



Developing an Individualized Surgical Algorithm in Ovarian Cancer: The MDACC's Women's Cancer Moonshot

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Concept: Make the Impossible...Possible

9/12/62



9/12/12

Women's Cancer Moonshot:

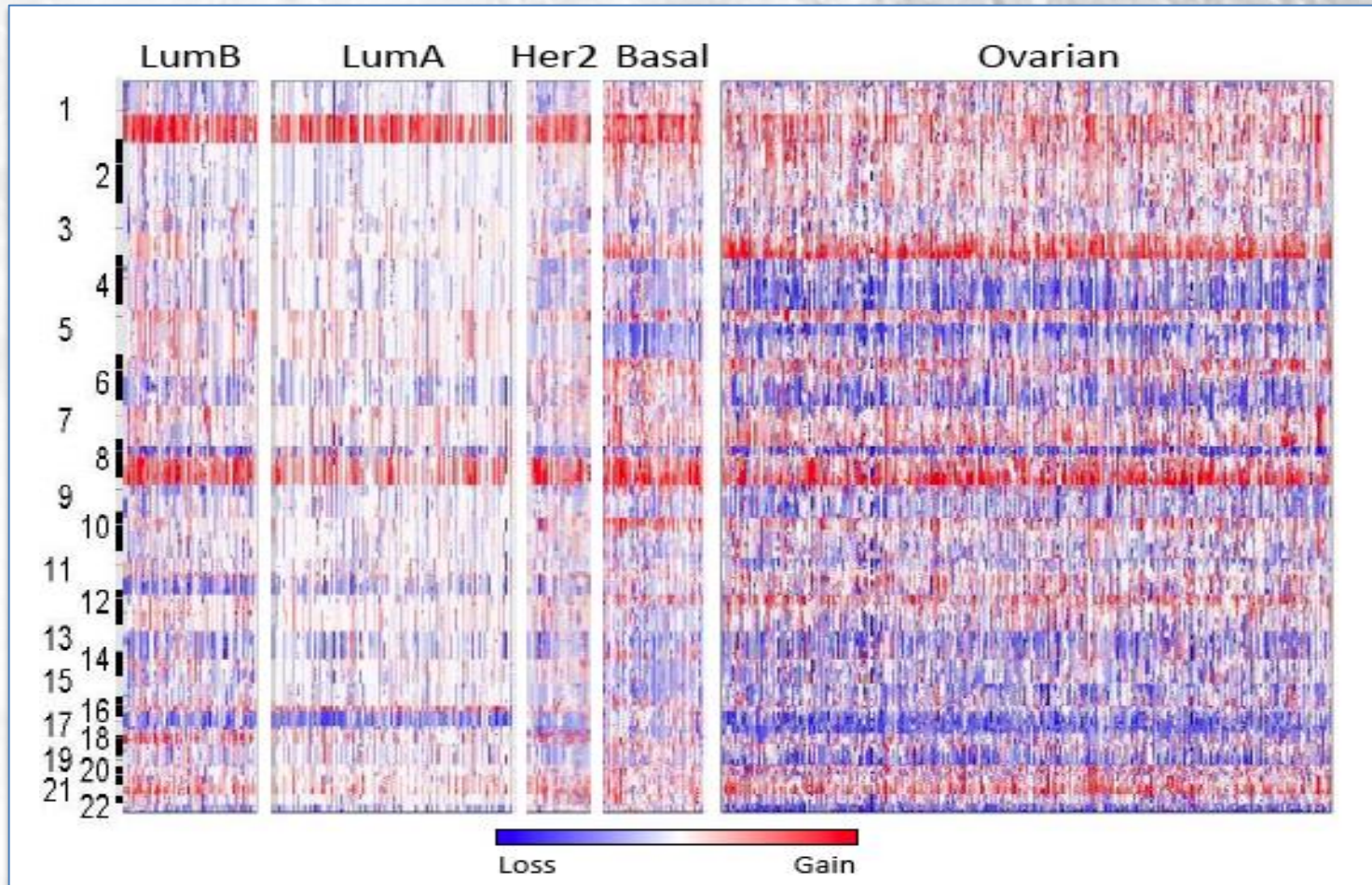
BREAST AND OVARIAN CANCER

- **Ovarian cancer (HGSOC):**
 - ❖ 190,000 new cases world-wide
 - ❖ 21,980 new cases in U.S. with 14,200 deaths in 2014
 - ❖ MDACC: 400 cases of HGSOC with more than half expected to die from their disease
- **Breast cancer (TNBC):**
 - ❖ 1,500,000 new cases world-wide
 - ❖ 229,060 new cases in U.S. with 39,920 deaths in 2014
 - ❖ MDACC: 800 cases of TNBC yearly with more than half expected to die from their disease

TNBC and HGSOC are copy number driven diseases

Few recurrent mutations other than TP53 and BRCA1/2

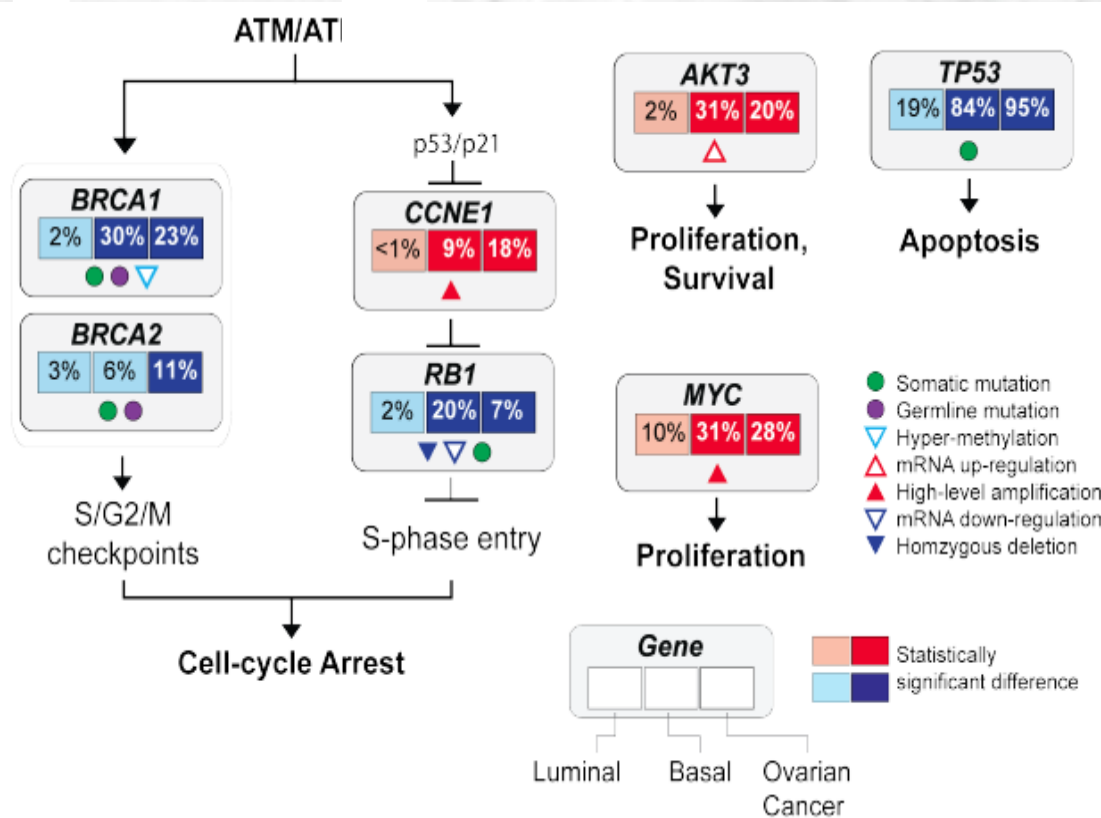
1.7 mutations per megabase



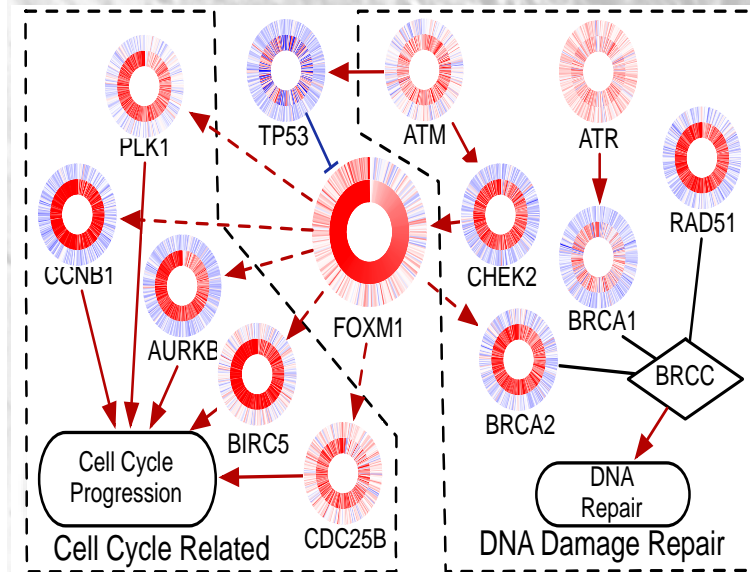
WOMEN'S CANCER MOONSHOT

TNBC/Basal breast cancer has more in common with HGS ovarian cancer than with luminal breast cancer

Integration of breast and ovary



FOXM1 is a key transcriptional integration point

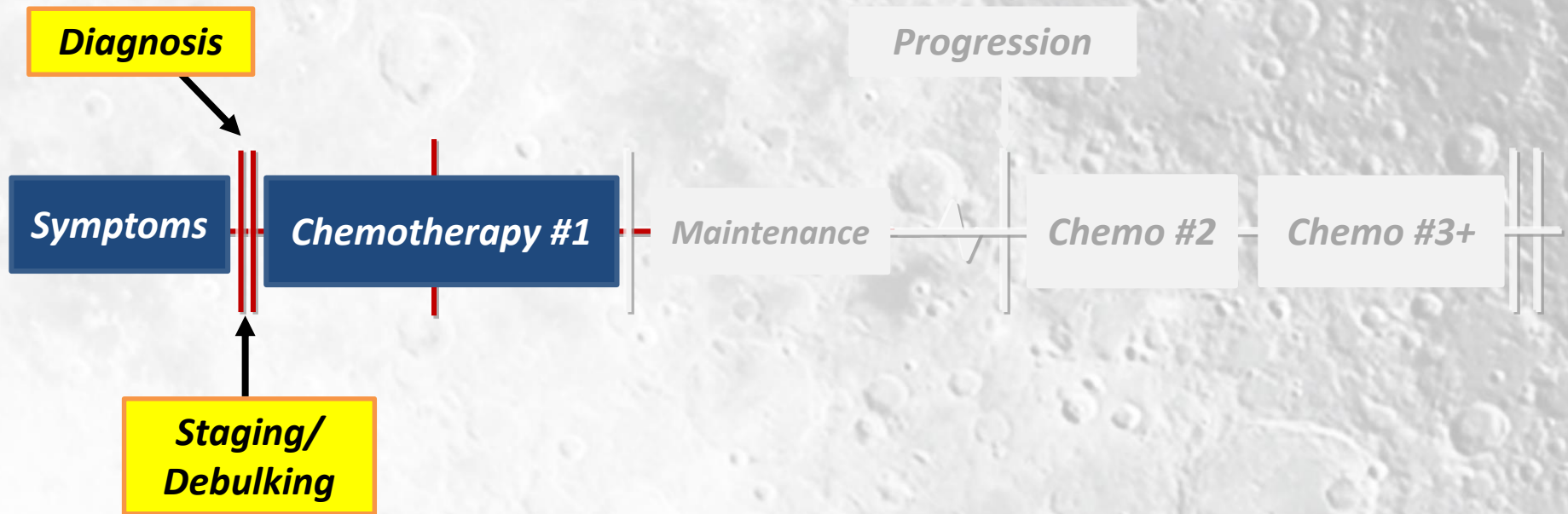


WOMEN'S CANCER MOONSHOT

FLAGSHIP PROJECTS: **THE START**

- Will have **immediate impact** on patient outcomes
- Can be implemented **without “new knowledge”**
- **Broadly applicable** across disease
- **Engage** the community: Faculty, patients and outreach
- **Leverage the efficiencies** offered by Moon Shot “Platforms”
 - Integrated systems for development, discovery, manufacturing, biomarker development and patient sample investigation

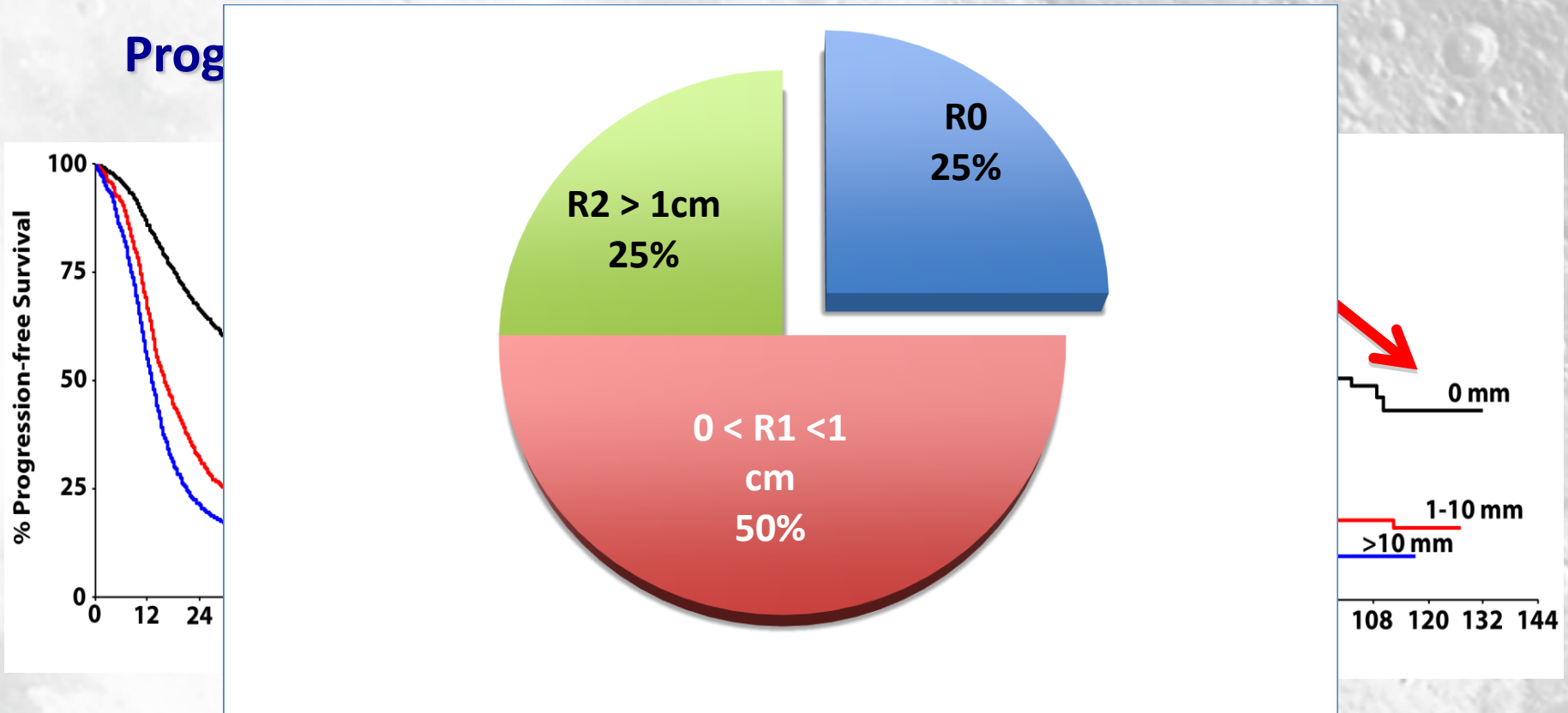
Gaps in knowledge: Improve Primary Therapy



Primary disease

- Strategically improve R0 surgical resection rates and identify new biological treatment partners and schedules for adjuvant therapy

The Impact Of Residual Tumor: What Is Optimal Debulking?



Opportunity For Quality Improvement: Personalized Surgical Therapy

- ❖ Implementation of evidence-based patient care guidelines
 - Multidisciplinary approach
 - Improvement in the quality of surgical care
 - Standardized care
- ❖ Improvement in rates of complete gross resection (R0) with reciprocal improvement in patient overall survival
- ❖ Developing a personalized surgical approach that translates across different clinical practice settings

PERSONALIZED SURGICAL THERAPY: Laparoscopic Prediction Model

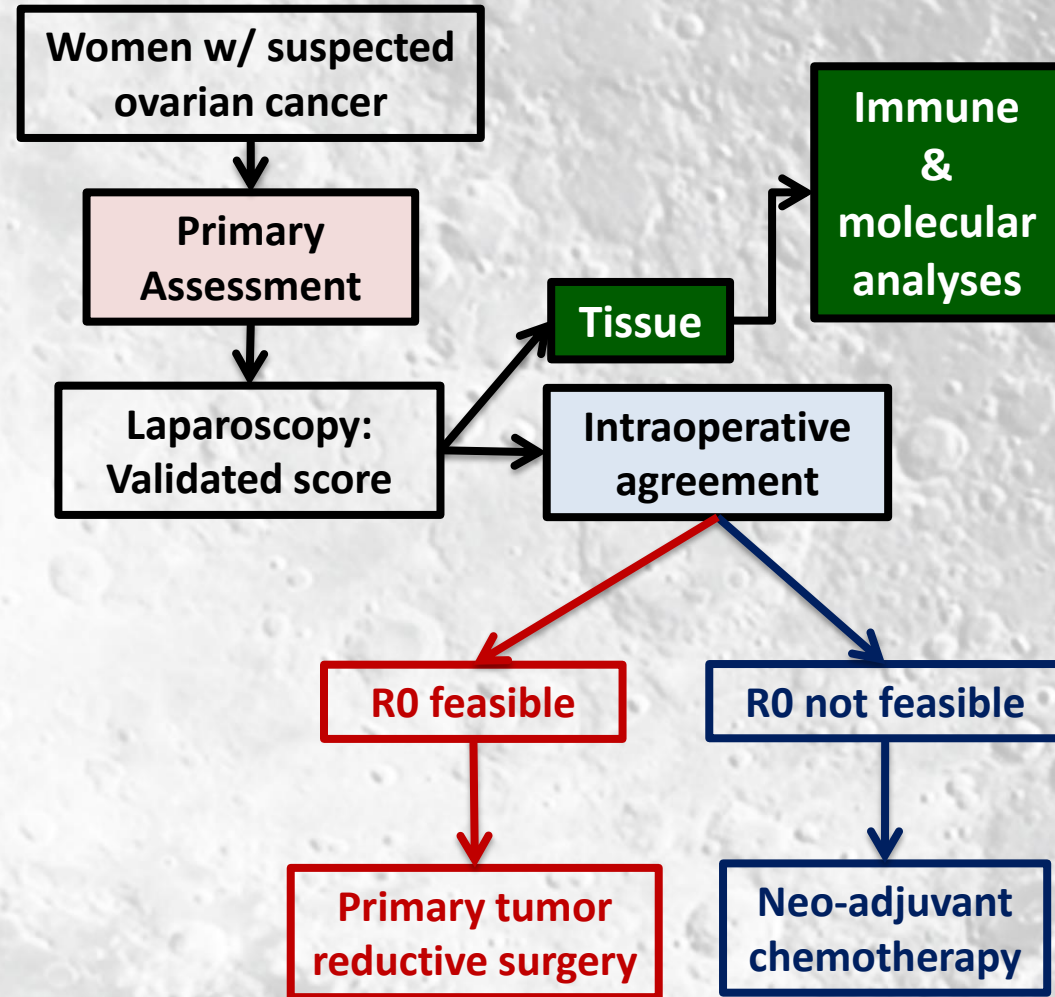
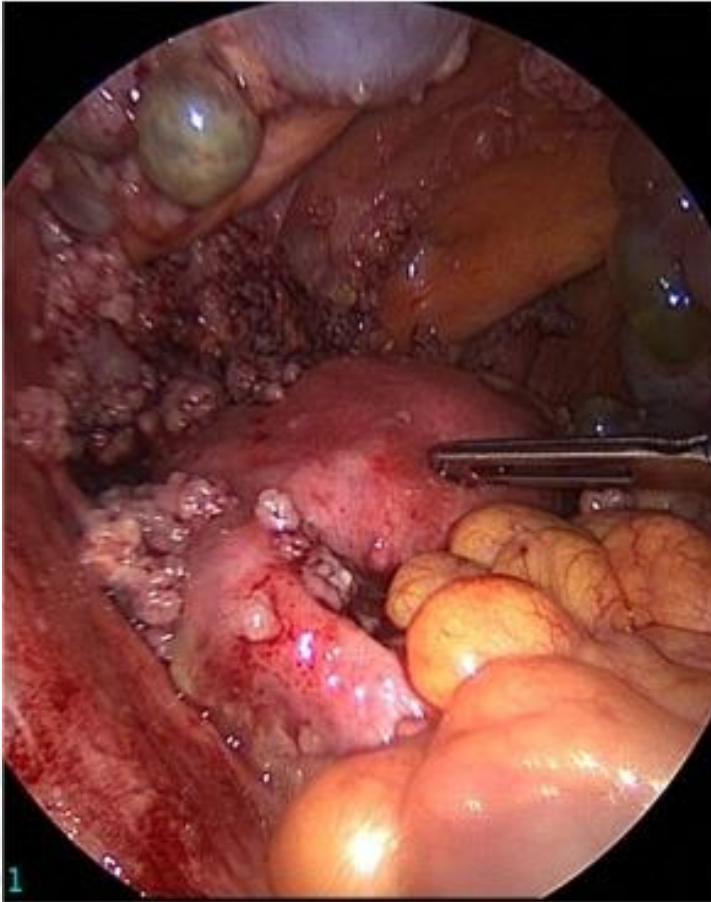
	Score = 2	Score = 0
Peritoneal carcinomatosis	Unresectable massive peritoneal involvement + miliary pattern of distribution	Carcinomatosis involving a limited area surgically removable by peritonectomy
Diaphragmatic disease	Wide spread infiltrating carcinomatosis or confluent nodules to most part of the diaphragmatic surface	Isolated diaphragmatic disease
Mesenteric disease	Large infiltrating nodules or involvement of the root of the mesentery supposed by limited movements of various intestinal segments	Small nodules potentially treatable with argon beam coagulation
Omental disease	Tumor diffusion up to the large curvature of the stomach	Isolated omental disease
Bowel infiltration	Bowel resection assumed to be required or miliary carcinomatosis on the mesenteric junction	
Stomach infiltration	Obvious neoplastic involvement of the gastric wall	
Liver metastasis	Any surface lesions	

***Total Predictive Index Value (PIV) = sum of scores**

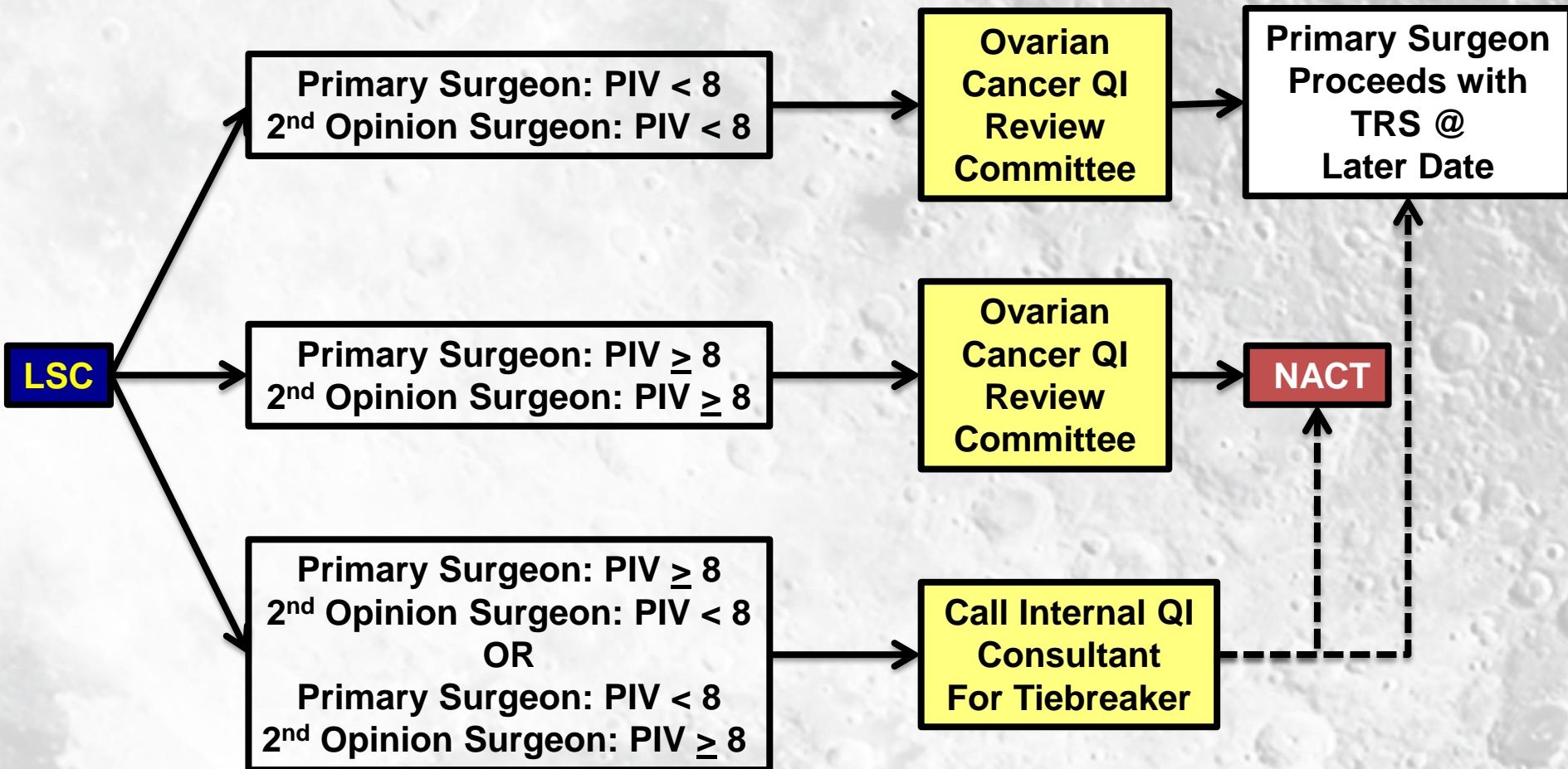
If $PIV \geq 8$, probability of R0 = 0 →

the patient should be dispositioned to NACT

Opportunity For Quality Improvement: Personalized Surgical Therapy



PERSONALIZED SURGICAL THERAPY: LAPAROSCOPIC PREDICTION MODEL



Personalized Surgical Therapy: Metrics, Deliverables & Timelines

- **Metrics:**

- % patients missed by screening process
- Interim Analysis measuring adherence to the surgical guidelines
- % improvement in “R0” rates

- **Deliverables & Timelines:**

- Implementation: Quality Improvement Board approval
- 0-3 Months: Implement management schema
- 4-9 Months: Interim Analysis
- 10-12 Months: Molecular analyses of prospectively collected samples

Surgical Outcomes (**R0 Rates**) since implementation of Flagship 2A

- ❖ Major effort focused on R0 resection included education, clinical retreats (consensus among all 21 gynecologic oncologists), and engaging other specialties (e.g., thoracic, GI surgery)
- ❖ Compliance is over 95%

	Pre-implementation		Post-implementation
Primary cytoreduction	20%	→	88% (n = 96)
NACT → Interval cytoreduction	60%	→	78% (n = 165)

Time to Chemotherapy

- **Primary cytoreduction**

- Pre-implementation

- 23 days [Range 5-61 days]

- Post-implementation to Date

- 26.5 days [Range 15-38 days]

} **$P = 0.15$**

- **NACT**

- Pre-implementation

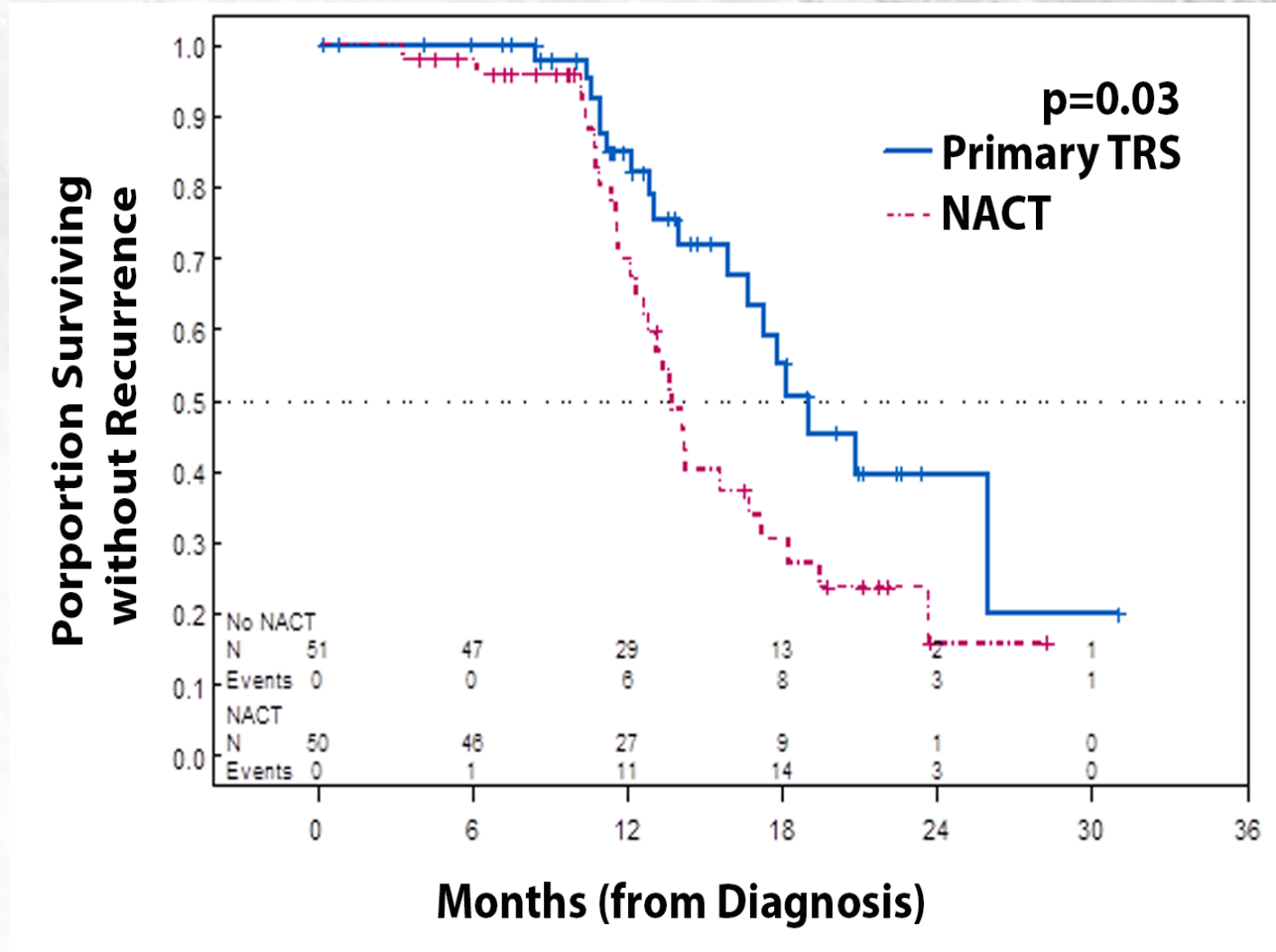
- 12 days [0-52 days]

- Post-implementation to Date

- 6 days [Range 1-14 days]

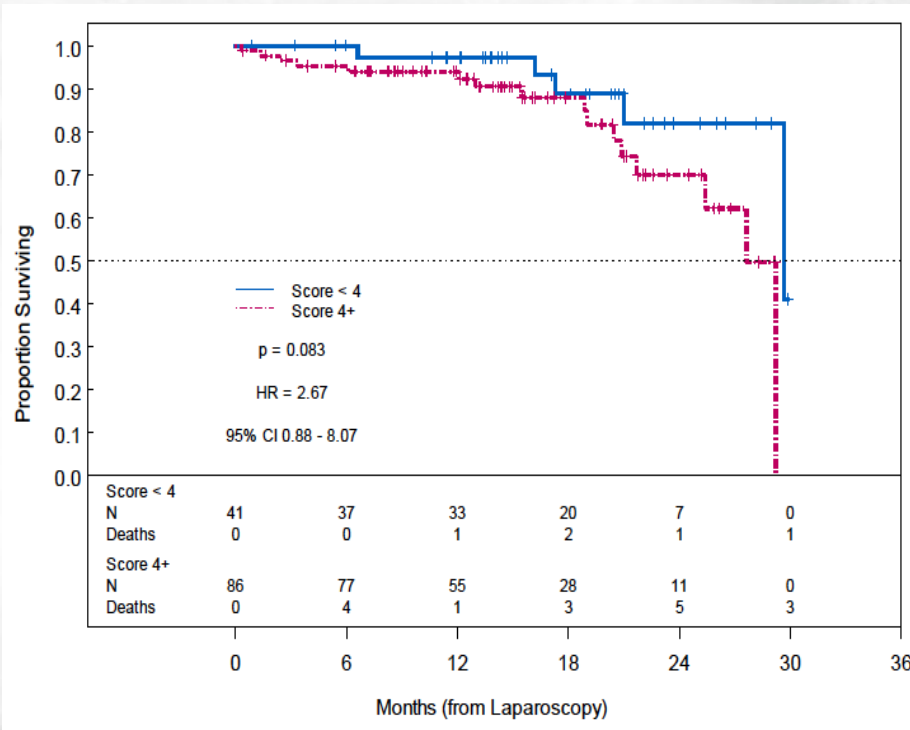
} **$P < 0.01$**

Event-free survival of patients with HGSOC: R0 upfront vs. R0 at interval surgery

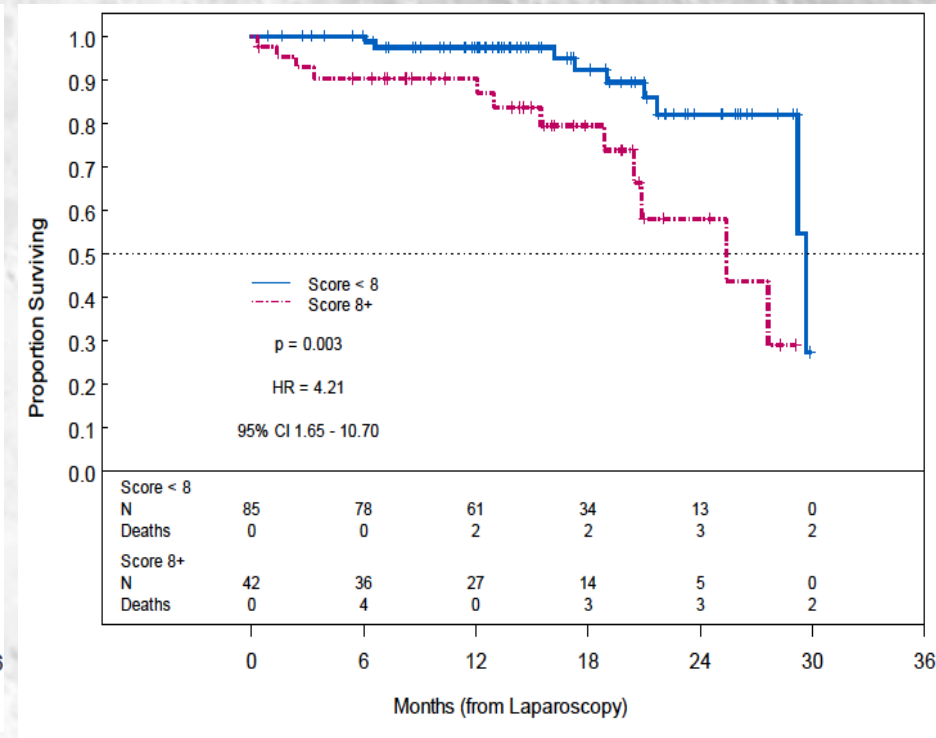


CT imaging may not predict disease resectability

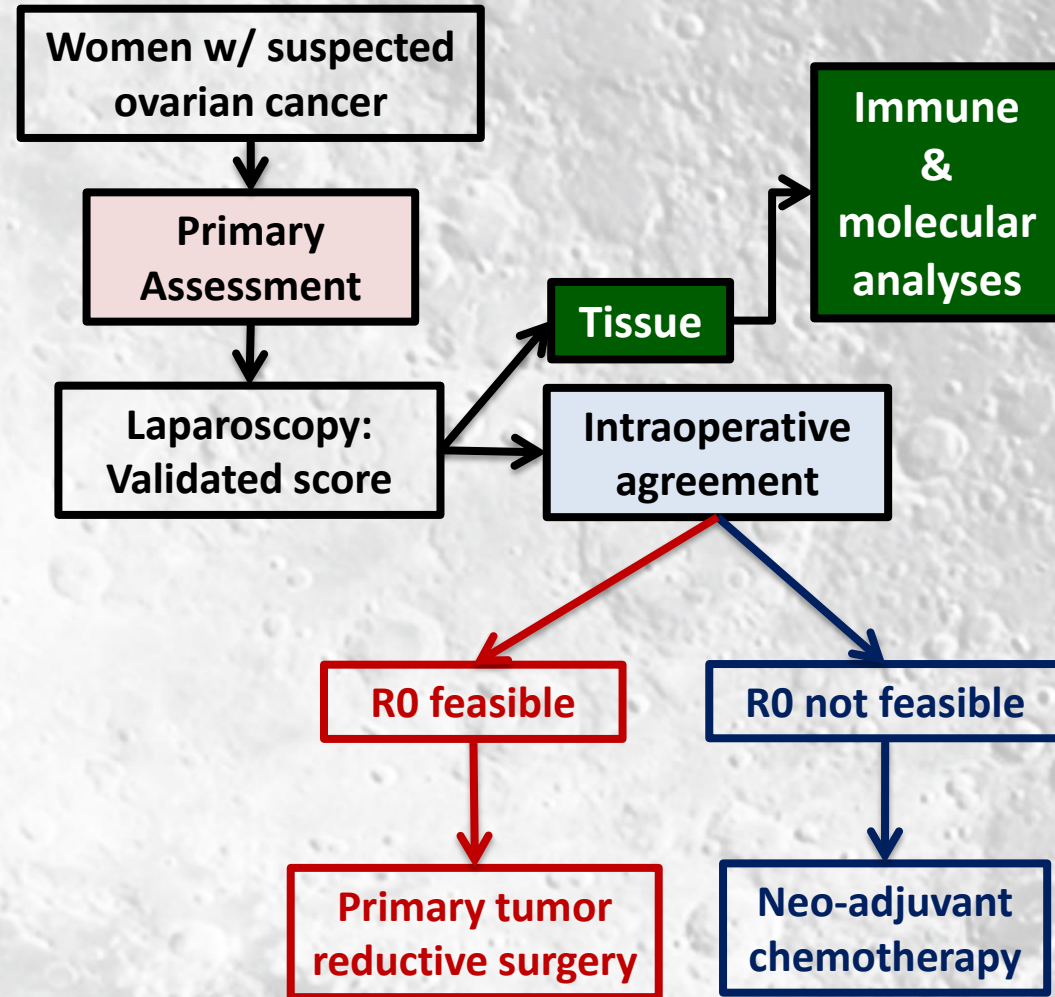
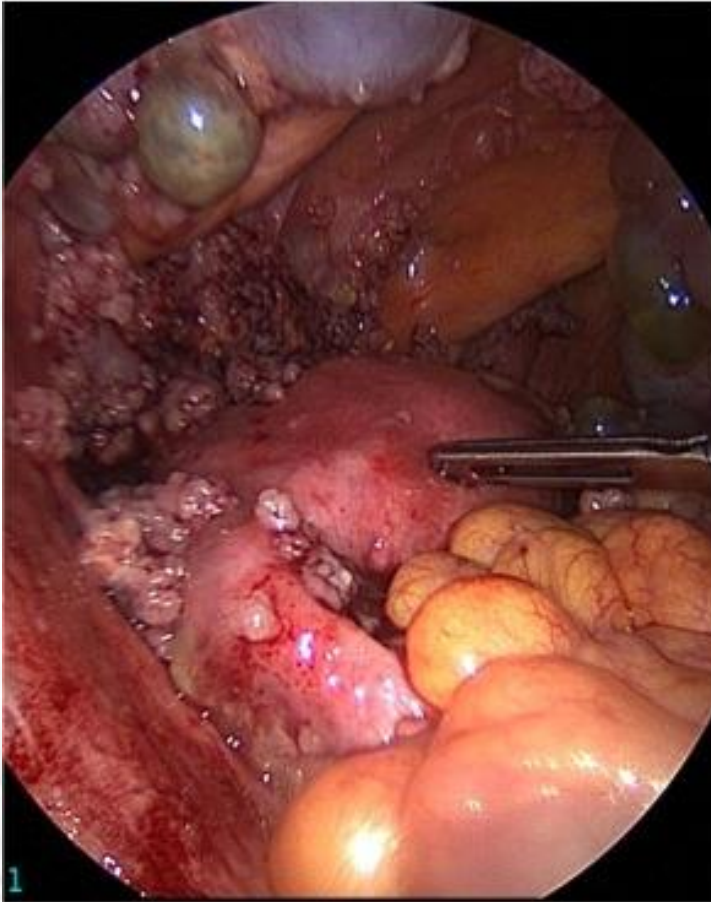
Structured radiology score



Anderson Algorithm score



Opportunity For Quality Improvement: Personalized Surgical Therapy



TARGETED TISSUE SAMPLES

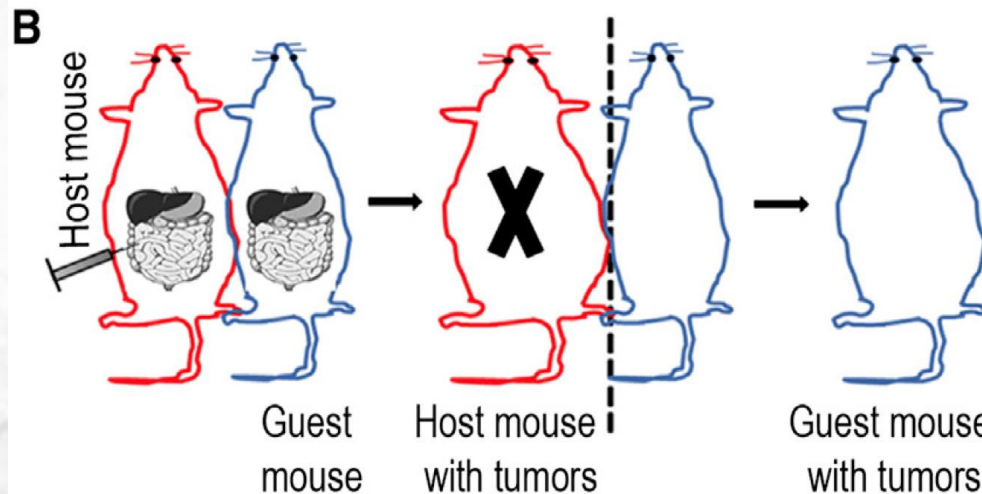
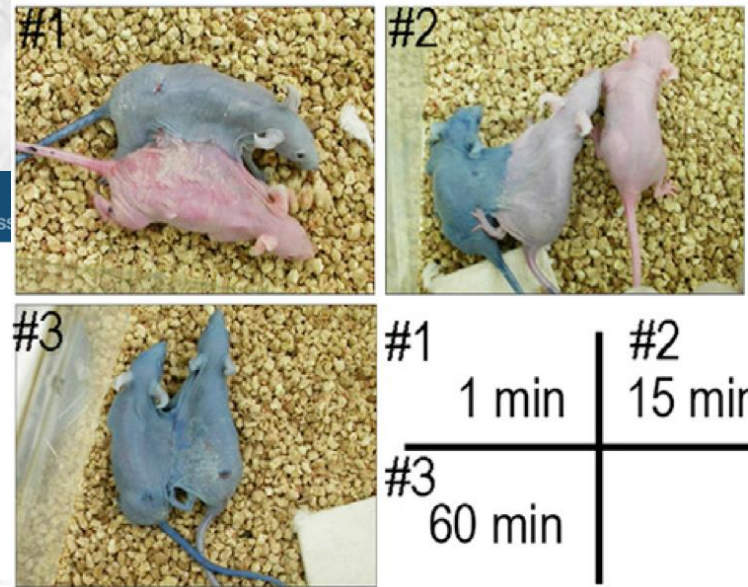
Cancer Cell
Article

CellPress

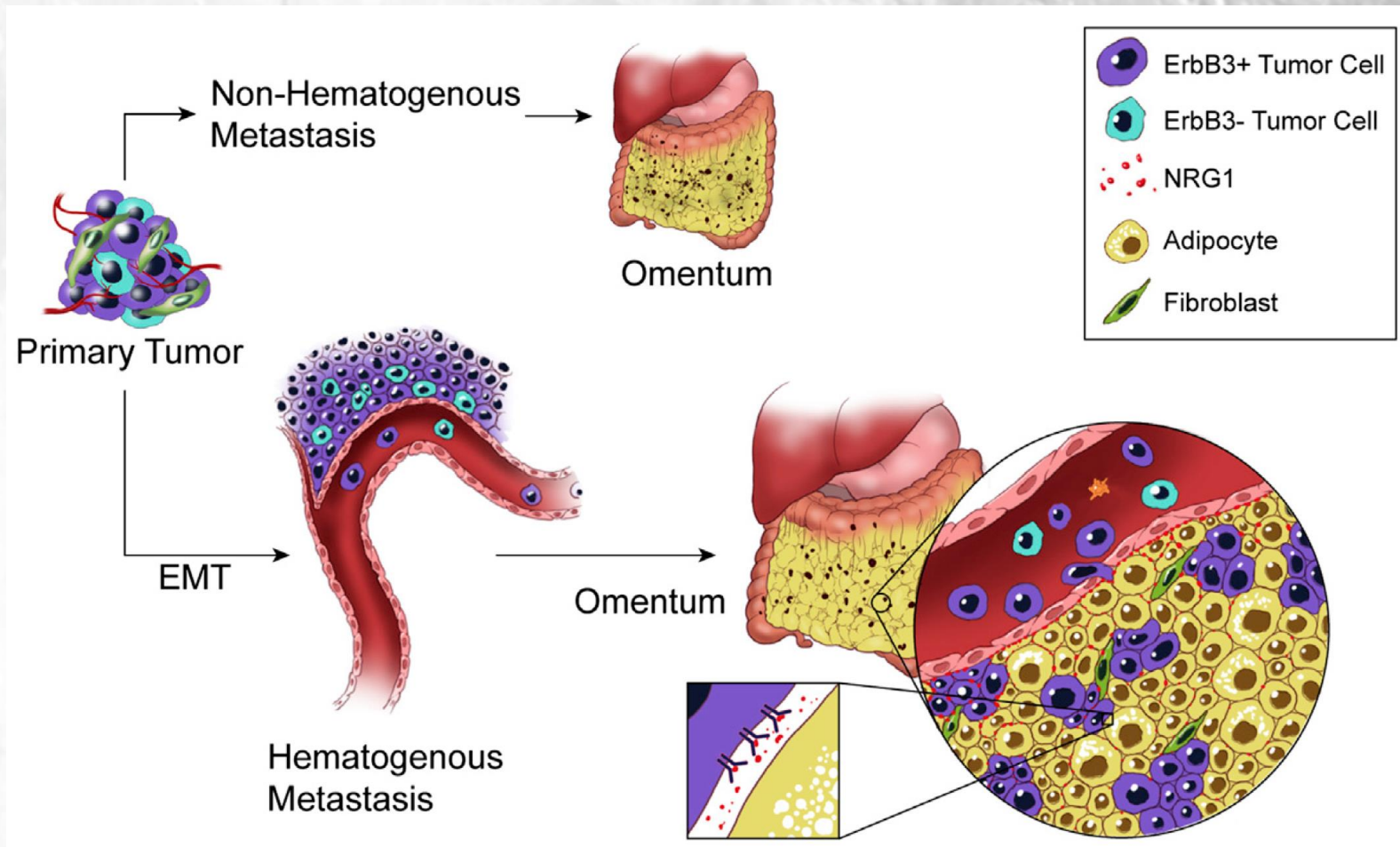
Hematogenous Metastasis of Ovarian Cancer: Rethinking Mode of Spread

Sunila Pradeep,¹ Seung W. Kim,² Sherry Y. Wu,¹ Masato Nishimura,¹ Pradeep Chaluvally-Raghavan,³ Takahito Miyake,¹ Chad V. Pecot,⁴ Sun-Jin Kim,² Hyun Jin Choi,¹ Farideh Z. Bischoff,¹⁰ Julie Ann Mayer,¹⁰ Li Huang,² Alpa M. Nick,¹ Carolyn S. Hall,⁵ Cristian Rodriguez-Aguayo,^{6,7} Behrouz Zand,¹ Heather J. Dalton,¹ Thiruvengadam Arumugam,² Ho Jeong Lee,² Hee Dong Han,^{1,7,11} Min Soon Cho,⁸ Rajesha Rupaimoole,¹ Lingegowda S. Mangala,^{1,7} Vasudha Sehgal,³ Sang Cheul Oh,^{3,12} Jinsong Liu,⁹ Ju-Seog Lee,³ Robert L. Coleman,¹ Prahlad Ram,³ Gabriel Lopez-Berestein,^{6,7} Isaiah J. Fidler,² and Anil K. Sood^{1,2,7,*}

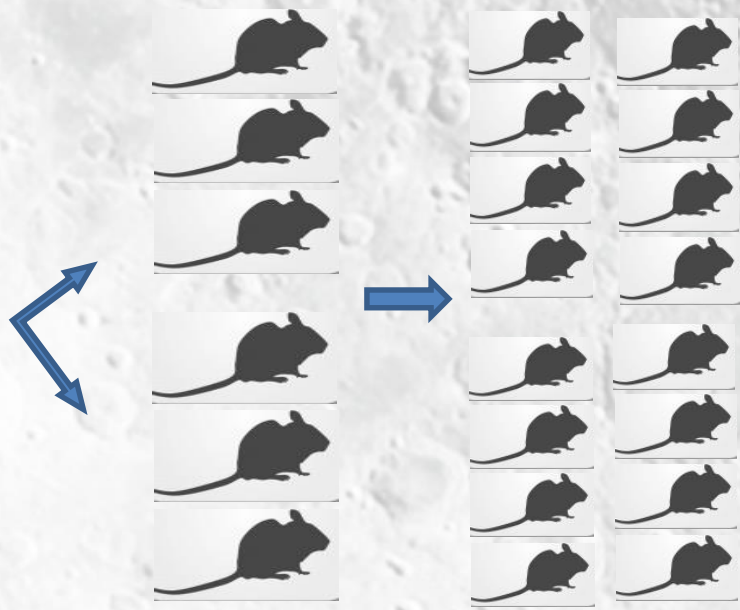
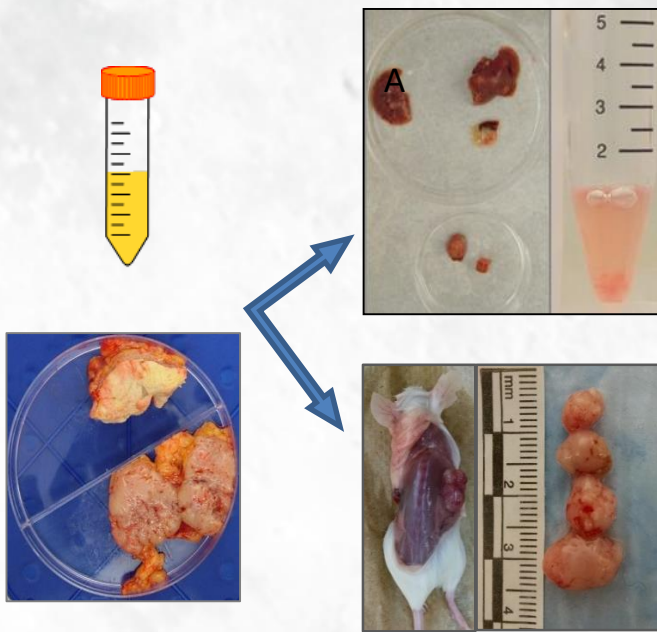
¹Department of Gynecologic Oncology and Reproductive Medicine
²Department of Cancer Biology



TARGETED TISSUE SAMPLES



Schematic of Ovarian Cancer PDX Establishment



Fresh ascites cells
(media:matrigel) IP
or tissue

Implant SCID or
NOD mice

Tumor is harvested
when reaches 1.5 cm²
and implanted
subcutaneous into
mice and in-vitro cell
culture

Test of in-vivo
and in-vitro
drug treatment
Biological
studies,
biomarkers

Ovarian Cancer PDX Models

- **>32 samples tried in the past year, mostly HGSC.**
- **Currently 18 PDX or 2/3 of all are now considered to be successful models.**
- **Ascites samples have the highest success rate (>75%).**
- **Solid tumors from ovary or omentum have ~25% success rate.**

Ovarian PDX Models

PDX ID	Diagnosis	BRCA status	Sample type	PDX	Current generation
2414	HGSC	Not known	Ascites	IP of days ex-vivo	7 th & cell line
2427	HGSC	BRCA 2 (Q2858R)	Ovary	Implant	3 rd
2428	HGSC	No mutations	Solid	SQ injection	7 th
2435	HGSC	No mutations	Ovary	Implant	4 th
2437	HGSC	Not tested	Ovary/Omentum	Implant	6 th & cell line
2440	HGSC	No mutations	Ascites/Ovary	Ascites SQ injection	6 th
2441	MMT	No mutations	Omentum	Implant	7 th
2442	HGS	BRCA 1	Omentum	Implant	7 th
2444	HGSC	No mutations	Ascites	SQ injection	5 th
2445	HGSC	Not tested	Fallopian tube,	IP of Fallopian Tumor	7 th & cell line
2455	PNET	Not tested	Ascites	SQ injections	5 th
2462	HGSC	BRCA 1 mutation	Ascites	IP	3 rd
2463	HGSC	Not tested	Ascites	IP	3 rd & cell line
2468	Clear Cell Carcinoma	Not tested	Ascites	IP & Implant	3 rd
2470	MUCINOUS	Not tested	Ovary	Implant	2 st
2471	ENDOMETRIOID CA	Not tested	Ovary	Implant	2 nd
2474	HGSC	No mutations	Ascites	IP	2 nd
2489	CARCINOSARCOMA	No mutations	Fallopian tube	Implant	2 nd
2501	LGSC	No mutations	Ascites	IM OMT & OVT	1 st
2510	HGSC	Not known	Asscites	IP & IM	2 nd 23

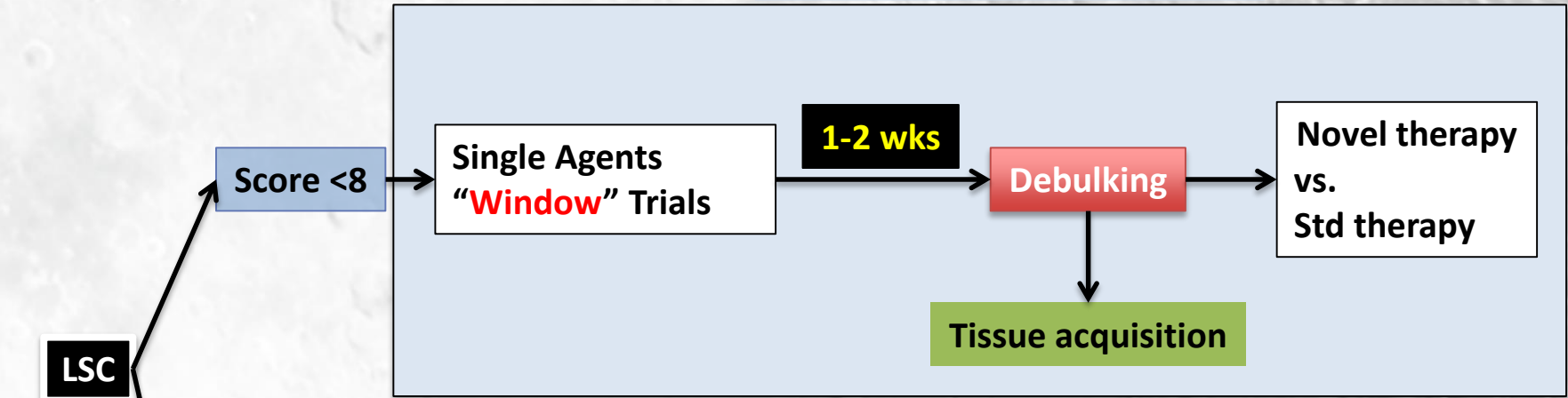
ONGOING PROGRAMS/EFFORTS

- **Development of novel clinical trials**
 - Window of opportunity trials
 - Novel biologic combinations plus standard NACT
- **Comparative effectiveness assessment**
 - Economic modeling/cost effectiveness
 - Cost comparison with quality adjustment (process: 1 step, 2-step, IR-guided biopsy)
- **Expansion into other institutions**
 - Sister Institution Network

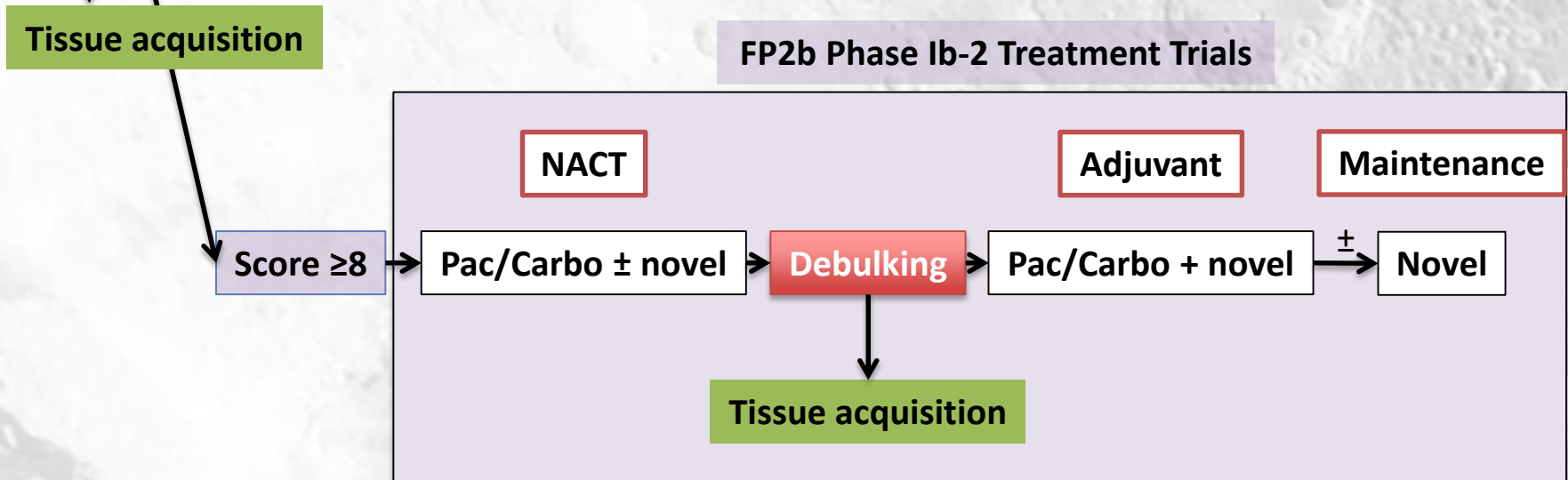
Flagship 2B: Information-rich clinical trials (HGSOC)

Flagship Project 2

FP2b Phase 0 "Window" trials



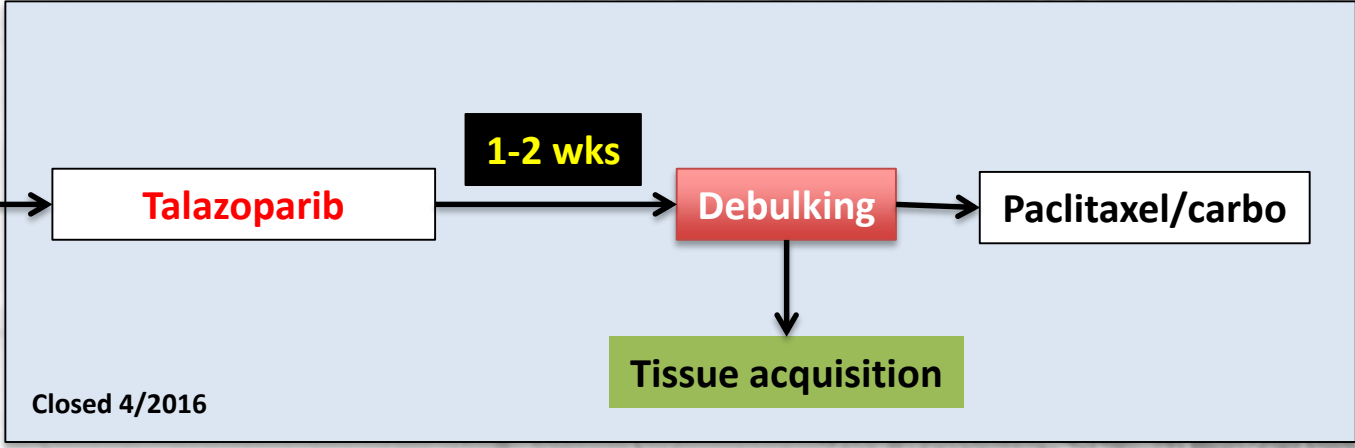
FP2b Phase Ib-2 Treatment Trials



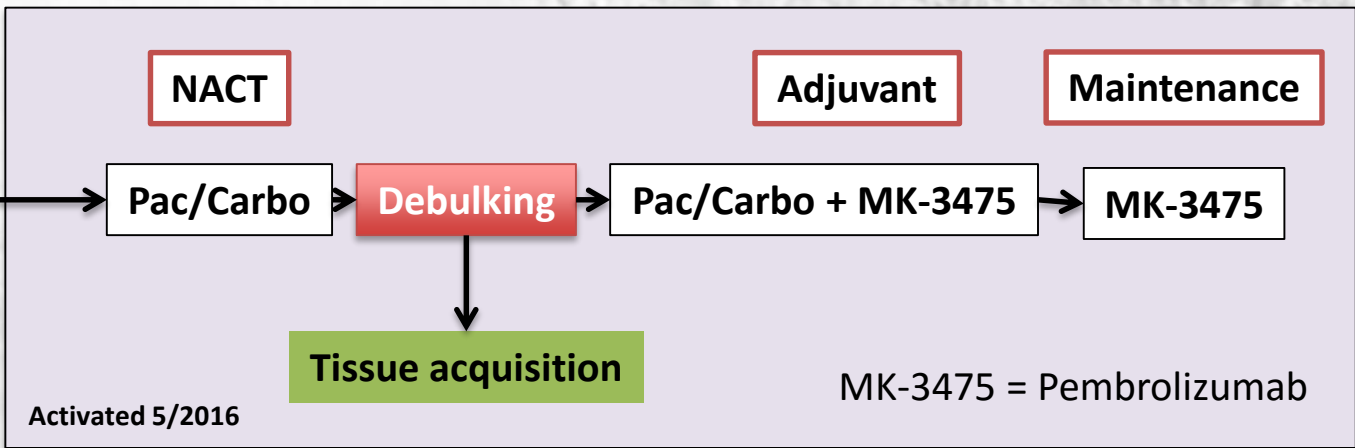
Flagship 2B: Information-rich clinical trials (HGSOC)

Flagship Project 2

FP2b Phase 0 "Window" trials



FP2b Phase Ib-2 Treatment Trials

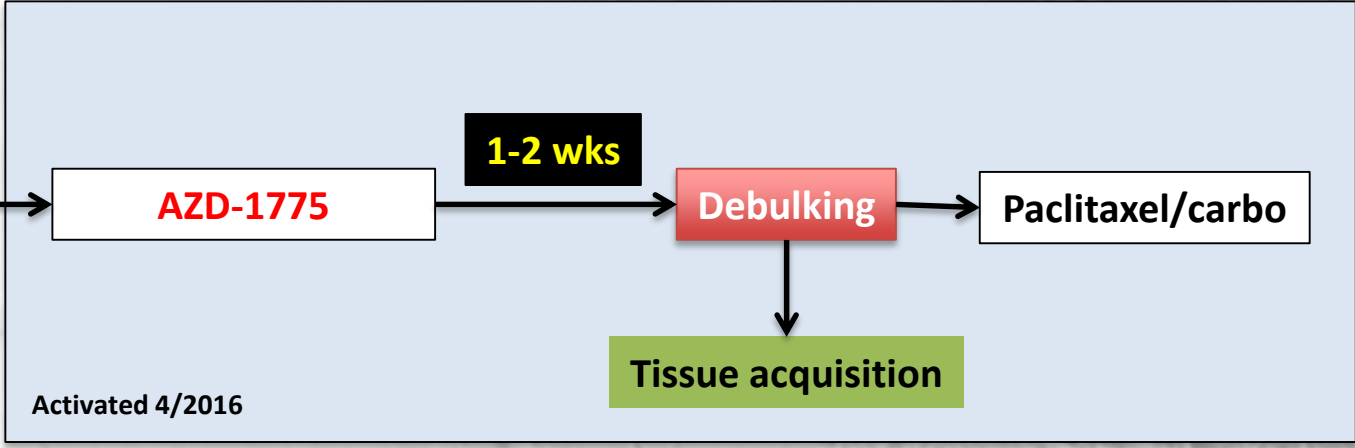


MK-3475 = Pembrolizumab

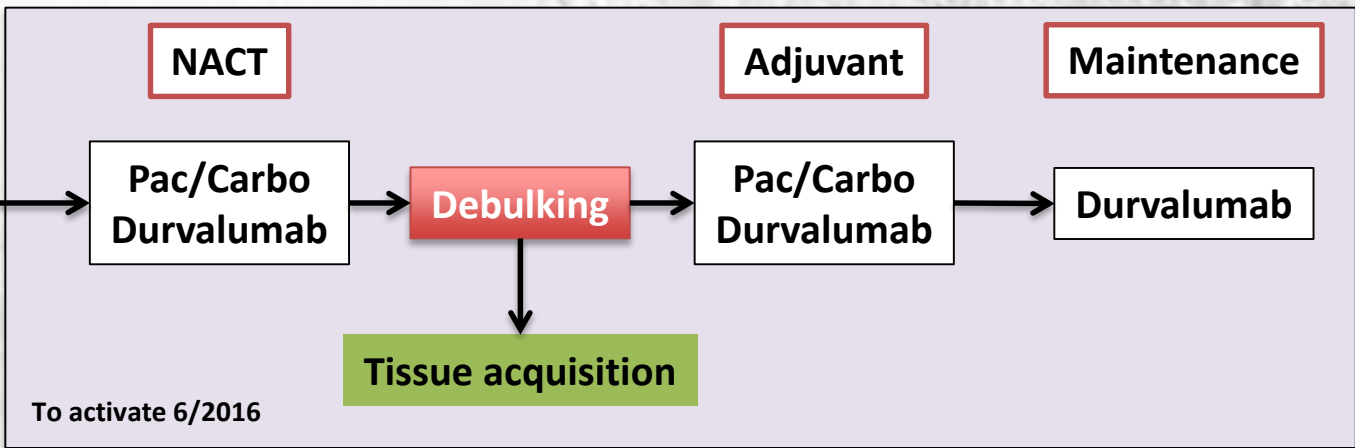
Flagship 2B: Information-rich clinical trials (HGSOC)

Flagship Project 2

FP2b Phase 0 "Window" trials



FP2b Phase Ib-2 Treatment Trials



EXPANSION OF THE CLINICAL TRIALS PLATFORM

- **Alliances/partnerships**
 - PARPi: **BMN-673**, **olaparib**, rucaparib, others
 - PI3K pathway: BYL709, BKM120, **AZD2014**, **AZD5363**
 - Angiogenesis: Dll4 (**demcizumab**), **TAMs (emactuzumab)**, Ang2
 - Immune: PD-1 (**MK-3475**)
 - P53: MK-1775, **COTI-2**, **Selinexor**
 - Platelets: **SPD535**
 - Others: Prolanta (Prl), FAKi, PTI-112 (phosphoplatin)
- **Clinical trials network**

Personalized and Comprehensive Therapy (PACT) against Ovarian Cancer

IDENTIFYING INNOVATIVE COMBINATIONS

Window-of-Opportunity: Identifying biomarkers

- Targeting p53 and HRD
- Detailed marker analysis to understand biological effects

*Lead agents: BMN-673; KPT-330; COTI-2

IMPROVING 1° THERAPY

Immune Therapy

R0 resection → IP chemotherapy (paclitaxel/ platinum + immunotherapy*)

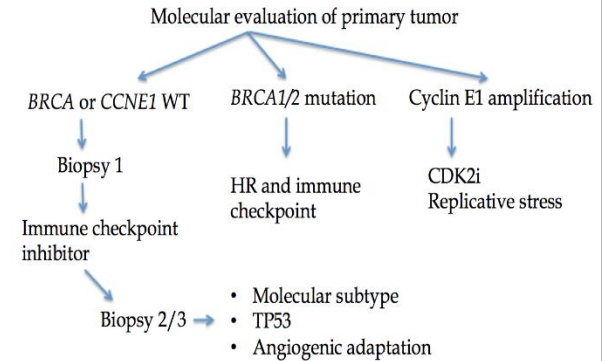
Assessments:

- 1) Peritoneal fluid (immune)
- 2) PFS

*Lead agents: pertuzumab, durvalumab)

RELAPSED DISEASE

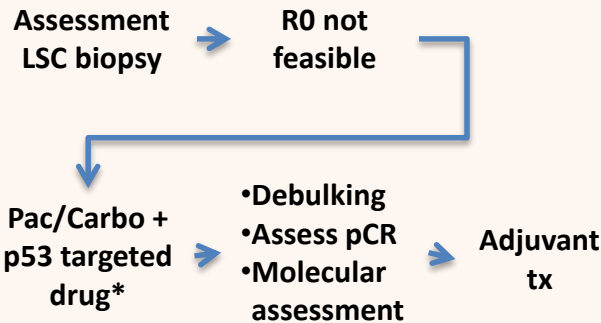
“Umbrella Trial”: Platinum-Sensitive



Co-Clinical Trials: Overcoming Resistance

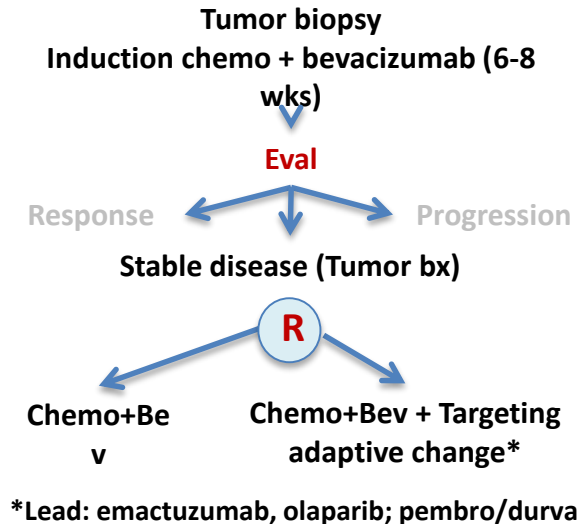
- Molecularly characterized mouse models (PDX, GEMM, other)
- Identify rational combinations
- Start:
 - PARPi + anti-angiogenic agents
 - Anti-VEGF Ab + CSF1Ri
 - Targeting “undruggable” - RNAi

NACT: Targeting p53



*Lead agents: KPT-330, COTI-2, MK1775 (WEE1i)

Overcoming Adaptive Changes: Platinum-Resistant



*Lead: emactuzumab, olaparib; pembro/durva

Women's Cancer Moonshot Leadership

Executive Committee: Anil Sood, Gordon Mills, Mien-Chie Hung, Gabe Hortobagyi

Clinical

HGSOC

Robert Coleman
David Gershenson

TNBC

Funda Meric-Bernstam
Naoto Ueno
Gabriel Hortobagyi
Jennifer Litton

Translational Biology

Anil Sood
Laurence Cooper
Gordon Mills

Dihua Yu
Laurence Cooper
Mien-Chie Hung

Cancer prevention and early detection

Karen Lu
Robert Bast
Sam Hanash

Banu Arun
Powel Brown
Sam Hanash

Survivorship

Andy Futreal
Diane Bodurka
Karen Basen-Engquist

Andy Futreal
Jennifer Litton
Richard Theriault

Pathology

Jinsong Liu
Russell Broaddus

Aysegul Sahin
Yun Wu

Women's Cancer Moonshot Team



THE TIME IS NOW

Together we will end cancer



SUMMARY YEAR 1 - FLAGSHIP 2: ACCOMPLISHMENTS AND IMPACT

❖ 2A-Impact of Altering R0 Resection

- Our primary R0 rate was approximately 20%
- Doubling (to 40%) would increase OS for the entire ovarian cohort from 49 to 62 months (25% improvement)
- Current R0 rates in triaged population are 88% (primary surgery) and 87% (NACT)

❖ 2B-Implement a biomarker approach using both retrospectively and prospectively collected patient samples

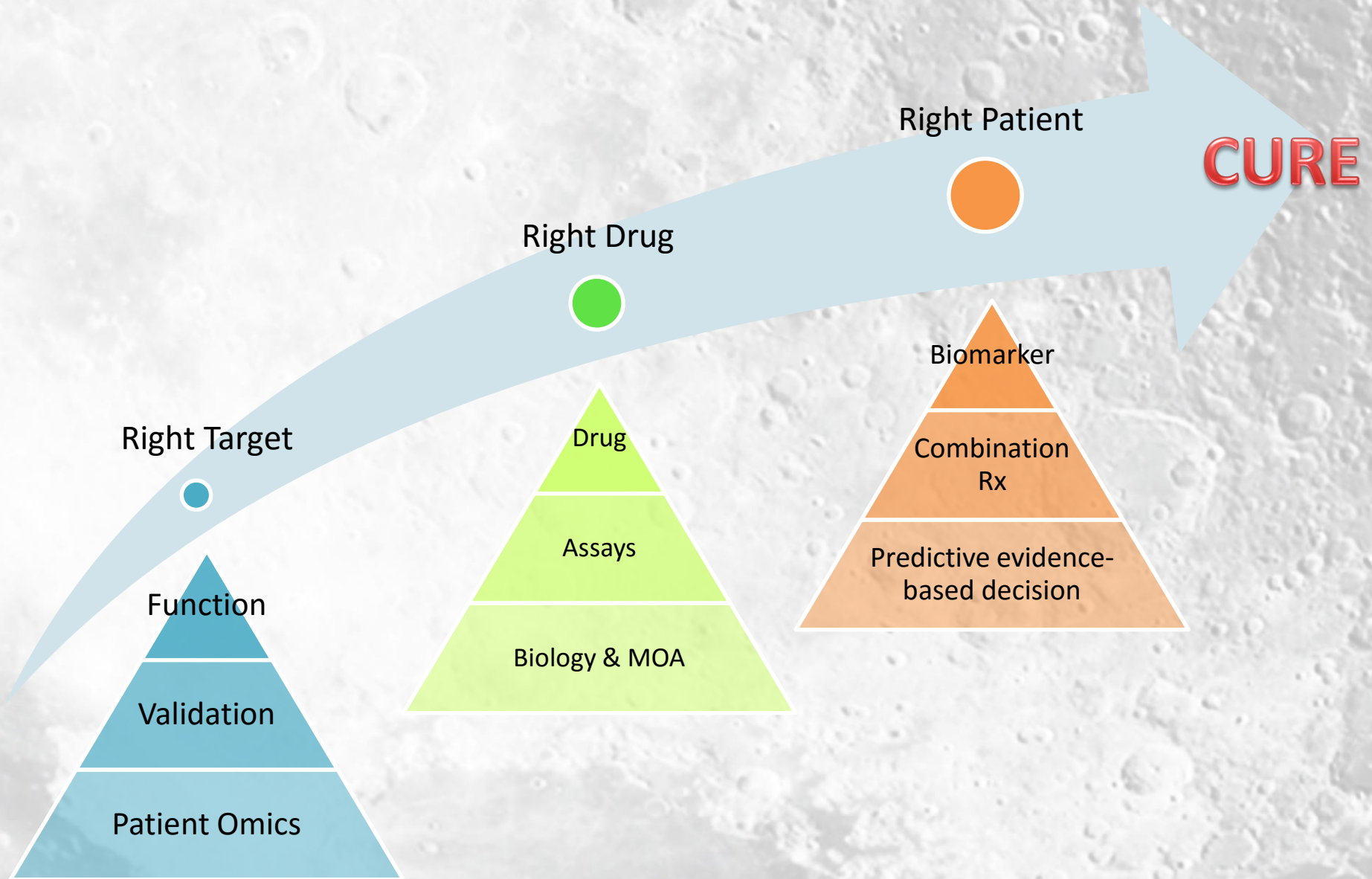


THE MDACC CANCER MOONSHOT

A MOON SHOT IS COMPREHENSIVE BRINGS ALL OF MDACC 'S CAPABILITIES TO BEAR ON THE PROBLEM



ACHIEVING **CURE** IN ESTABLISHED CANCERS

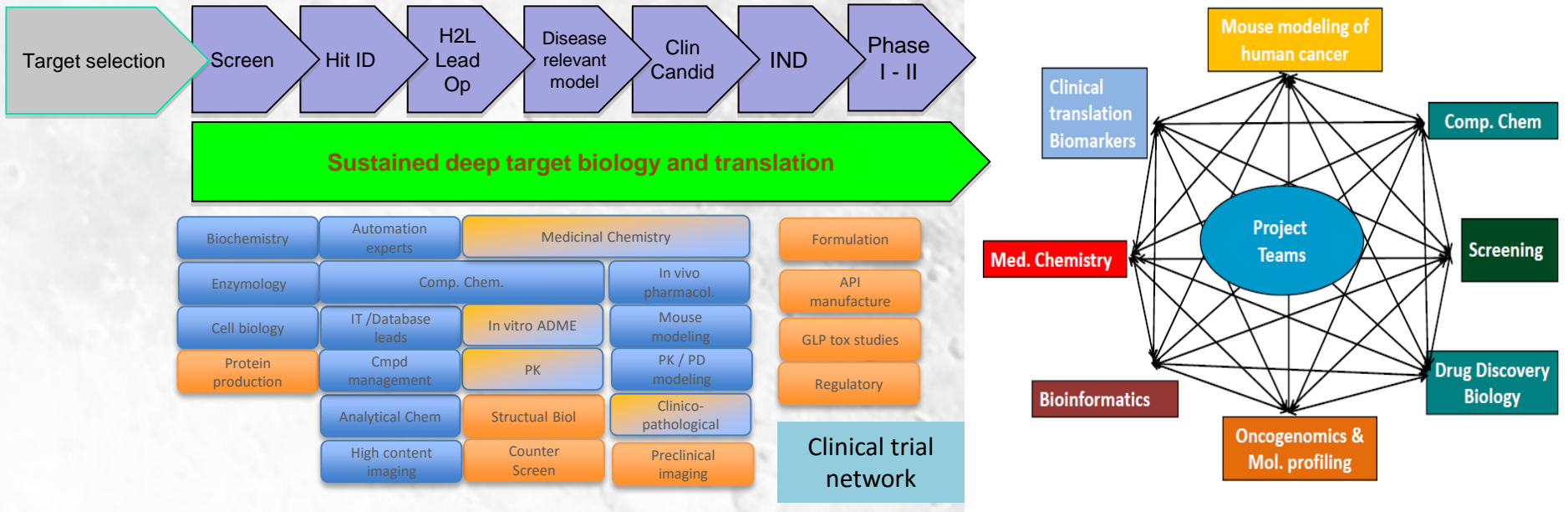


RESOURCES: PLATFORMS

- Clinical Genomics
- Bioinformatics
- Massive Data Analytics
- Cancer Control
- Early Detection
- Big Data
- Diagnostics development
- Institute for Applied Cancer Science
- Institute for Personalized Cancer Therapy
- Center for Co-Clinical Trials
- Adaptive Learning in Genomic Medicine

Translational Research Continuum

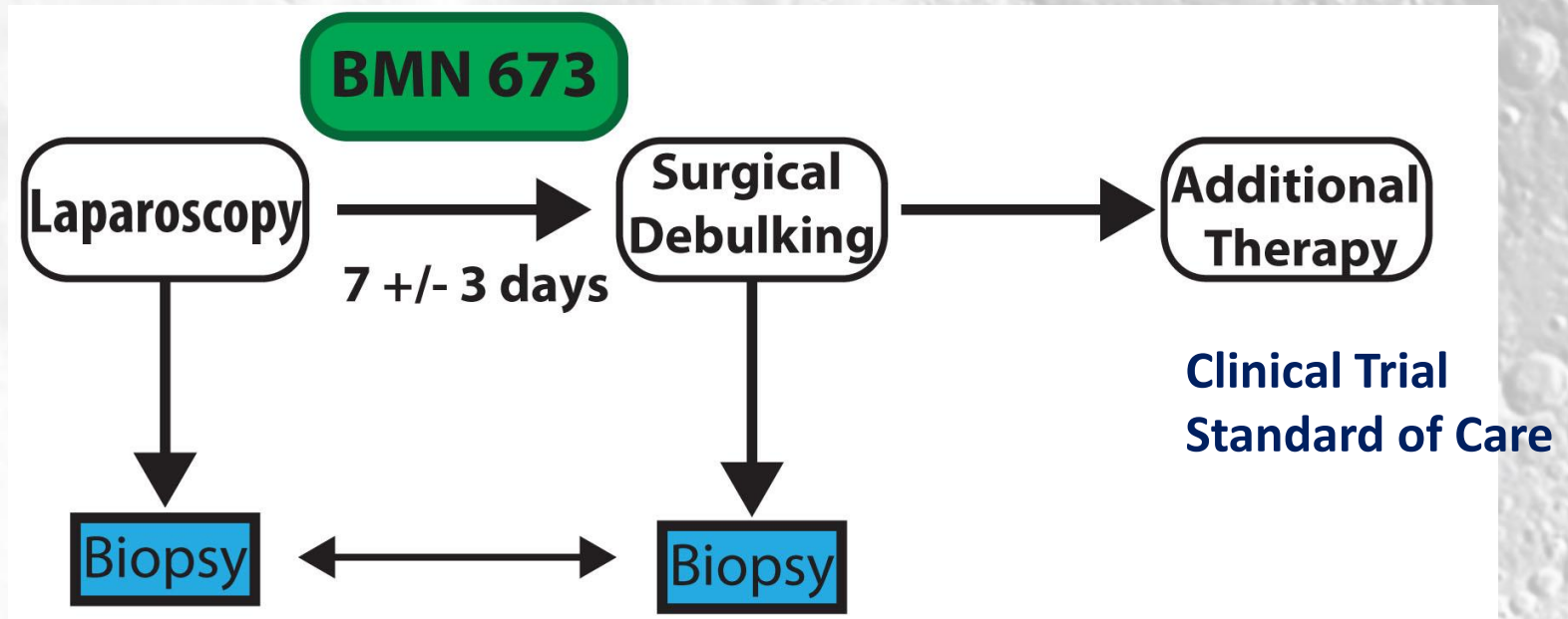
THE INSTITUTE FOR APPLIED CANCER SCIENCE



Accelerating drug discovery by combining the best of academia and industry:

- Professional drug discovery capability by industry-seasoned experts
- Organized in highly integrated cross-functional teams
- Milestone-driven goal-oriented execution
- Committed to science-driven drug discovery by integrating seamlessly with the best and the latest science from academia

OVARIAN CANCER: “WOO” (WINDOW OF OPPORTUNITY) TRIALS

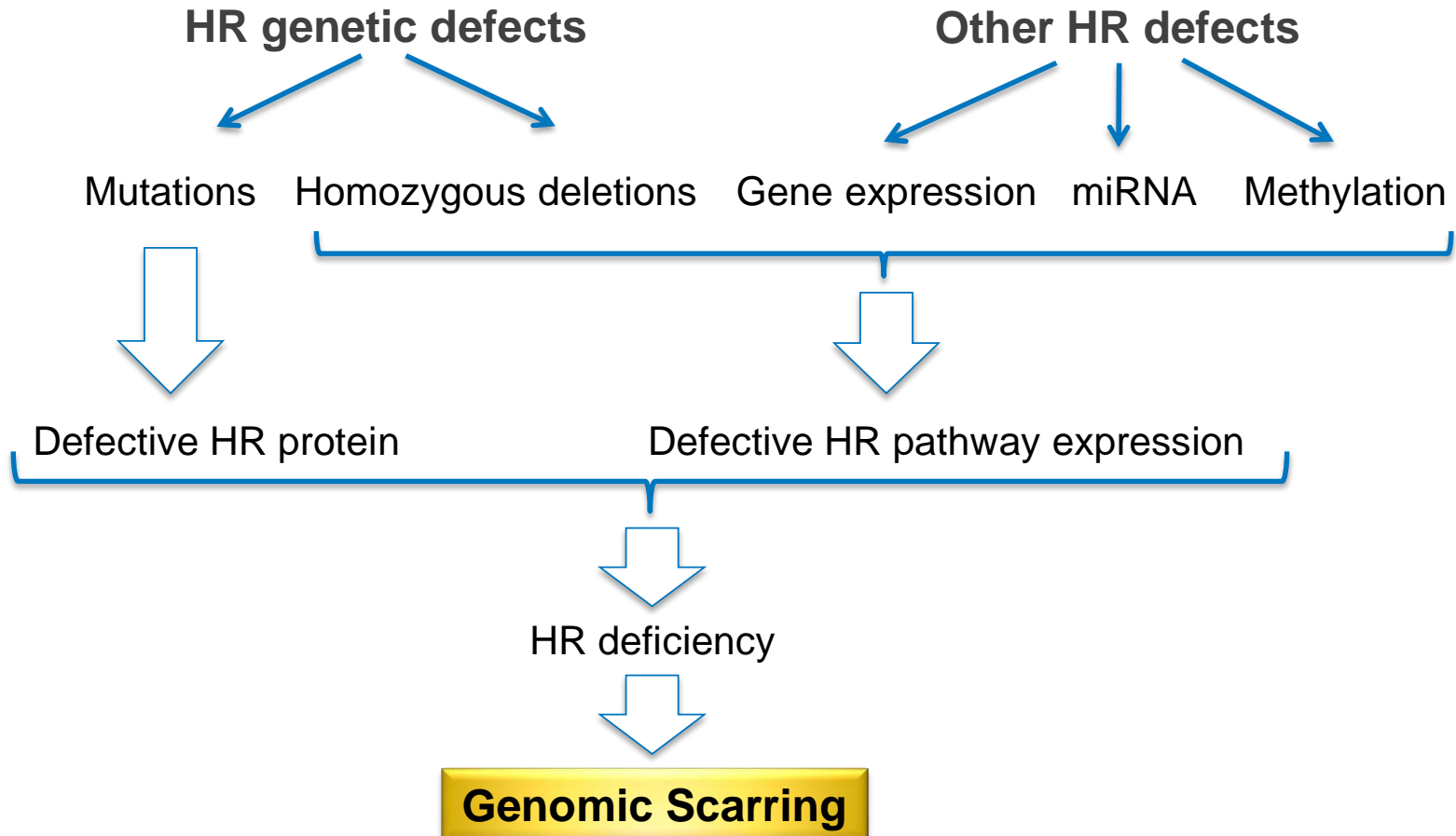


Analysis:

- HRD assessment
- Immune profile

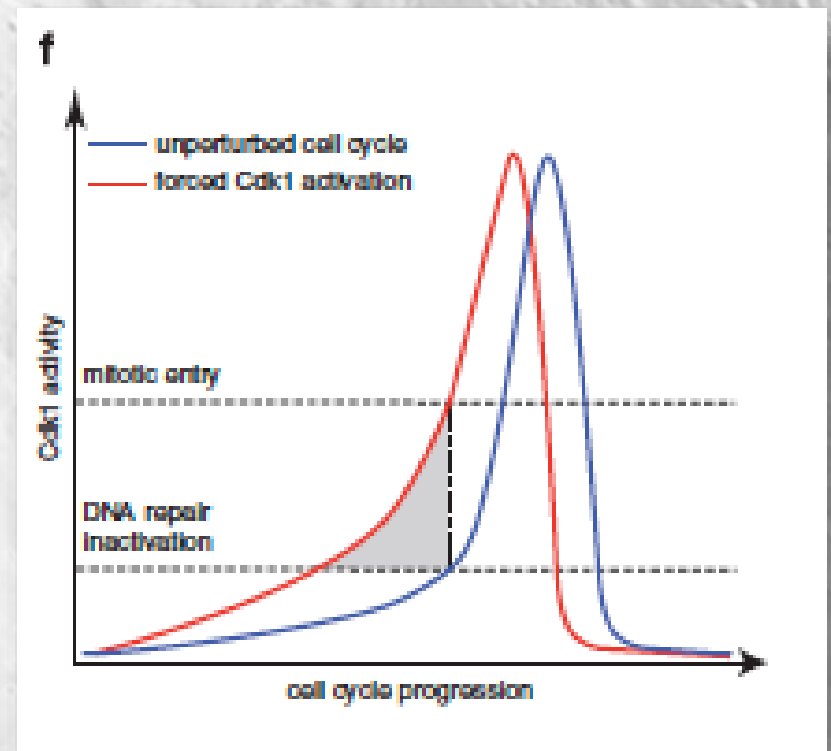
Matched sites

- Ovary/Primary
- Omentum
- Diaphragm
- Other peritoneum

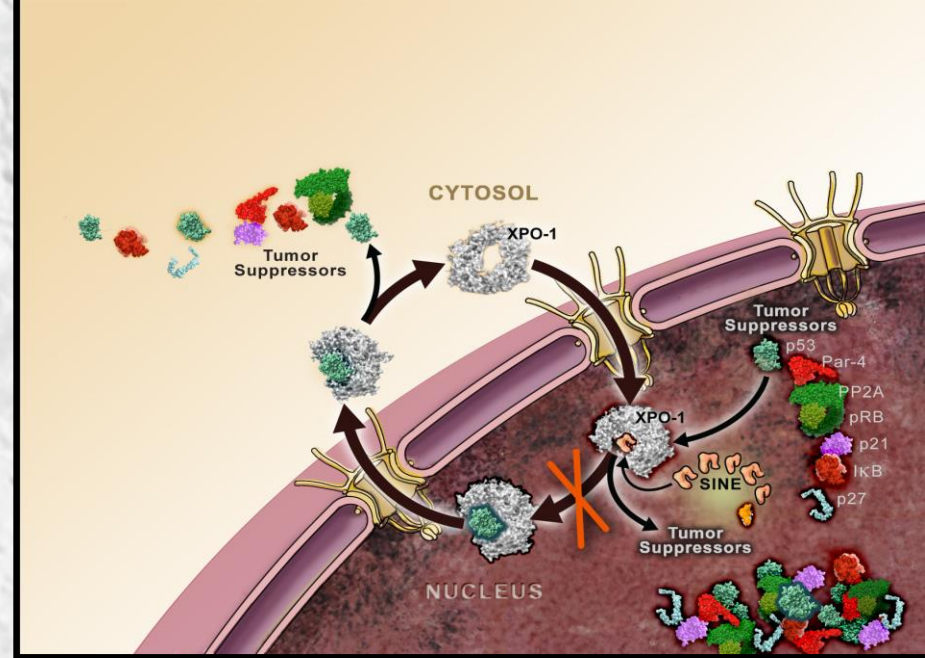


INTERACTION OF WEE1 AND HR

- HR restricted to late S and G2 phases
- Wee1 inhibition
 - Activated CDK1
 - Earlier mitosis
 - Impaired HR based on *in vivo* assays
 - Increased pBRCA2

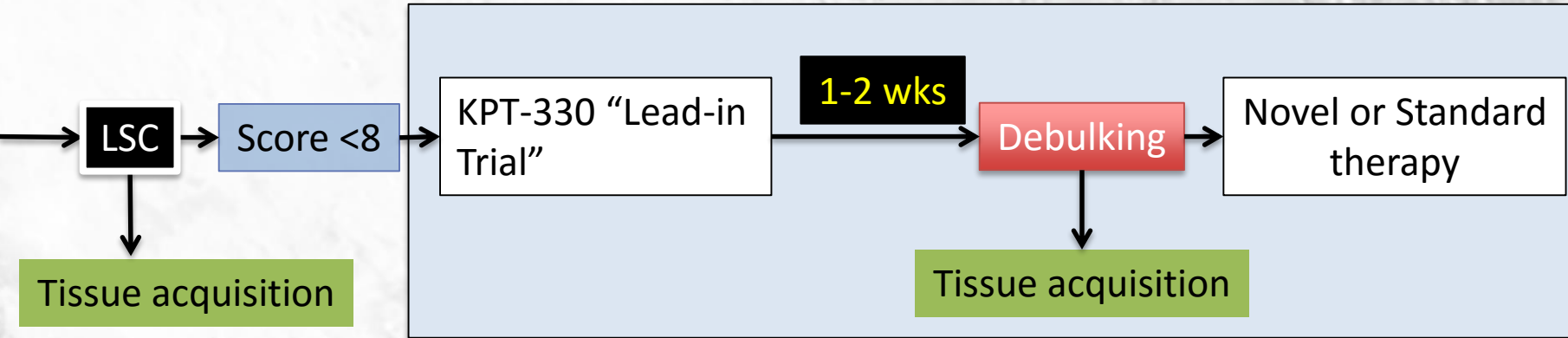


NEW MOONSHOT PROJECTS-FP2B OVARIAN

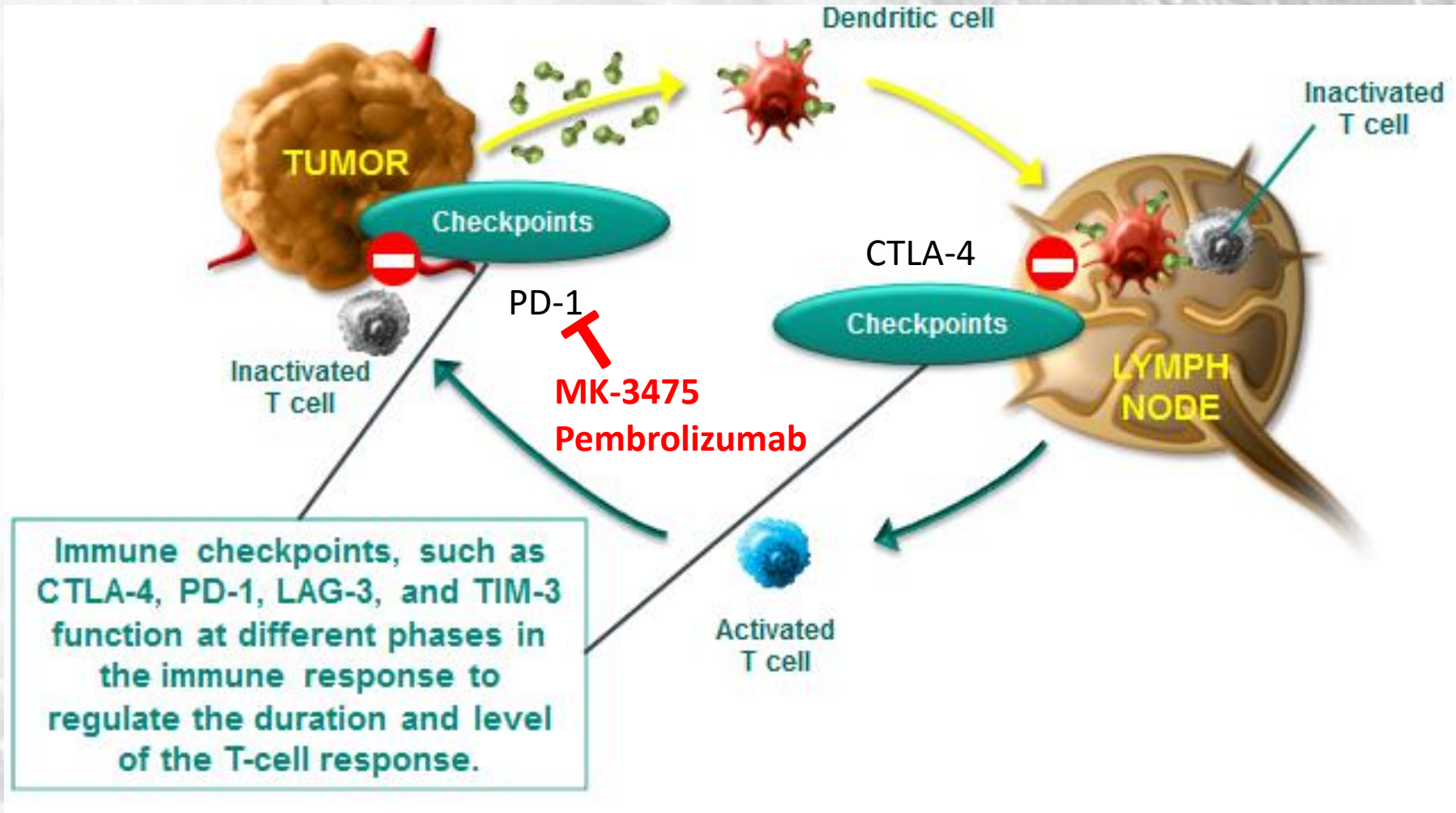


Flagship Project 2b Phase 0 trial

Ovarian Cancer Patient



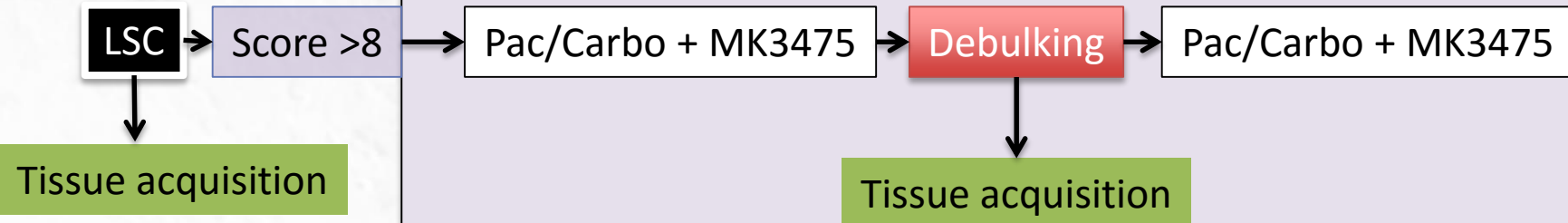
IMMUNOTHERAPY



NEW MOONSHOT PROJECTS-FP2B OVARIAN

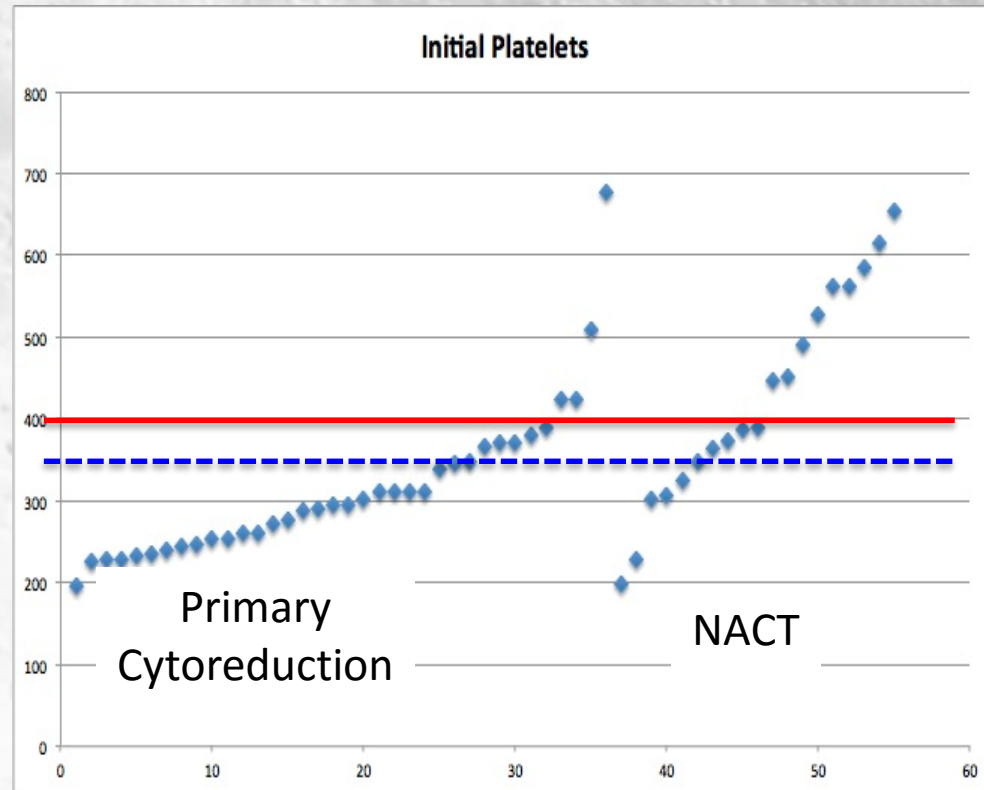
Flagship Project 2

FP2b Phase Ib-2 Treatment Trials



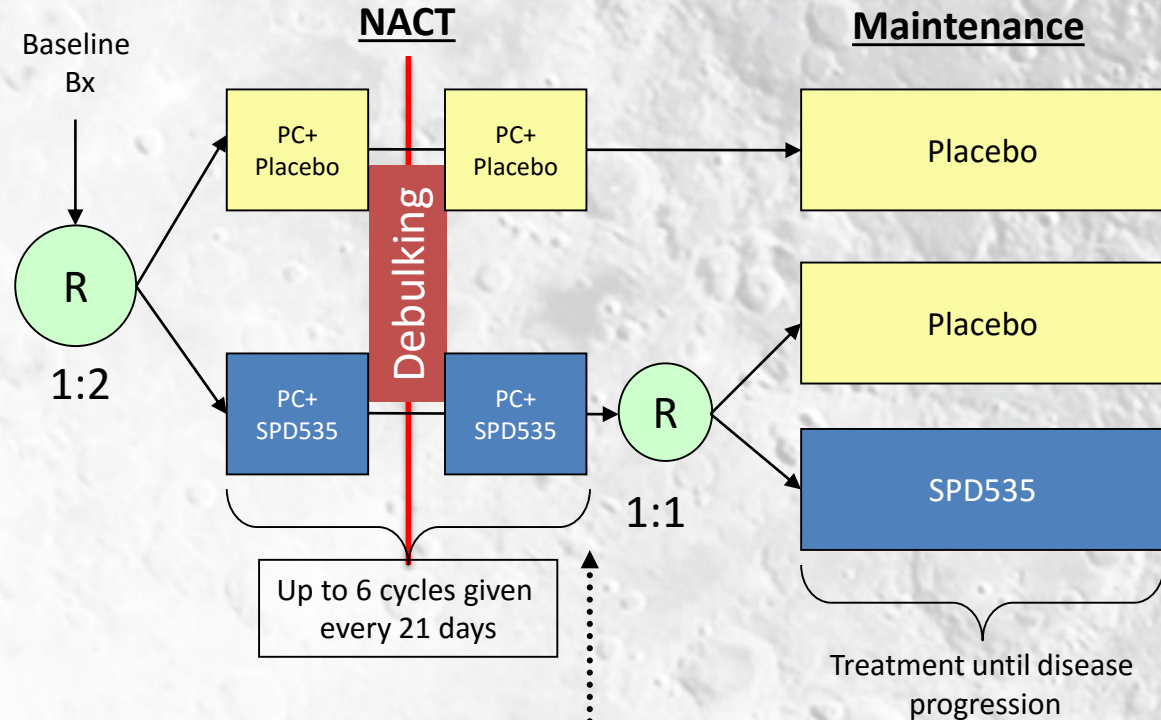
PLATELETS IN PRE-OP SAMPLES OF PATIENTS ON THE MOON SHOT P2

- Primary surgery: 36/55 (65%) following scope and score
- NACT: 19/55 (35%)
- Platelet counts
 - Primary surg: 289.5 vs NACT: 452
 - $P < 0.0001$
- Number of patients above 350 = 22 (40%)
 - 13 of these (59%) were NACT patients
- Number of patients $> 400 = 13$ (24%)
 - 9 of these (69%) were NACT patients



CONCEPT IN DEVELOPMENT FOR P2B

- N=132
- Newly diagnosed advanced (stage III/IV) ovarian cancer
- Thrombocytosis (PLT > 350K)
- Measureable disease amenable to biopsy
- ECOG of 0 or 1



SPD535:

- Megakaryocyte-targeted agent
- Lowers platelet count
- Inhibits TPO receptor activation
- Reduces thrombogenic cytokines

Month 2 & 4

- Incidence of VTE
- Objective response
- Repeat Bx (month 2) for tumor biomarkers
- Safety and tolerability

Month 16

- Incidence of VTE
- PFS
- Overall survival
- Safety and tolerability