different analogues, and we would be putting it in the belly. Today, the vistas of anti-angiogenesis therapy have opened

around us, and with eight positive phase III studies in ovarian cancer, it is going to be about different combinations, different disease settings, different pathways, and translational science. Moving forward it will be up to you to define ‘The Message’ for the next decade, and whether this will involve poly ADP-ribose polymerase (PARP) inhibition or immunotherapy or something else entirely, it will undoubtedly improve the lives of women with ovarian cancer.

This handbook has been intentionally designed so that the evidence-based medicine contained within is mirrored by the underlying science and by the historical precedents. All of the landmark clinical trials that define the current practice of ovarian cancer have been concisely summarized, but do yourself a favor and pull the original papers.

Krish Tewari & Brad Monk

Javier’s Cantina at Crystal Cove in Newport Beach, CA (January 2014)

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