Targeted Therapies in Ovarian & Other Gynecologic Cancers

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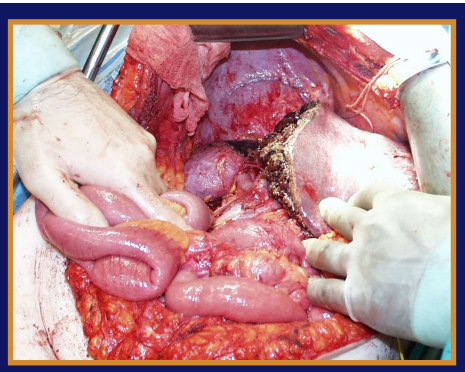
Disclosures

- **Scientific Advisor:**
  - Morphotek, AZ, Roche, J & J, Caris, Clovis, Tesaro

Ovarian Seminal Studies

Study	PI/Author	Results	Pub.
GOG 111 N = 384	McGuire	PFS = 18 vs 13 mos OS = 38 vs 24 mos	NEJM, 1996
EORTC-OV10 N = 680	Piccart	PFS = 16 vs 12 mos OS = 43 vs 44 mos	JNCI, 2000
AGO N = 798 C vs CDDP	Du Bois	PFS = 17 vs 19 mos OS = 43 vs 44 mos	JNCI, 2003
GOG 158 N = 792	Ozols	PFS = 19 vs 21 mos OS = 49 vs 57 mos	JCO, 2003

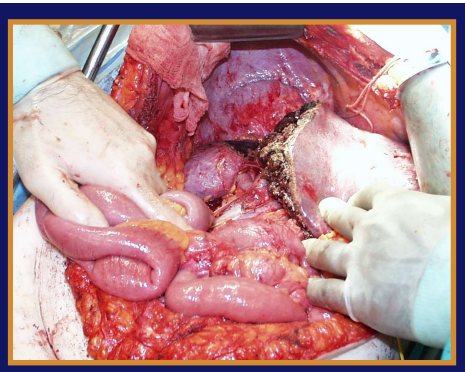
First-Line Therapy



Surgery with comprehensive staging or maximal cytoreduction

Platinum + Taxane Chemotherapy (Carboplatin + Paclitaxel)

First-Line Therapy



Surgery with comprehensive staging or maximal cytoreduction

Platinum + Taxane Chemotherapy (Carboplatin + Paclitaxel)

? ?

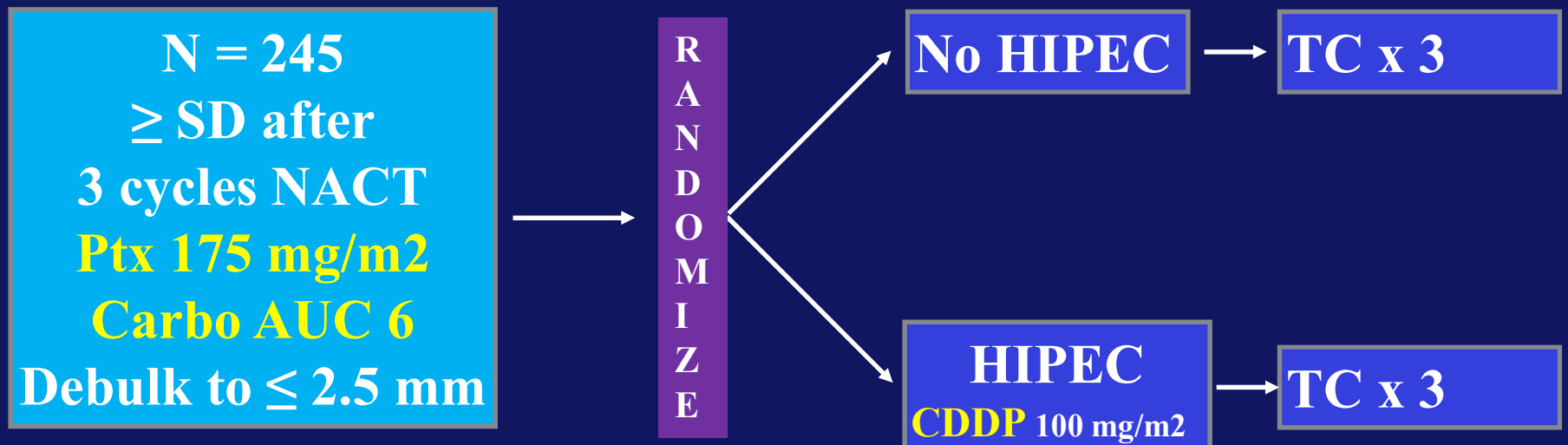
Maintenance | **Dose Dense** | **IP/HIPEC** | **Biologics**

Results IP Trials

	Median PFS (mo)		% Inc.	Median OS (mo)		% Inc.
Study	IV	IP		IV	IP	
Alberts INT0051	--	--	--	41	49	20
Markman GOG 114	22	28	27	52	63	21
Armstrong GOG 172	18.3	23.8	26	50	67	29

(All differences statistically significant)

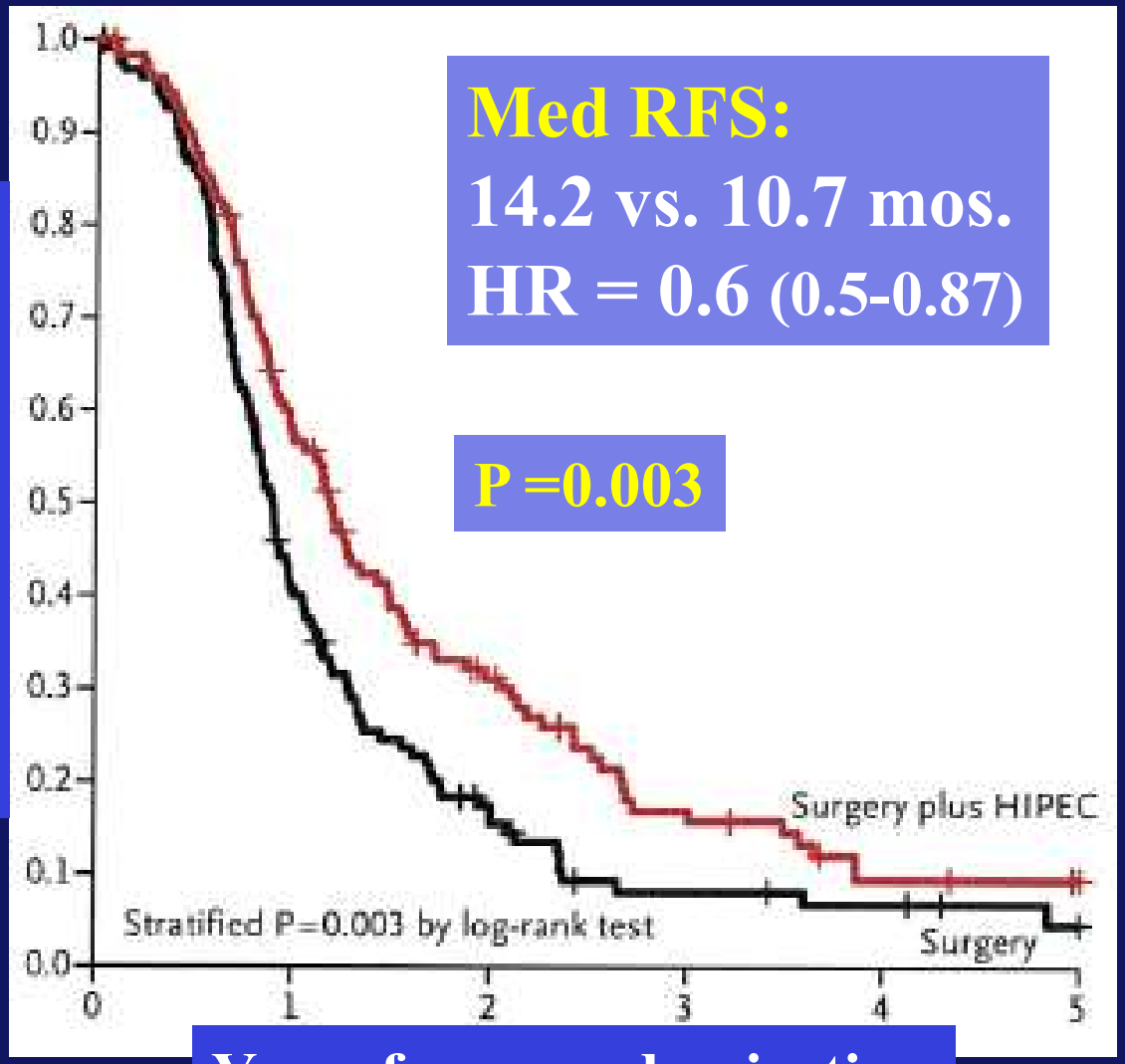
Ph III HIPEC



1° Endpoint - PFS
2° Endpoint - OS, toxicity, QOL

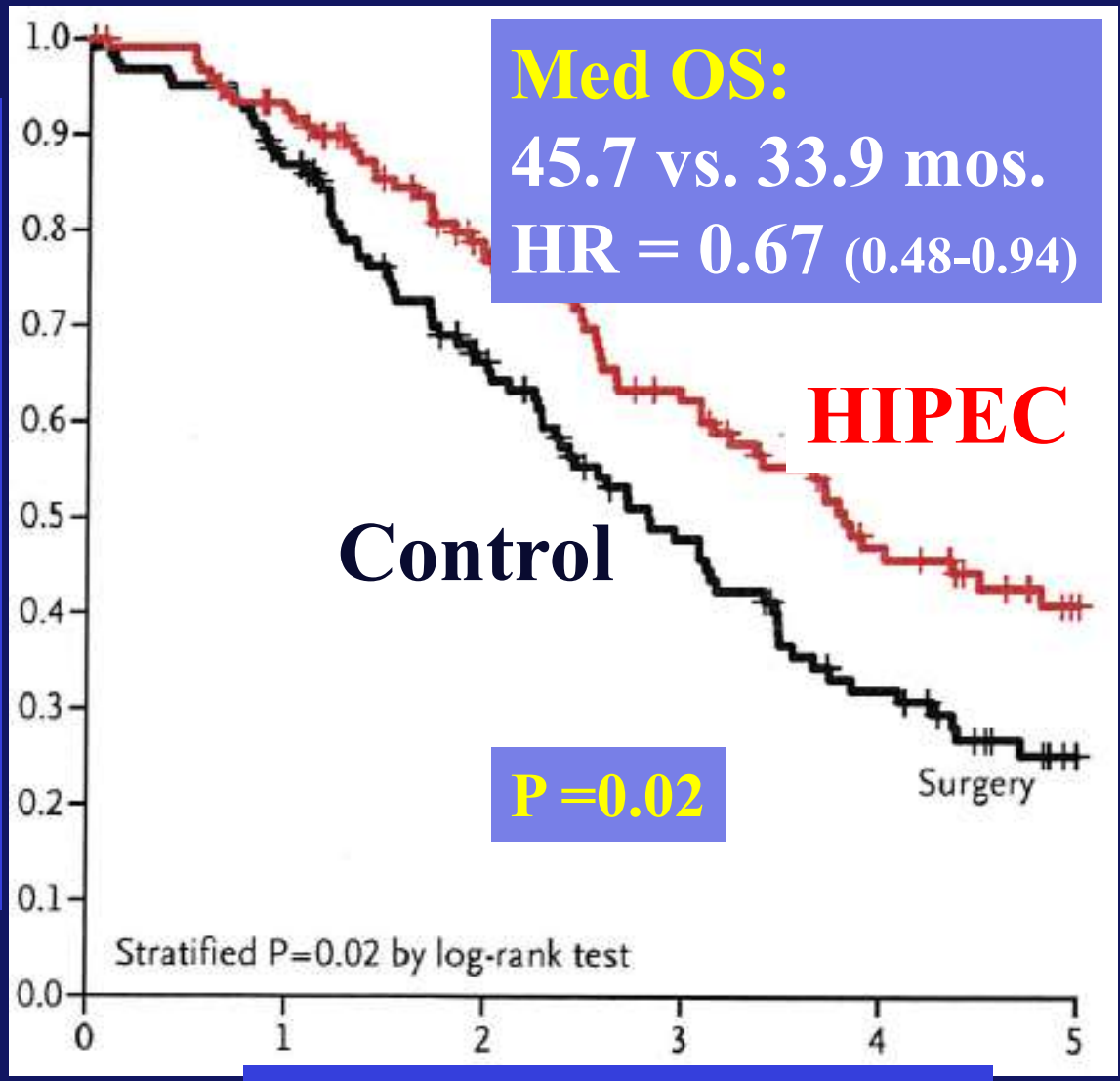
Van Driel WJ, NEJM 2018

RFS: HIPEC



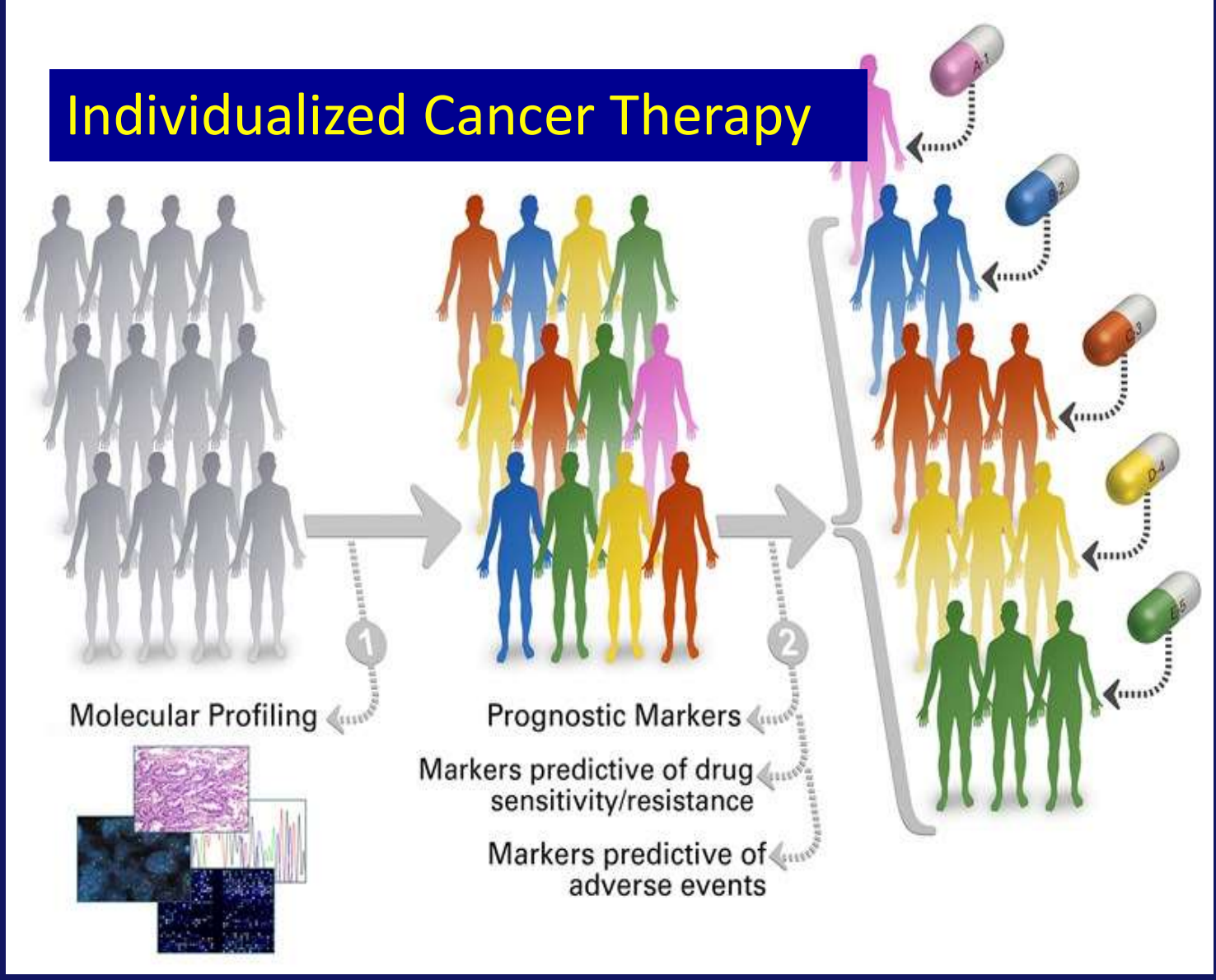
Van Driel WJ, NEJM 2018

OS: HIPEC

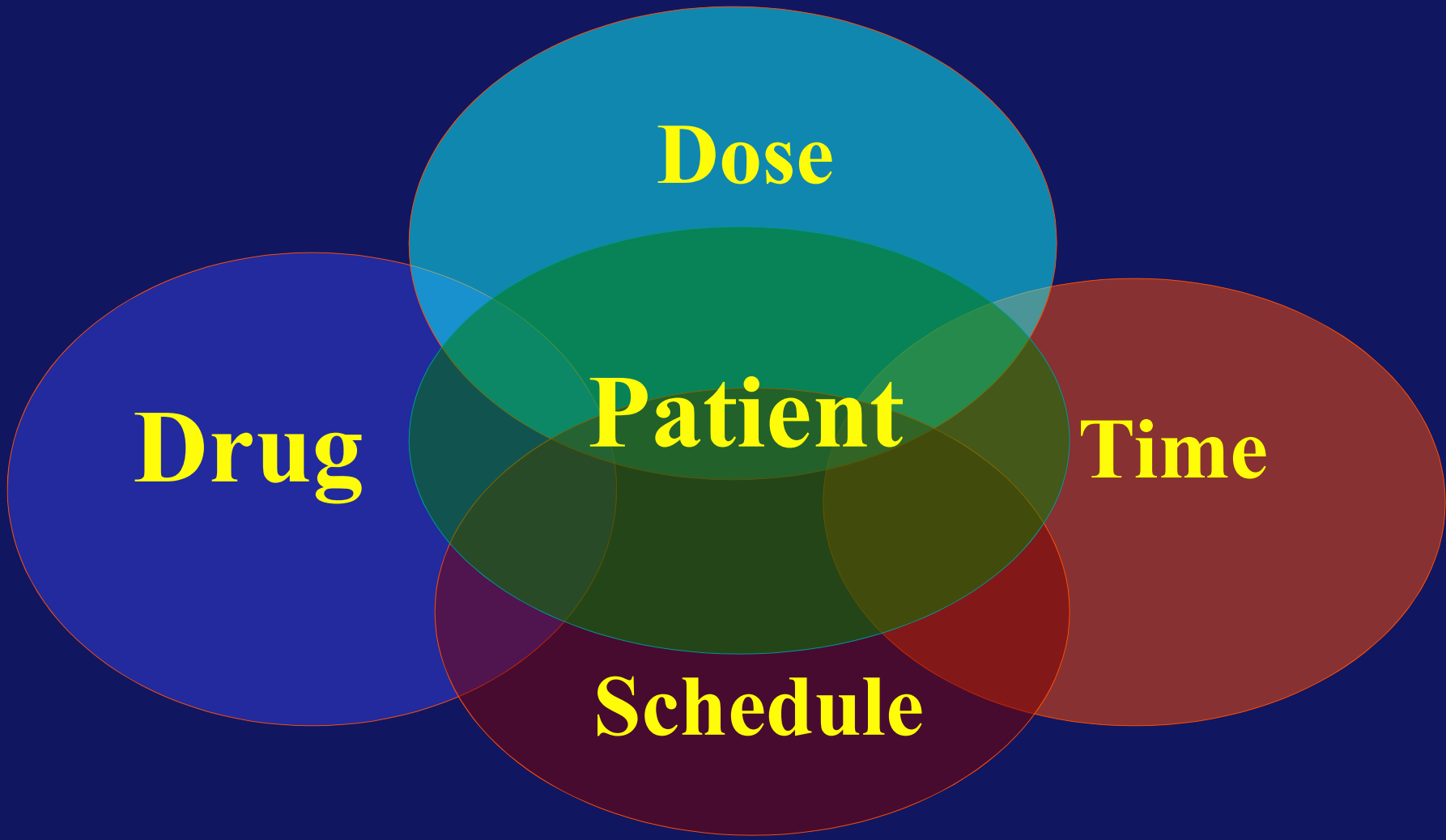


Van Driel WJ, NEJM 2018

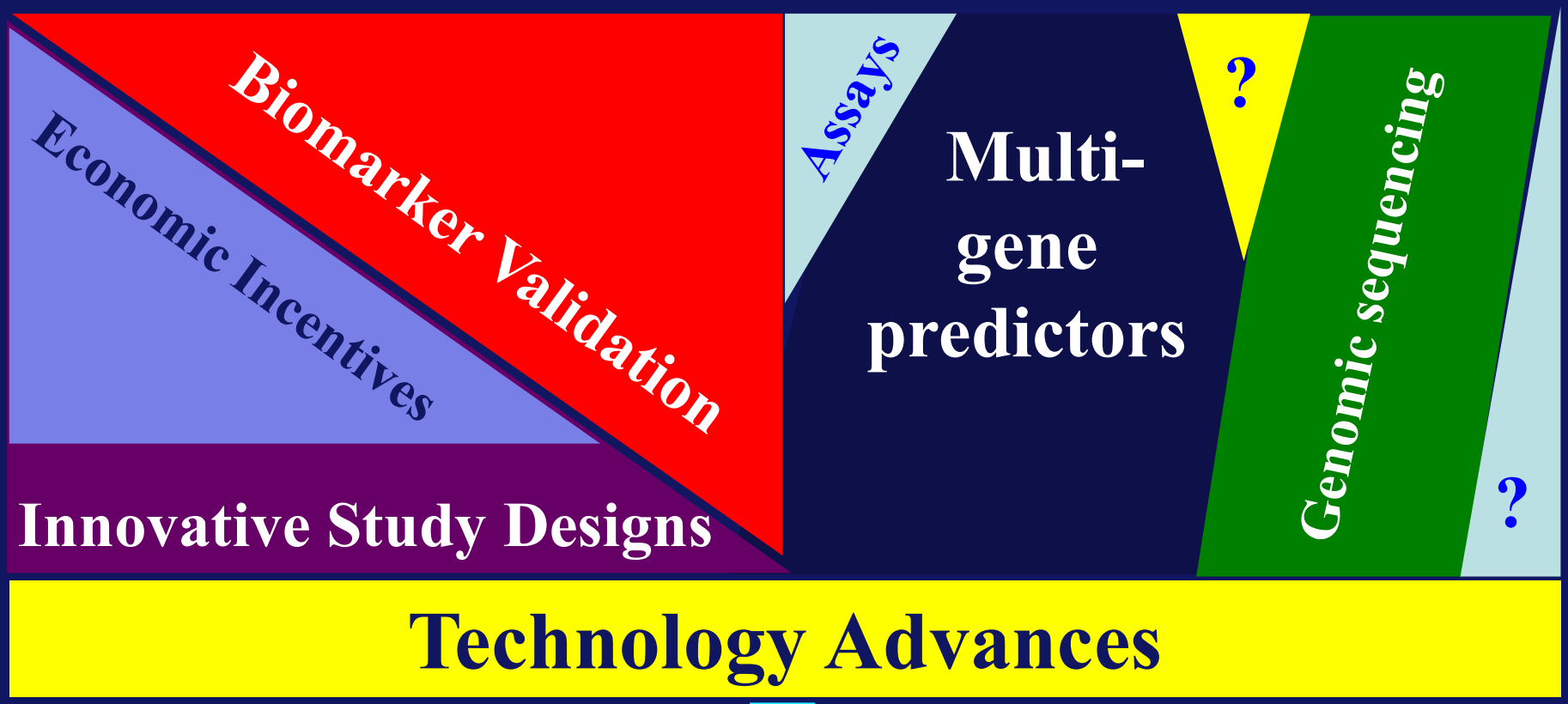
Can We Do Better?



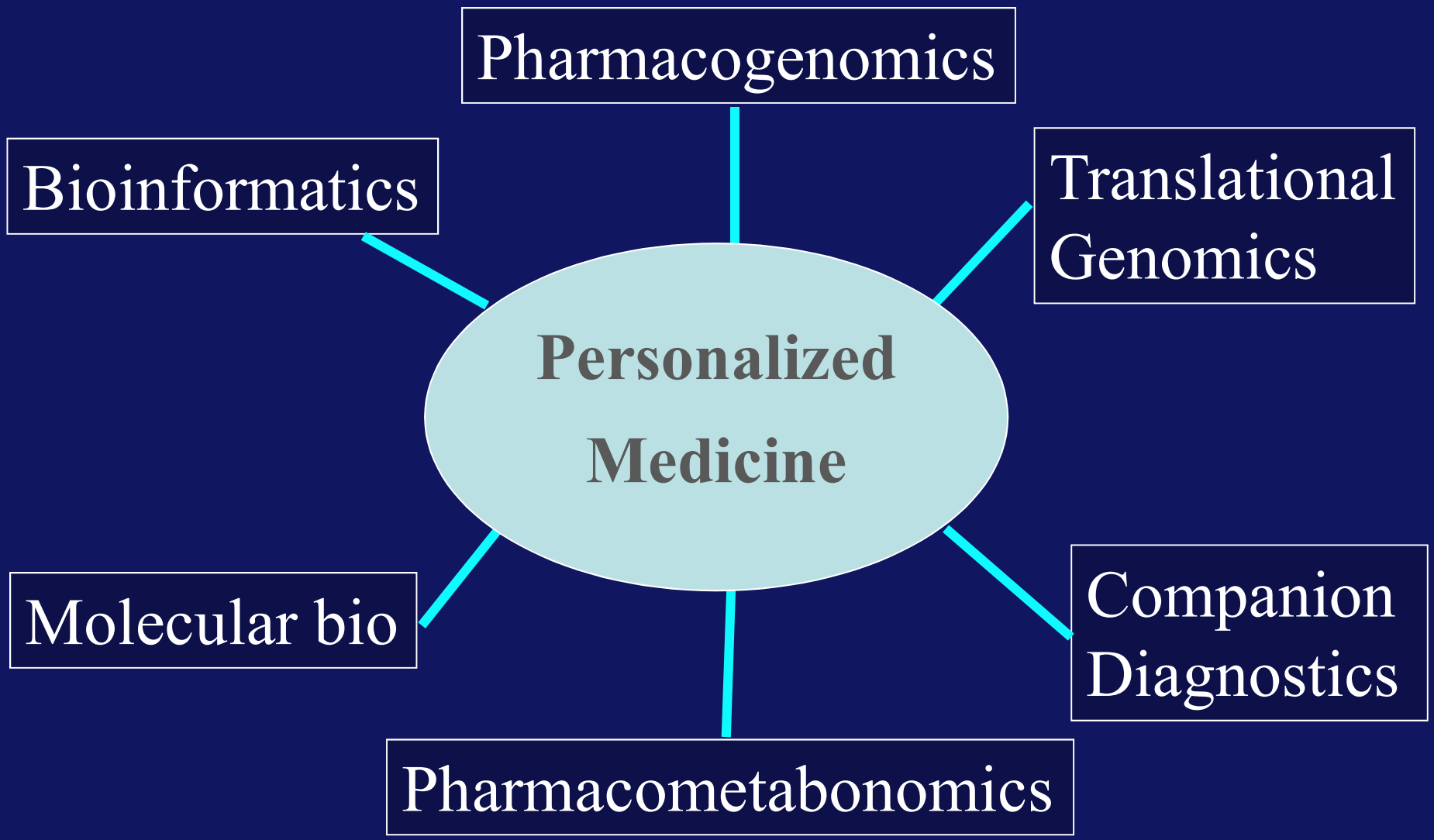
Precision Medicine



Personalized Medicine: How Do We Get There?

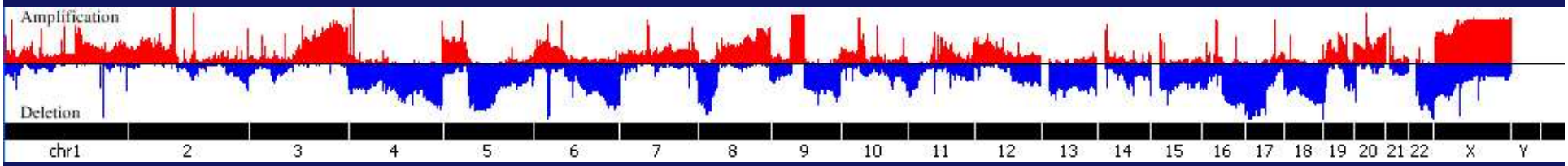


Confluence of Multiple Advances

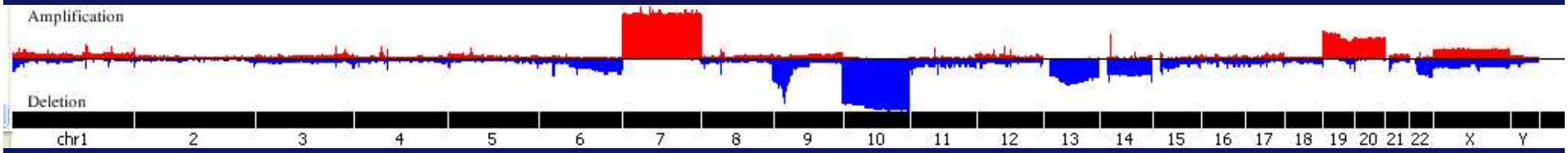


Serous Ca-Ovary –TCGA aCGH on Agilent 244K

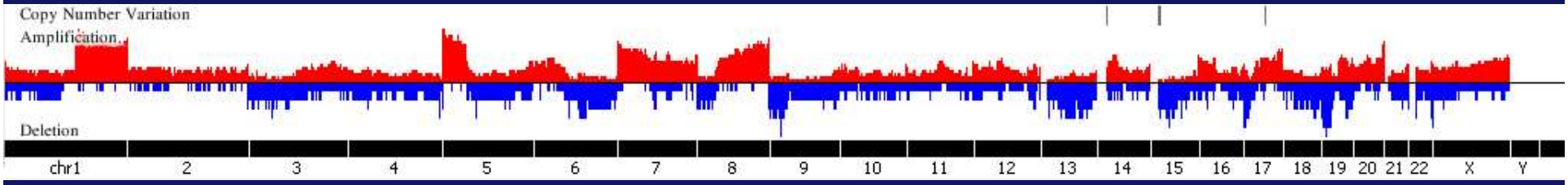
- Ovarian - TCGA



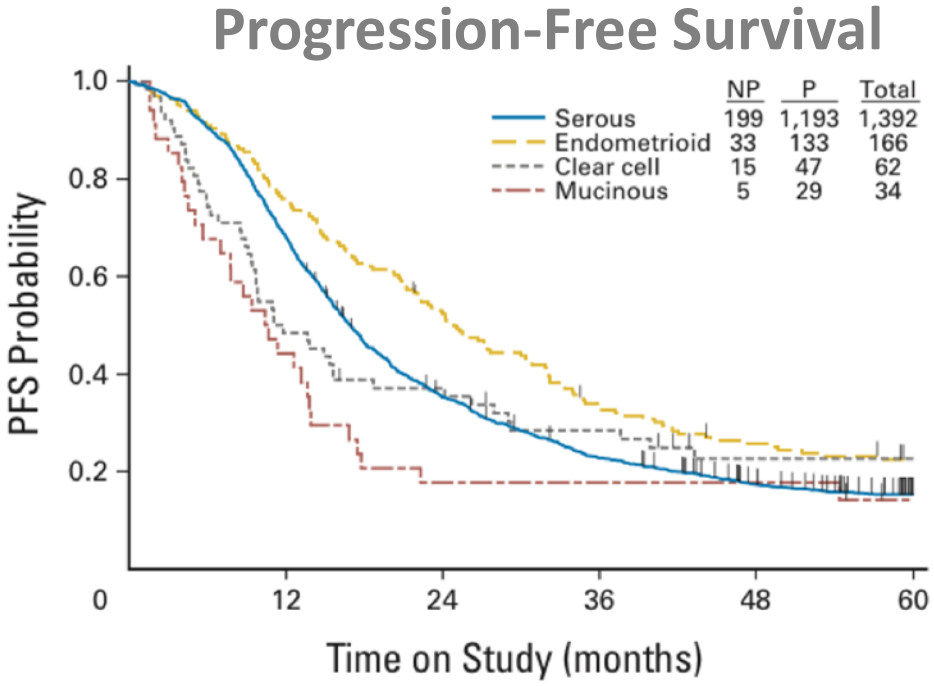
- GBM - TCGA

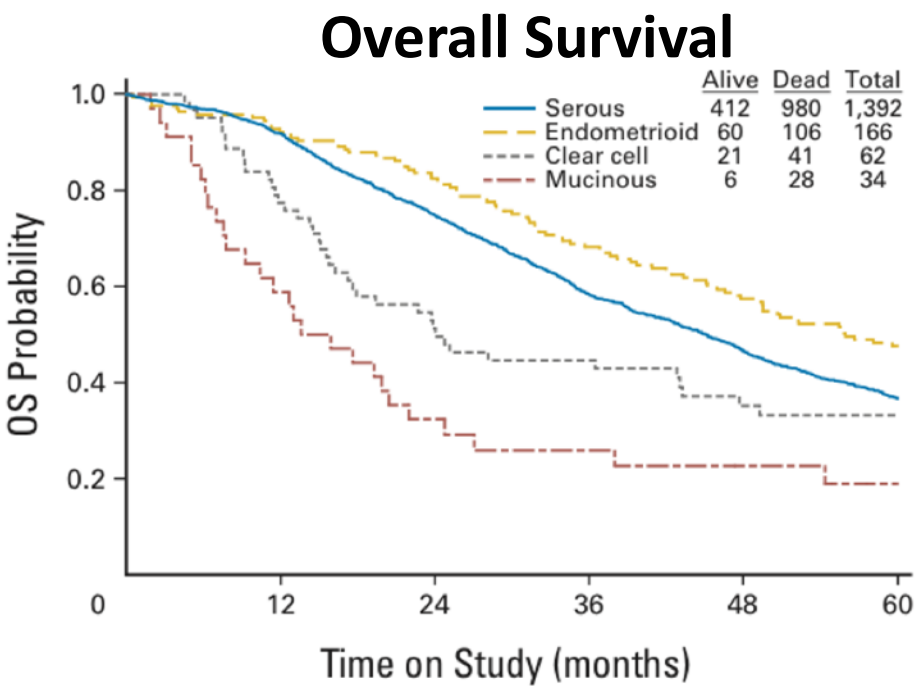


- Lung - TSP



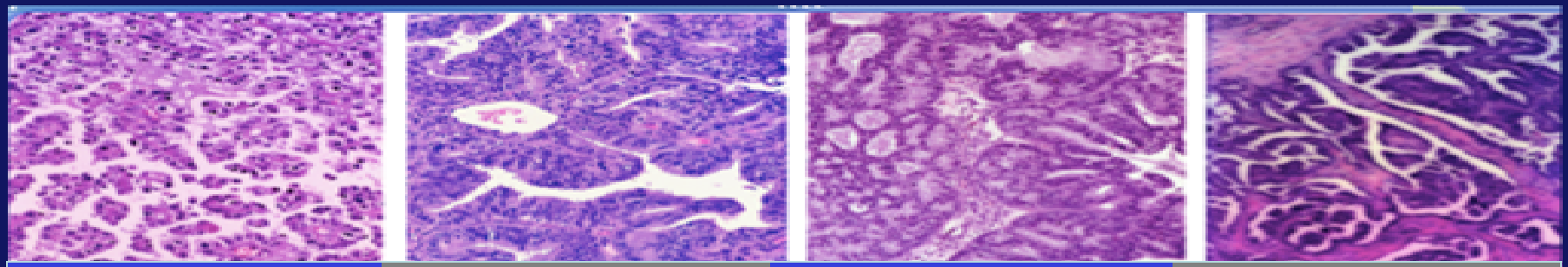
Stage III Epithelial Ovarian Cancer: Prognosis by Cell Type





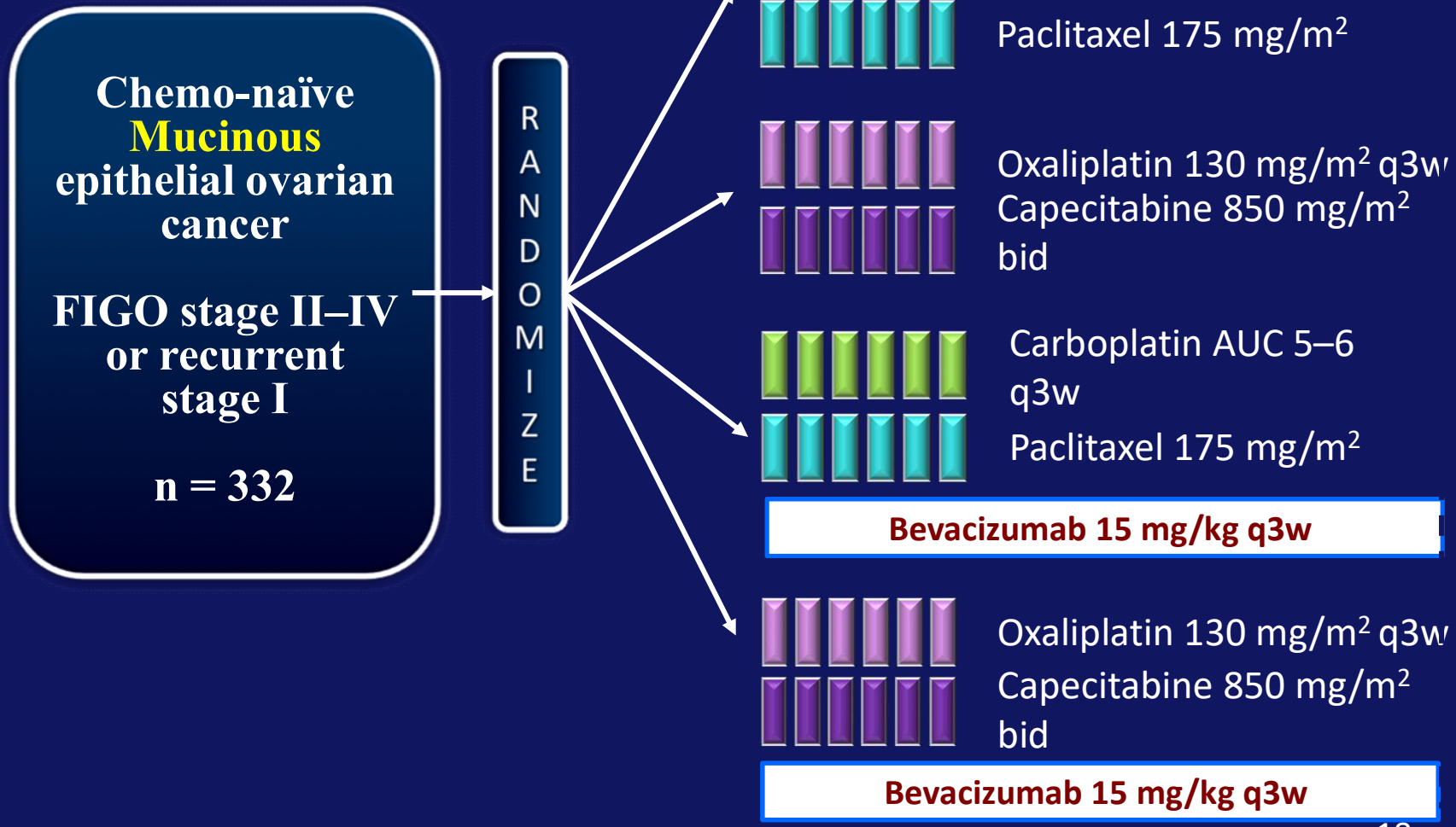
Ovarian Cancer: No longer A Single Disease

Histology

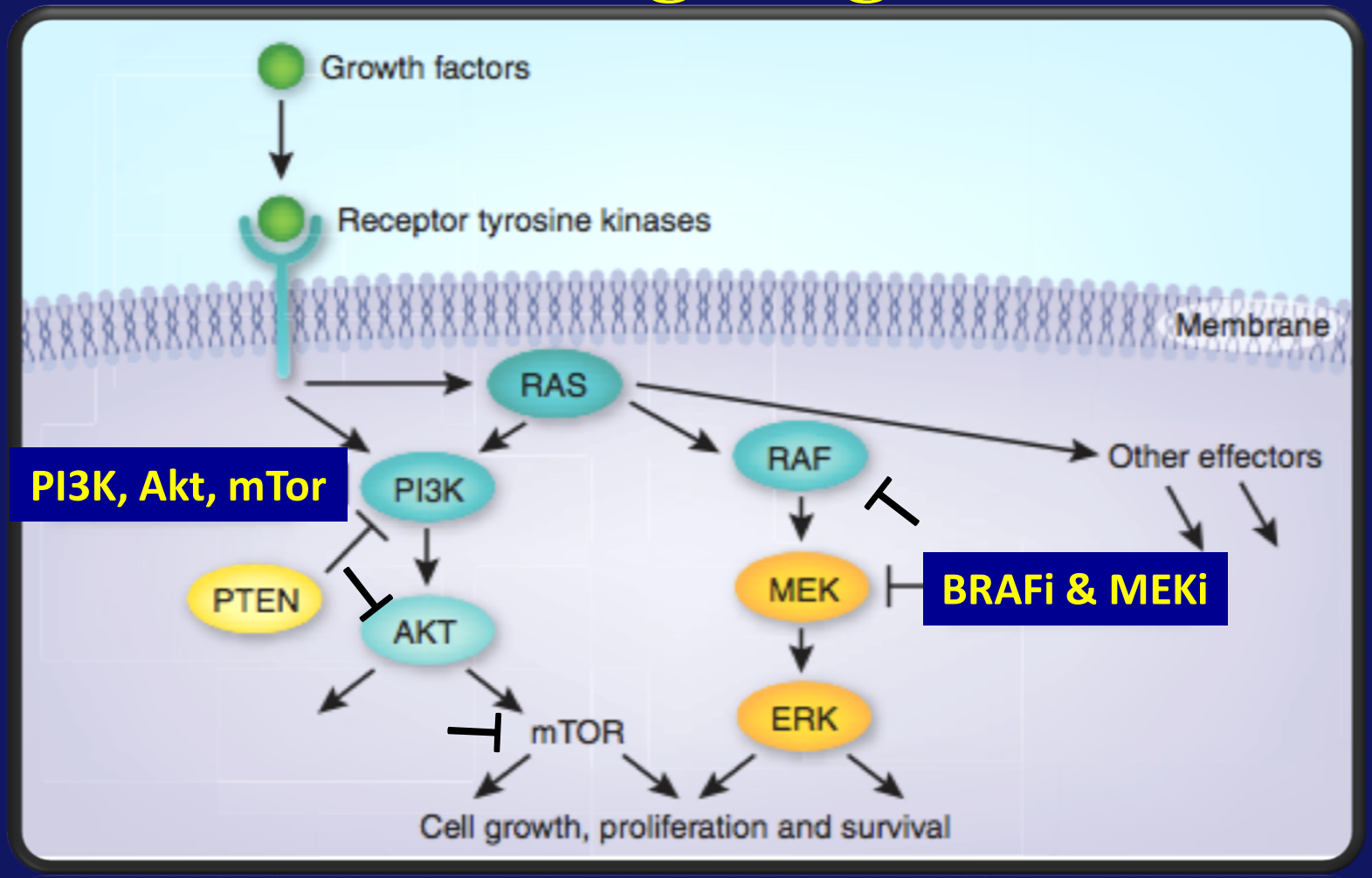


Serous	Mucinous	Endometrioid	Clear Cell
P53 Genomic Instability	K Ras	PTEN PI3K	ARID1A

GOG 241: Phase III Trial



Low Grade Serous: Biological Targeting



Rare Epithelial Ov Tumors

Clinical Trial	Phase	Disease Setting	Investigational Drug	Histologic Subtype	Results
GOG 0241	III	Newly diagnosed	Oxaliplatin Capecitabine Bevacizumab	Mucinous	Pending (Closed prematurely)
GOG 0239	II	Recurrent	Selumetinib	Low-Grade Serous	RR = 15%
GOG 0281	II/III	Recurrent	Trametinib	Low-Grade Serous	Ongoing
GOG 0268	II	Newly diagnosed	Temsirolimus	Clear Cell	Pending
GOG 0254	II	Recurrent	Sunitinib	Clear Cell	RR = 7%
GOG 0283	II	Recurrent	Dasatinib	Clear Cell	Ongoing
GY-001	II	Recurrent	Cabozantinib	Clear Cell	Ongoing

Herzog et al. FDA Workshop; 2015

Why Targeted Therapies?

Improved Efficacy

Overcoming drug resistance
Enhanced tumor delivery
Tumor specificity

Altered Toxicities

< Myelosuppression
< Alopecia
< Neuropathy
> Hemorrhage
> DVT

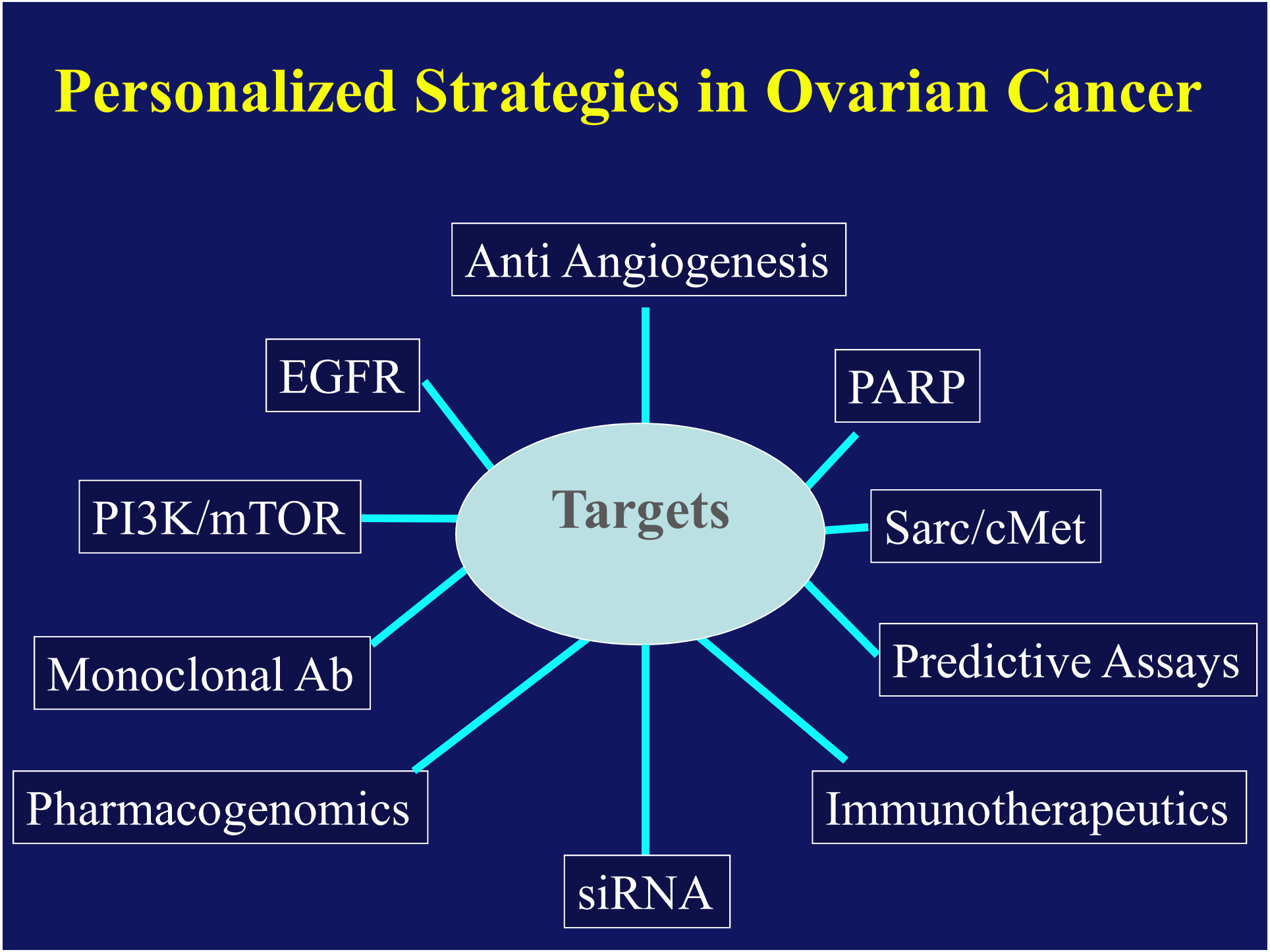
Intellectual Appeal

Rational Targets
New era
Numerous molecular aberrancies

Challenges

Assessing Activity
Defining relevant targets
Costs

Personalized Strategies in Ovarian Cancer



GOG Ovarian Biologic 170 Series

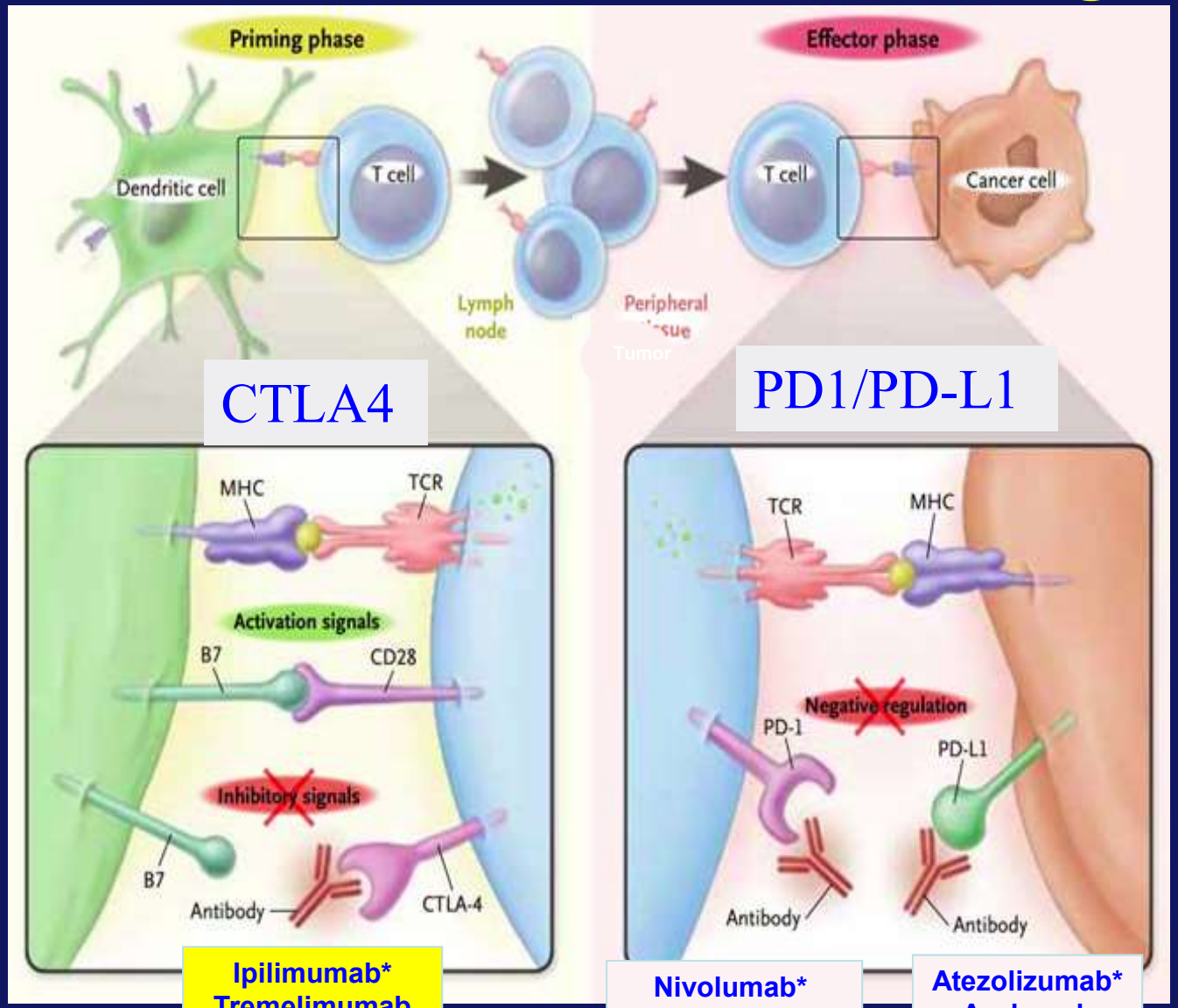
Protocol	PI	Agent	N=	RR	% PFS 6 mo
170-B	Hurteau	IL-12	26	4%	Not reported
170-C	Schilder	Iressa	27	4%	15%
170-D	Burger	Bevacizumab	62	21%	40%
170-E	Schilder	Gleevec	26	2%	40%
170-F	Matei	Bay 43-9006 (raf kinase-I)	68	3%	24%
170-G	Garcia	Lapatinib	28	15%	8%
170-H	Modesitt	Vorinostat	27	4%	7%
170-I	Behbakht	Temsorilomus	44	9%	24%
170-J	Usha L	Enzastaurin	27	7%	11%
170-L	Schilder	AMG-706	34	5%	Too Toxic
170-M	Schilder	Dasatinib	34	0%	21%
170-N	Gold M	Urokinase Deprived Peptide	31	0%	7%
170-P	Martin	AMG -102	31	Pending	
170-Q	Alvarez	EGEN-001 Il-12 Plasmid IP		Pending	

Angiogenesis as a Target: Ovarian

Study	Agent	Target	HR-PFS (95% CI)	HR-OS (95% CI)
GOG 218[1]	Bevacizumab	VEGF Ligand - Antibody	0.72 (0.63-0.82)	0.89 (0.75-1.04)
ICON7[2]	Bevacizumab		0.81 (0.70-0.94)	0.99 (0.85-1.14)
AURELIA[5]	Bevacizumab		0.48 (0.38-0.60)	0.85 (0.66-1.08)
OCEANS[7]	Bevacizumab		0.53 (0.41-0.70)	0.96 (0.76-1.21)
AGO-OVAR12[3]	Nintedanib	VEGFR, FGFR, PDGFR	0.84 (0.72-0.98)	NR
AGO-OVAR16[4]	Pazopanib		0.77 (0.64-0.91)	0.99 (0.75-1.32)
ICON6[8]	Cediranib	VEGFR 1/2/3	0.57 (0.44-0.74)	0.70 (0.51-0.99)
TRINOVA-1[6]	Trebananib	Angiopoietin ligand	0.66 (0.57-0.77)	0.86 (0.69-1.08)

2. Perren TJ et al . *N Engl J Med*. 2011;365:2484–2496.
3. du Bois A et al. *J Clin Oncol*. 2013;31(18suppl):LBA5503.
4. du Bois A et al. LBA ESGO 2013 Liverpool, UK
6. Monk BJ, et all., LBA ESGO, Liverpool, UK
7. Aghajanian C et al. *J Clin Oncol*. 2012;30:2039–2045.
8. Ledermann JA et al . *Eur J Cancer*. 2013;*49*(suppl):LBA

Blockade of PD-1/PD-L1 or CTLA-4 Signaling



Ipilimumab*
Tremelimumab

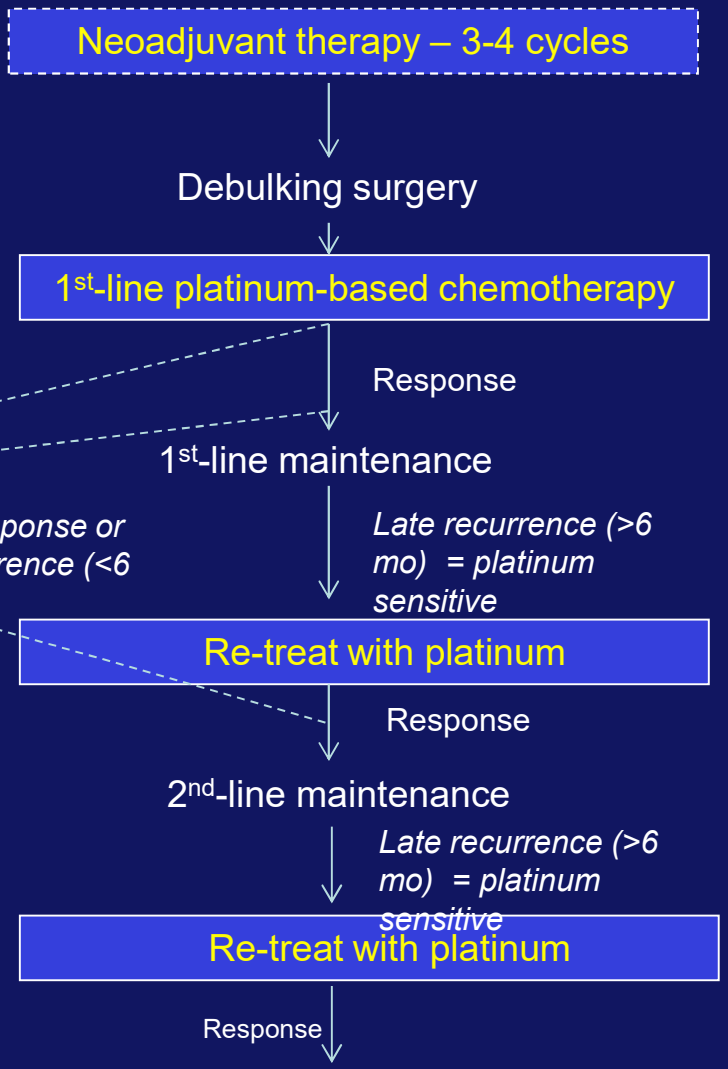
Nivolumab*
Pembrolizumab*

Atezolizumab*
Avelumab
Durvalumab

* FDA-approved

Adapted from Ribas A. *N Engl J Med*. 2012;366(26):2517-2519.

Potential Impact of Immuno-Oncology Agents on Ovarian Cancer Treatment Paradigm



= frontline

- JAVELIN Ovarian 100 (avelumab)
- Pembrolizumab + chemotherapy

Resistant/ refractory

- JAVELIN Ovarian 200 (avelumab)
- NRG GY-009 (atezolizumab)
- KEYNOTE 100 (pembrolizumab)
- Pembrolizumab + bevacizumab
- EORTC-1508 (atezolizumab)

= recurrent = PS = PS recurrence

- ATALANTE (atezolizumab)
- KEYNOTE 100 (pembrolizumab)
- Pembrolizumab + bevacizumab

PS, platinum sensitive.

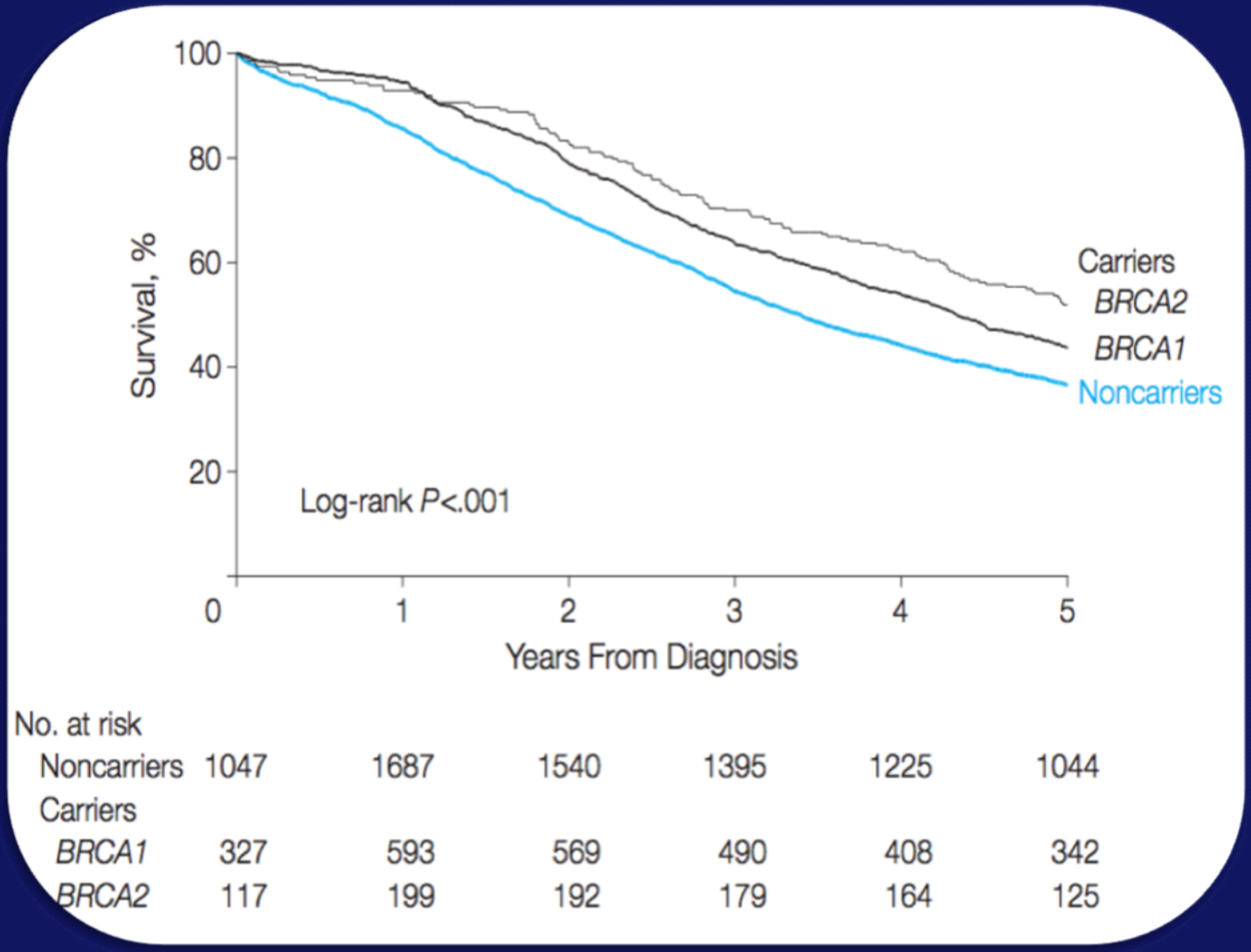
1. NCCN guidelines. Version 1.2016. 2. Clinicaltrials.gov. Accessed October 11, 2016. 3.

BRCA Deficiency in Unselected Ovarian Cancers

Type of Aberration	Frequency
Germline BRCA 1 or 2 mutation	11%
Somatic BRCA 1 or 2 mutation	7%
BRCA 1 or 2 deletions	1%
BRCA 1 or 2 expression loss	13%
Overall BRCA mutation + expression loss	**30%**

Prognostic

Why Does it Matter?



No. at risk						
Noncarriers	1047	1687	1540	1395	1225	1044
Carriers						
BRCA1	327	593	569	490	408	342
BRCA2	117	199	192	179	164	125

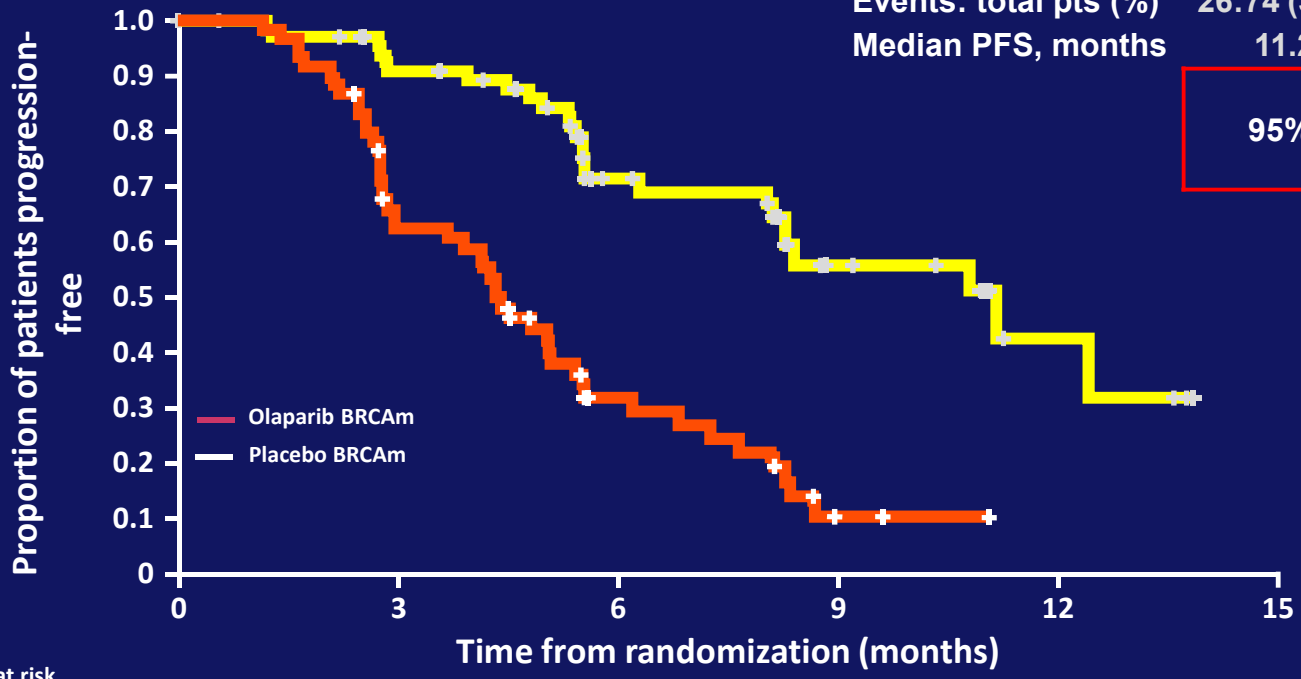
Bolton JAMA 2012

Predictive

PFS by BRCAm status

	BRCAm (n=136)	
	Olaparib	Placebo
Events: total pts (%)	26:74 (35.1)	46:62 (74.2)
Median PFS, months	11.2	4.3

HR=0.18
95% CI (0.11, 0.31);
P<0.00001

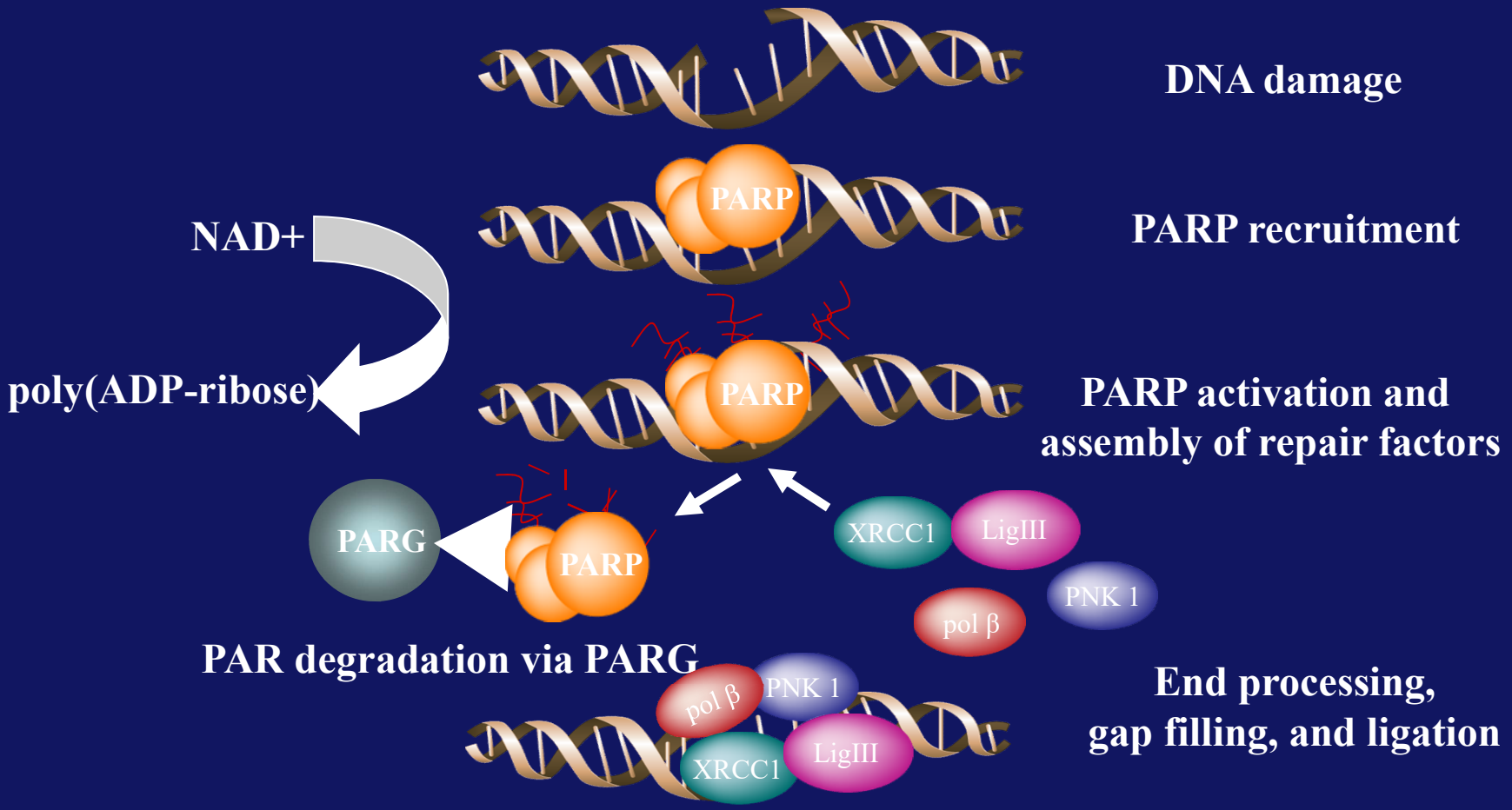


Number at risk						
Olaparib BRCAm	74	59	33	14	4	0
Placebo BRCAm	62	35	13	2	0	0

- 82% reduction in risk of disease progression or death with olaparib

Ledermann, ESMO/ECC 2013

PARP & Base Excision Repair



Ledermann J, et al. *Lancet Oncol.* 2014;15:852-861.
Khanna KK. *Nat Genet.* 2001;27:247-254.
Sanchez-Perez I. *Clin Transl Oncol.*2006;8:642-646.
Kennedy RD. *J Clin Oncol.* 2006;24:3799-3808.

BRCA1/2 Mutations in Ovarian Cancer: Who Should Be Tested?

Leading oncology societies recommend testing all women with ovarian cancer

NCCN[1]	SGO[2]	ASCO[3]
Genetic counseling and testing should be considered in women with a history of ovarian carcinoma, fallopian tube or primary peritoneal cancer	Women diagnosed with epithelial ovarian, tubal, and peritoneal cancers should receive genetic counseling and be offered genetic testing, even in the absence of family history	Genetic counseling and testing should be considered in women with epithelial ovarian, fallopian tube or primary peritoneal cancer even in the absence of family history

TEST ALL PATIENTS WITH OVARIAN CANCER

NCCN, National Comprehensive Cancer Network; SGO, The Society of Gynecologic Oncology; ASCO; American Society of Clinical Oncology.

1.NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 2.2016.
2.Lancaster et al. Gynecol Oncol. 2015;136(1):3-7.
3.Lu et al. J Clin Oncol. 2014;32(8):833-40.

PARP Inhibitors as Maintenance

- **Primary Therapy**
  - SOLO-1–Olaparib (*BRCA*^{mut} only)
- **Platinum-sensitive Recurrence**
  - SOLO-2–Olaparib (*BRCA*^{mut} only)
  - ARIEL 3–Rucaparib (Platinum-sensitive)
  - NOVA–Niraparib (*BRCA*^{mut} & HGS)

PARP Inhibitor Maintenance

	NOVA		ARIEL3		SOLO2		Study 19	
Biomarkers Assessed	BRACAnalysis CDx myChoice HRD		FoundationFocus CDx BRCA, Foundation LOH		BRACAnalysis CDx		BRACAnalysis CDx, Tumor BRACAnalysis CDx	
	Niraparib	Placebo	Rucaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
BRCA+ Med PFS	21.0	5.5	16.6	5.4	19.1	5.5	11.2	4.3
PFS Benefit	15.5		11.2		13.6		6.9	
Hazard Ratio	0.27 (p<0.001)		0.23 (p<0.0001)		0.30 (p<0.0001)		0.18 (p<0.0001)	
HRD+ Med PFS	12.9	3.8	13.6	5.4	N/A		N/A	
PFS Benefit	9.1		8.2					
Hazard Ratio	0.38 (p<0.001)		0.32 (p<0.0001)					
Overall cohort Med PFS	9.3†	3.9†	10.8	5.4	N/A		8.4	4.8
PFS Benefit	5.4†		4.3				3.6	
Hazard Ratio	0.45 (p<0.001)†		0.36 (p<0.0001)				0.35 (p<0.0001)	
BRCA-, HRD+ Med PFS	9.3	3.7	9.7	5.4	N/A		N/A	
PFS Benefit	5.6		4.3					
Hazard Ratio	0.38 (p<0.001)		0.44 (p<0.0001)					
HRD negative Med PFS	6.9	3.8	6.7	5.4	N/A		7.4*	5.5*
PFS Benefit	3.1		1.3				1.9*	
Hazard Ratio	0.58 (p=0.02)		0.58 (p=0.0049)				0.54 (p=0.0075)*	

†gBRCA negative

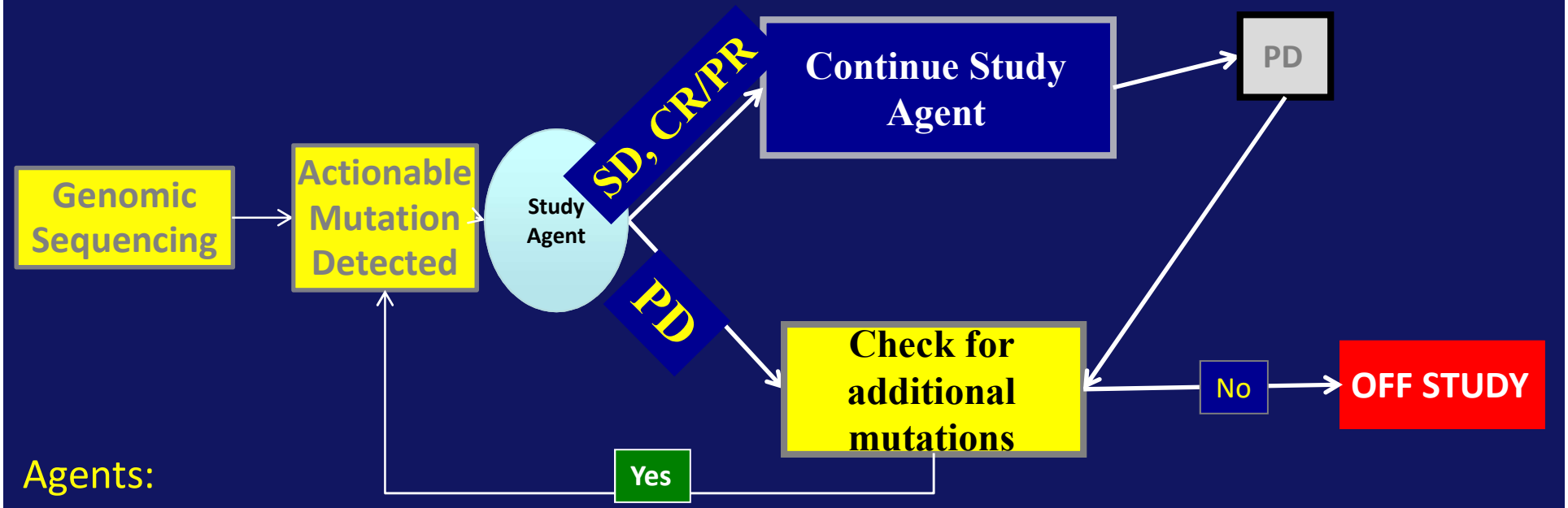
*tBRCA negative

Current Status of PARP Inhibitors

PARP inhibitors	FDA status	Indication
Olaparib	Approved	• Maintenance treatment in patients in a CR or PR to first-line platinum-based therapy • Maintenance treatment in patients with recurrent disease in a CR or PR to platinum-based therapy • Recurrent *BRCA*-mutated ovarian cancer, 3 or more lines of chemotherapy
Rucaparib	Approved	• Maintenance treatment in patients with recurrent disease in a CR or PR to platinum-based therapy • Recurrent *BRCA*-mutated ovarian cancer, 2 or more lines of chemotherapy
Niraparib	Approved	Maintenance treatment with response to platinum chemo
Veliparib	Still in studies	–

Lynparza [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018.
Rubraca [package insert]. Boulder, CO: Clovis Oncology, Inc.; 2018.
Zejula [package insert]. Waltham, MA: Tesaro, Inc.; 2019.

Molecular Analysis for Therapy Choice: NCI "MATCH"



Agents:

- AMG595: EGFRvIII – ADC (DM1)
- AZD9291: T790M mutation – irreversible EGFR inhibitor
- Trametinib: non-V600E BRAF activating mutation – MEKi
- Dabrafenib + Trametinib: BRAF V600E mutation

Stats: Simon 2-stage

- **30 patient cohorts**
- **5% < RR < 25%**
- **15% < PFS6 < 35%**

Potential Pitfalls & Barriers to Precision Medicine

Driver vs. Passenger
Noise: Signal
Complexity; Multi-omics

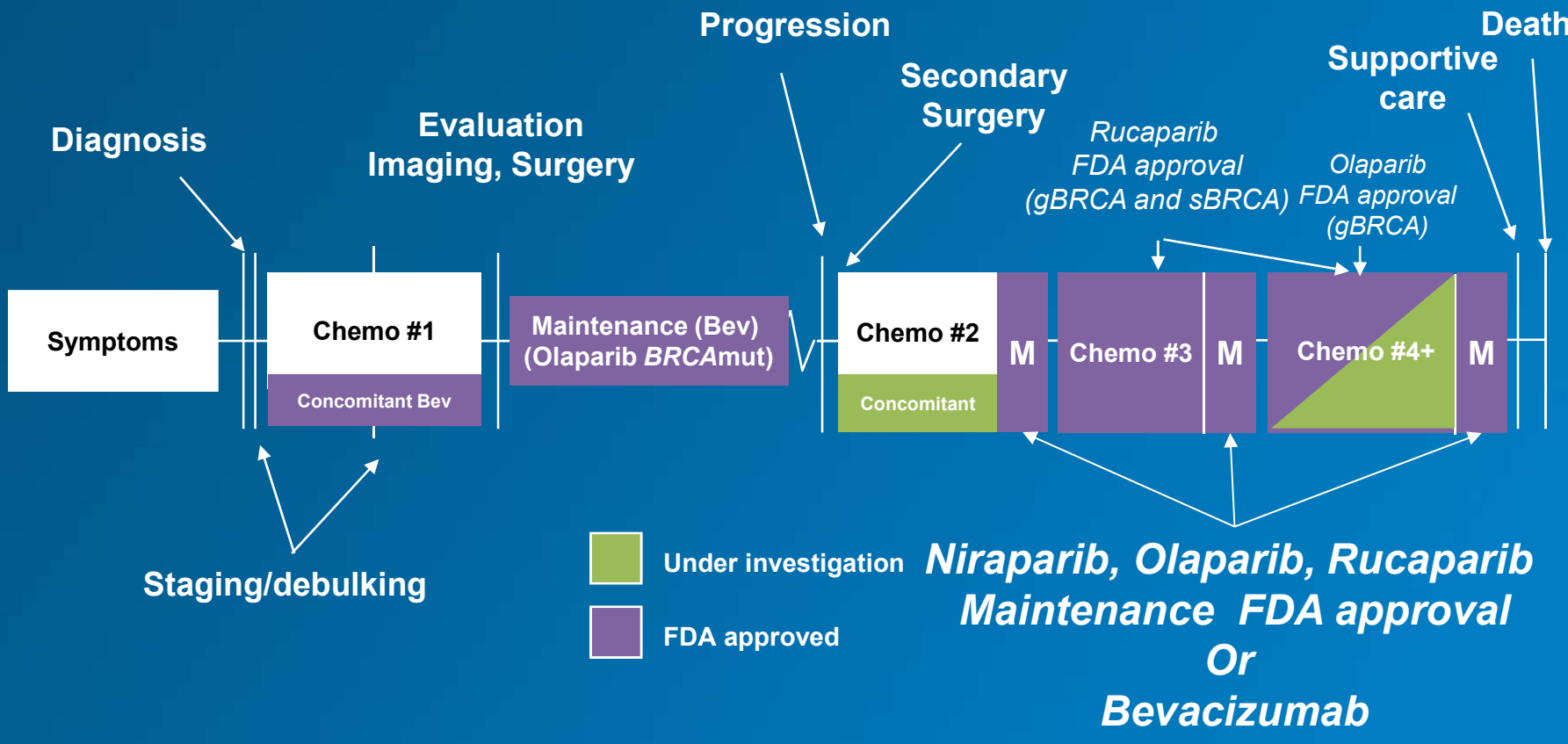
Immuno-Oncology
Tumor-stomal relationships
Sampling stroma

Prophylactic Surgery:
VUS or + Panel tests
with low penetrance genes

Validation
Prospective data lacking
Biomarker ID

Tumor Heterogeneity
Primary vs. Met
Intratumoral

Treatment Paradigm for 2019



Conclusions

- Individualization based on histology & pathways
- Recognition of unique drivers in rare tumors & those subject to innate or inducible synthetic lethality is ushering in tumor-specific therapy
- NextGen technologies & systems biology will dynamically profile vulnerabilities
- Need to better merge basic science discovery with clinical trial mechanisms
- Clinical trials must adapt to changing paradigms
  - Smaller, Smarter Trials with larger Deltas


Thank You!