
*Azienda Ospedaliera Universitaria Policlinco «P.Giaccone» Palermo*
*UOC Oncologia Medica*
*Direttore Prof. Antonio Russo*

# *Lo stato dell'arte nel carcinoma ovarico: Il Trattamento Medico*

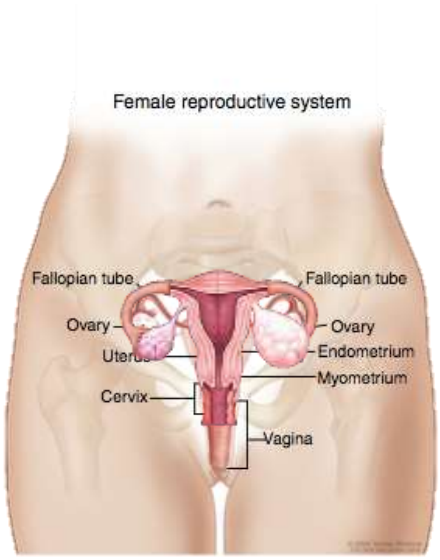
***Lorena Incorvaia***

# Dichiarazione conflitto di interessi

**Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.**

X Non ho rapporti (finanziari o di altro tipo) con le Aziende del farmaco

☐ Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco




# Ovarian Cancer: Setting the scene

# 1. Ovarian Cancer: Setting the scene

## 5 Y survival

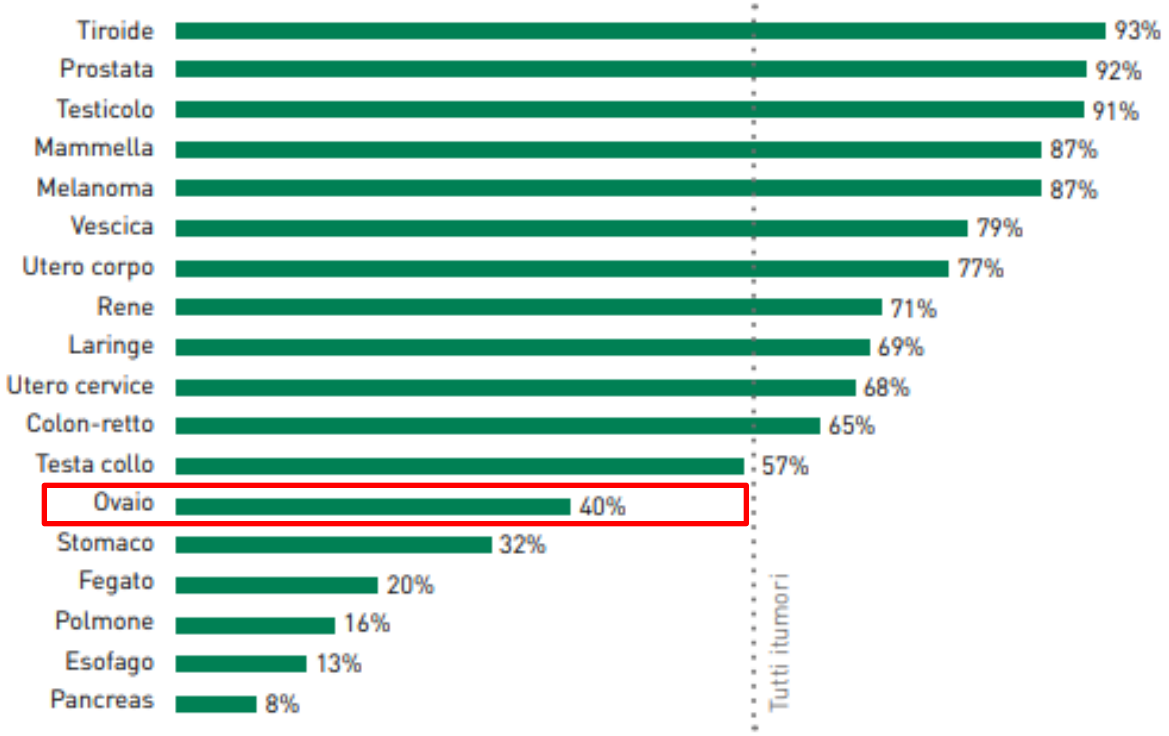




**FIGURA 6. Sopravvivenza netta a 5 anni dalla diagnosi (standardizzata per età) per il periodo di incidenza 2005-2009 (pool AIRTUM), uomini e donne**

→ **5 Y survival <25% for stage III/IV**

# 2. Ovarian Cancer: Setting the scene

## Mortality rates

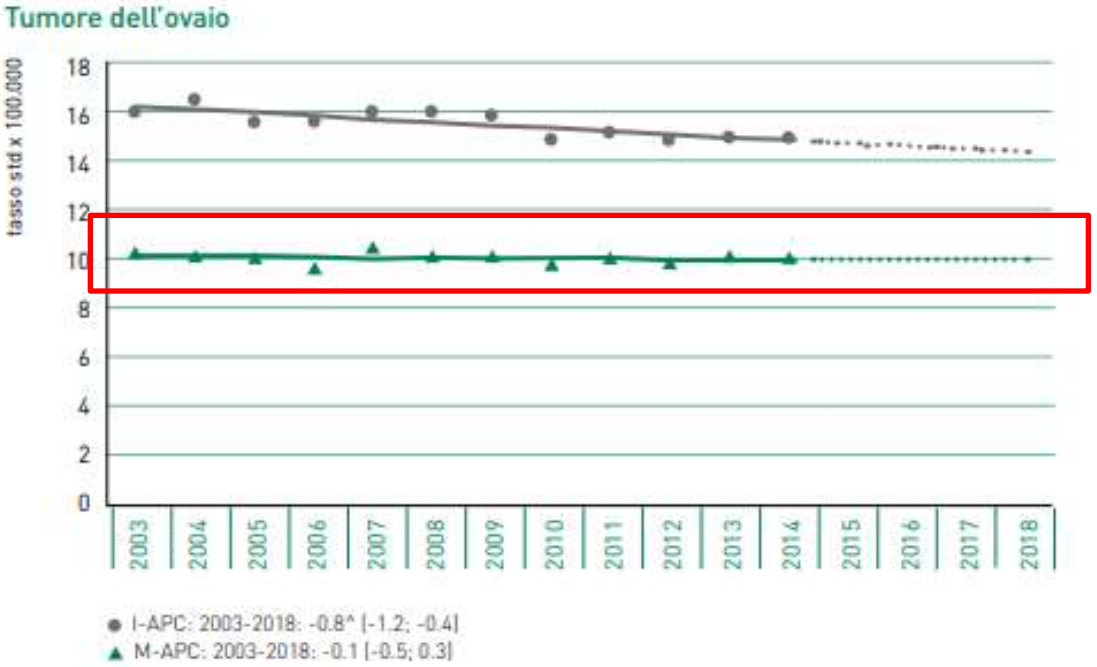
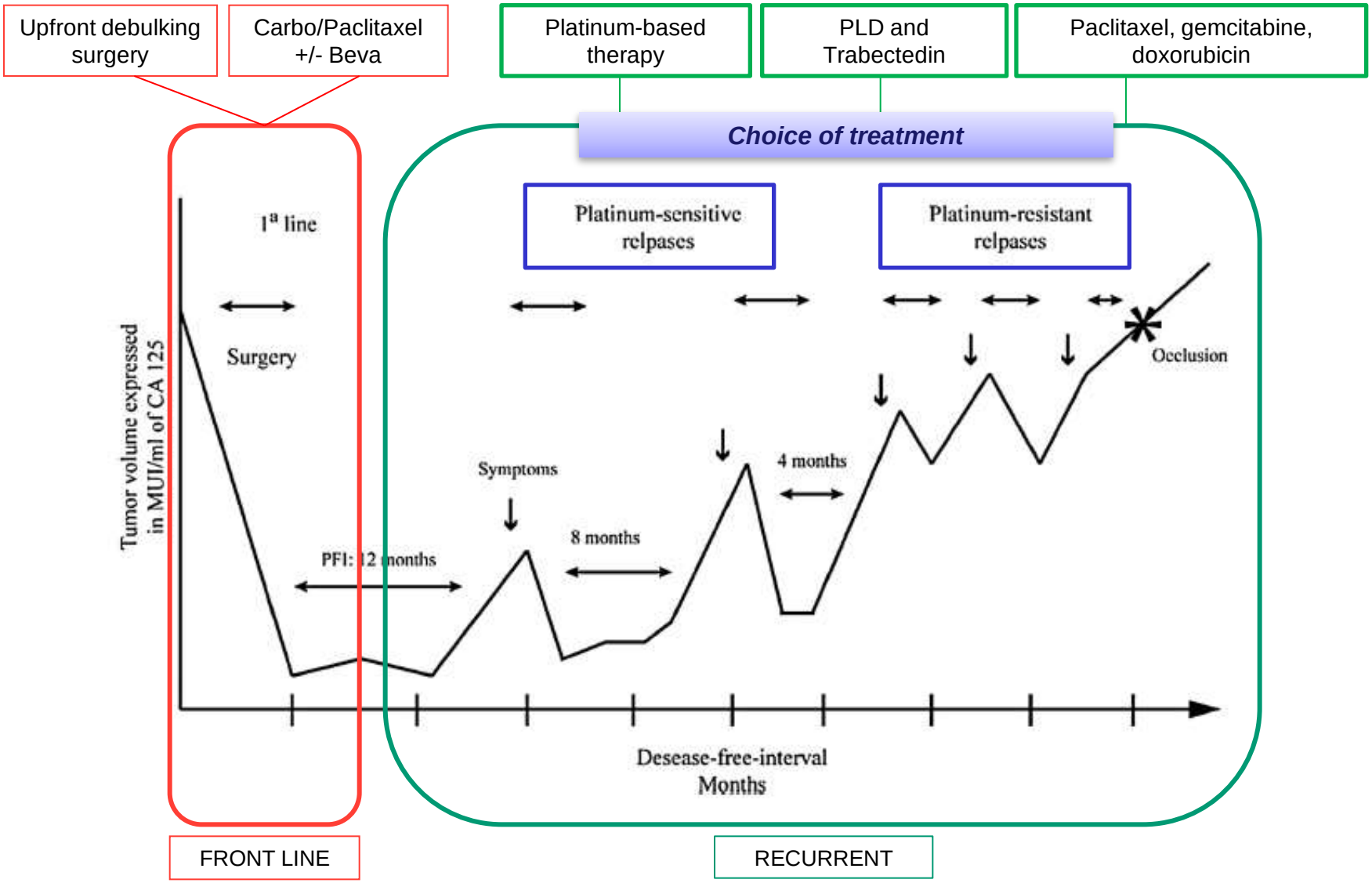




**FIGURA 26. Tumore dell'ovaio. AIRTUM: stima dei trend tumorali di incidenza e mortalità 2003-2018. Tassi standardizzati nuova popolazione europea 2013**

APC = Annual Percent Change (variazione percentuale media annua), I = incidenza, M = mortalità.

→ **No improvement in ovarian cancer mortality rates**

# 3. Ovarian Cancer: Setting the scene

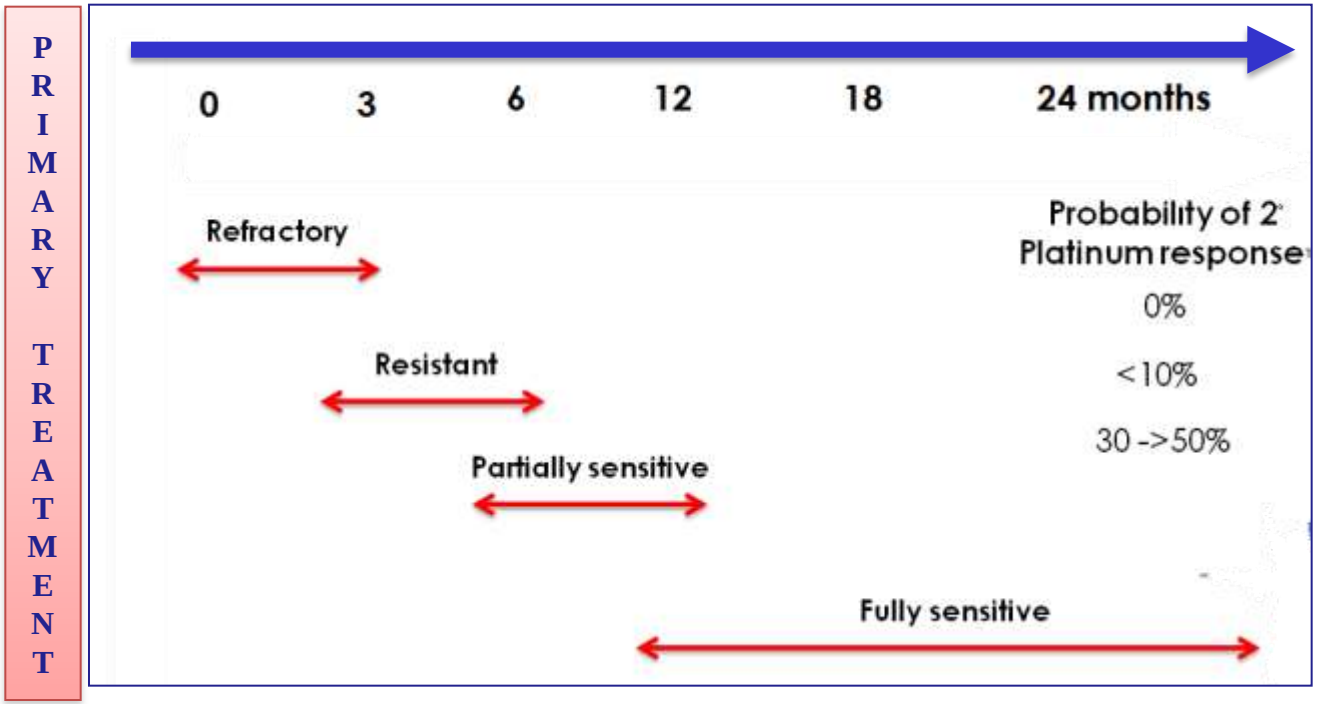



→ **No new front-line therapy for >20 years**

# *Choice of treatment: What did we know?*

## The *platinum free interval* dogma

Relapsed ovarian cancer categories



# Questions relavant to the medical treatment of patients with Advanced Ovarian Cancer

# 1) How to treat the patients in First Line

→ The importance of **optimal primary surgery.**

**Fundamental principles of therapy remain the same**

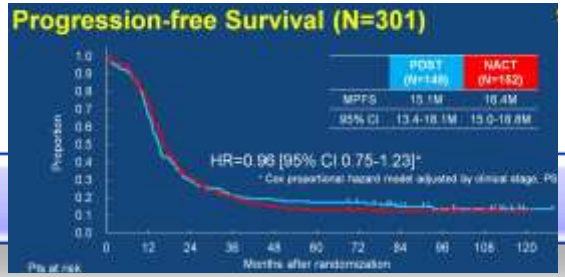
Complete tumour resection: the most important prognostic factor

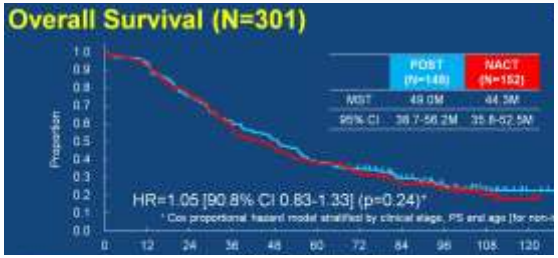
?

**Comparison of survival between upfront primary debulking surgery versus neoadjuvant chemotherapy for stage III/IV ovarian, tubal and peritoneal cancers in phase III randomized trial: JCOG0602.**

Onda T, Satoh T, Saito T, Kasamatsu T, Nakanishi T, Takehara K, Miyamoto K, Wakabayashi M, Okamoto A, Ushijima K, Kobayashi H, Kawana K, Yokota H, Takano M, Omatsu K, Watanabe Y, Yamamoto K, Yaegashi N, Kamura T, Yoshikawa H, Japan Clinical Oncology Group

UMIN Clinical Trials Registry: UMIN000000523



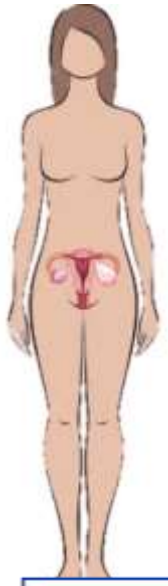




**Diagnosis**

Upfront **debulking surgery**

# 1) How to treat the patients in First Line

→ The role of **Chemotherapy** and **Maintenance**



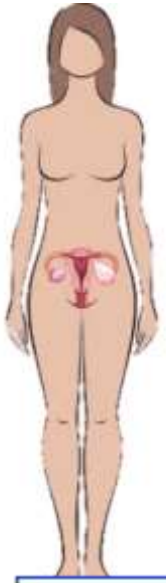
- → **Weekly regimens** not improve PFS or OS
- → **Intraperitoneal chemotherapy/HIPEC** is not a standard of care
- → 3-weekly **carboplatin-paclitaxel** remains the standard-of-care chemotherapy
- → **Bevacizumab** in stage III-IV should be considered in addition to carbo/paclitaxel: improves PFS

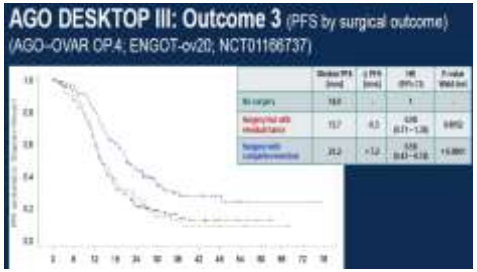
**Diagnosis**

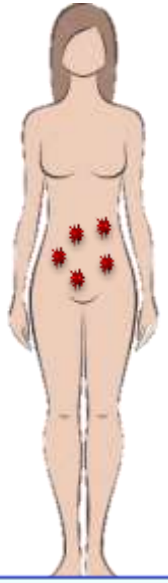
Upfront **debulking surgery**

3-weekly **carboplatin-paclitaxel**

**Bevacizumab** → Maintenance





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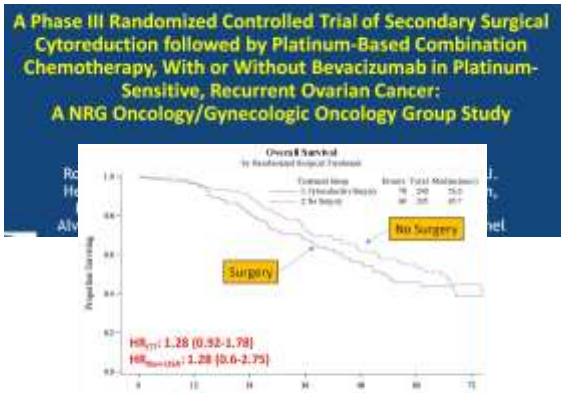
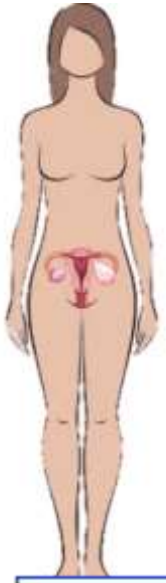


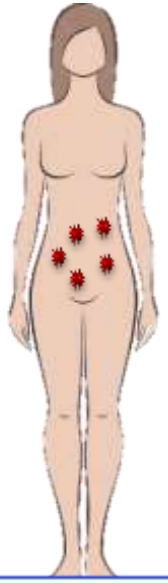

**Diagnosis** → **Recurrent Disease**

(Cytoreductive surgery)

# 2) How to Treat the Recurrence

→ **Surgery** at recurrence?





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Diagnosis

Recurrent Disease

(Cytoreductive surgery)

Platinum-based 2nd-line chemotherapy

**Bevacizumab**

**Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17**

Sandro Pignata, Domenica Lorusso, Florence Joly, Ciro Gallo, Nicoletta Colombo, Cristiana Sessa, Aristotelis Bamias, Carmela Pisano, Frédéric Selle, Eleonora Zaccarelli, Giovanni Scambia, Patricia Pautier, Maria Ornella Nicoletto, Ugo De Giorgi, Coraline Dubot, Alessandra Bologna, Michele Orditura, Isabelle Ray-Coquard, Francesco Perrone, Gennaro Daniele

on the behalf of MITO, GINECO, MaNGO, SAKK and HeCOG groups

# 2) How to Treat the Recurrence

**Bevacizumab:** - With platinum-based 2nd-line CT followed by **maintenance:** recommended
- After a bevacizumab containing I line: MaNGO OV2B-ENGOT OV17 Trial

**Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17**

Sandro Pignata, Domenica Lorusso, Florence Joly, Ciro Gallo, Nicoletta Colombo, Cristiana Sessa, Aristotelis Bamias, Carmela Pisano, Frédéric Selle, Eleonora Zaccarelli, Giovanni Scambia, Patricia Pautier, Maria Ornella Nicoletto, Ugo De Giorgi, Coraline Dubot, Alessandra Bologna, Michele Orditura, Isabelle Ray-Coquard, Francesco Perrone, Gennaro Daniele

on the behalf of MITO, GINECO, MaNGO, SAKK and HeCOG groups

# Study Design

RANDOM

1:1

**Standard**

**Platinum-Based Chemotherapy**

**Experimental**

**Platinum-Based Chemotherapy plus Bevacizumab**

**Platinum-based Chemotherapy:**

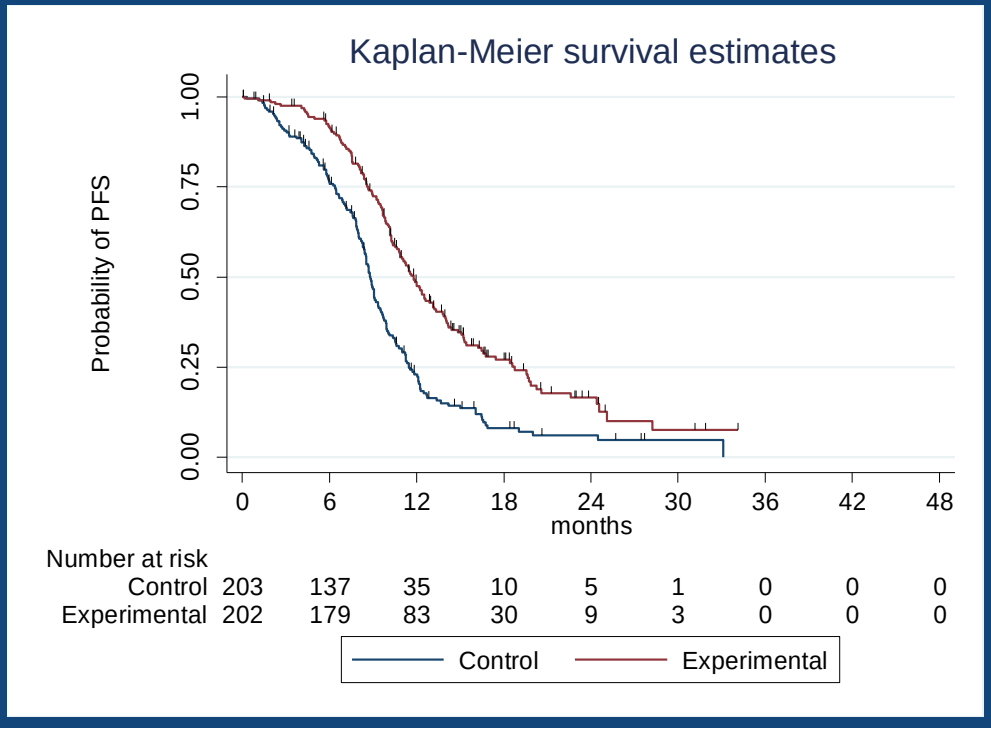
- Carboplatin + Paclitaxel +/- Beva 15mg/kg q 21
- Carboplatin + Gemcitabine +/- Beva 15mg/kg q 21
- Carboplatin + PLD q 28 +/- Beva 10mg/kg q 14

**Stratification:**

- center
- relapse during or after 1° line Beva
- performance status
- chemo backbone

Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17

# PFS Investigator assessed (primary end-point)




| | Standard | Experimental | Log-Rank P |
|---|---|---|---|
| # events | 161 | 143 | |
| Median PFS | 8.8 mos | 11.8 mos | <0.001 |
| HR* (95%CI) | 0.51 (0.41-0.65) | | |

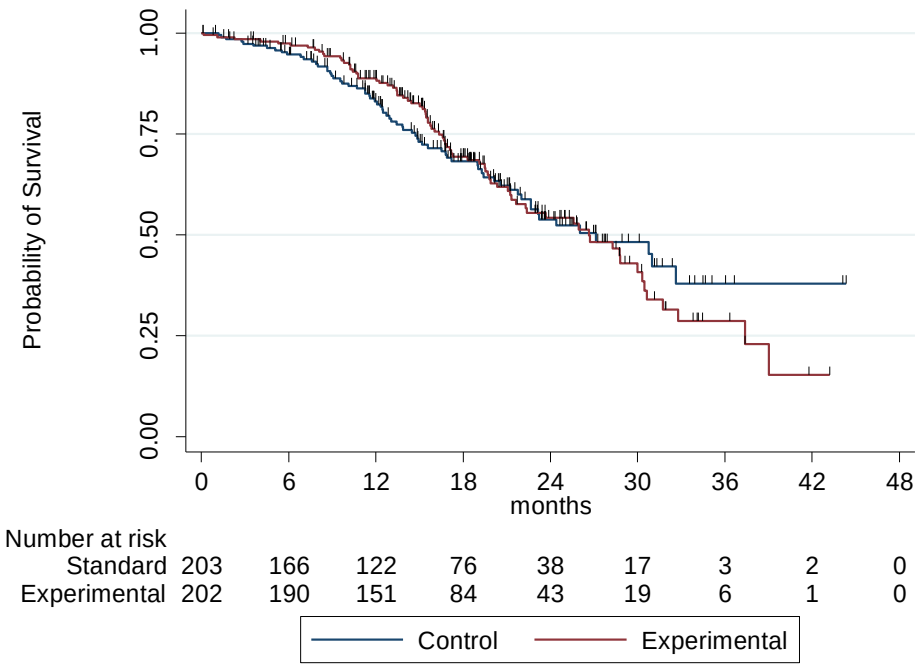
*adjusted by: age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at ini_al surgery

# Overall survival

**Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line. The randomized phase 3 trial MITO16B - MaNGO OV2B - ENGOT OV17**

Sandro Pignata, Domenica Lorusso, Florence Joly, Ciro Gallo, Nicoletta Colombo, Cristiana Sessa, Aristotelis Bamias, Carmela Pisano, Frédéric Selle, Eleonora Zaccarelli, Giovanni Scambia, Patricia Pautier, Maria Ornella Nicoletto, Ugo De Giorgi, Coraline Dubot, Alessandra Bologna, Michele Orditura, Isabelle Ray-Coquard, Francesco Perrone, Gennaro Daniele

on the behalf of MITO, GINECO, MaNGO, SAKK and HeCOG groups




| | Standard | Experimental | Log-Rank P |
|---|---|---|---|
| # events | 68 | 79 | |
| Median OS | 27.1 mos | 26.6 mos | 0.98 |
| HR* (95% CI) | 0.97 (0.70-1.35) | | |

*adjusted by: age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at ini_al surgery

# Ovarian Cancer Medical Treatment: State of art Summary

**Fundamental principles of therapy remain the same**

- ✓ The importance of **optimal surgery** upfront
- ✓ (also at recurrence?)

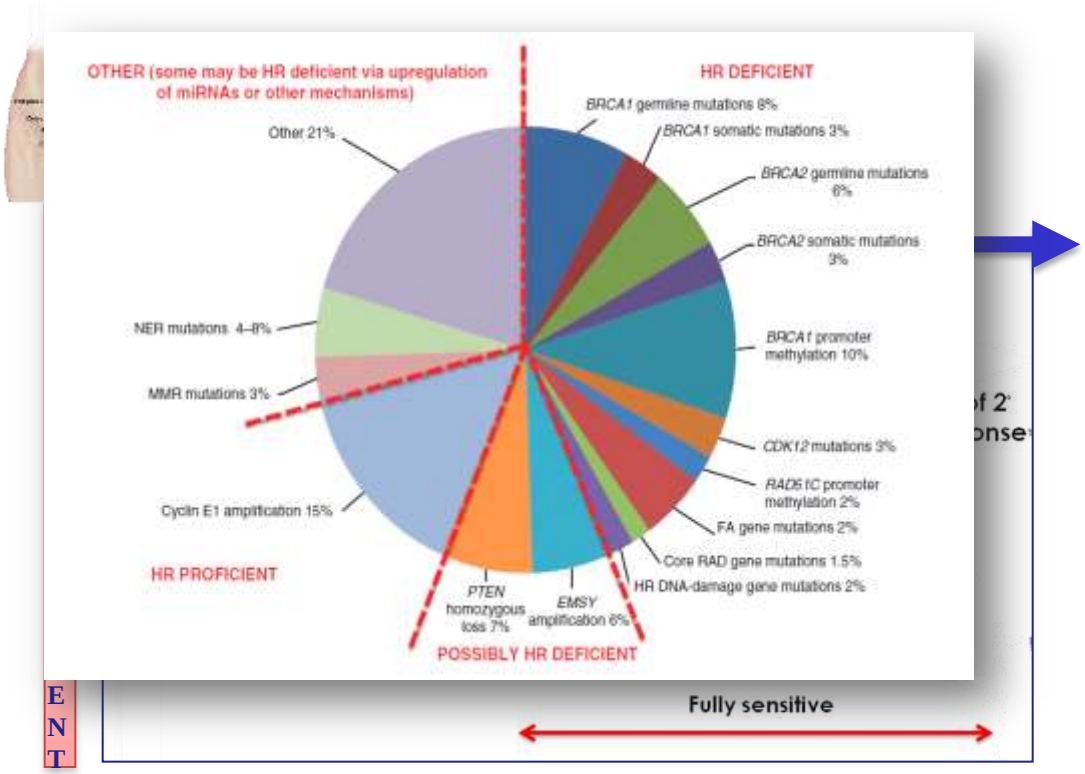
- ✓ Confirmed the role of **Chemotherapy** and **Maintenance treatment**
- ✓ Necessary further investigating of the mode of administration (intraperitoneal, with or without hyperthermia)

**Firmly introduced PARP –Inhibitors**

- ✓ **OLAPARIB** Study 19, 2014 — Indicated as maintenance therapy-**BRCA mut**
- ✓ **NIRAPARIB** Study 19, 2014 — Indicated as maintenance therapy
- ✓ **RUCAPARIB** ARIEL 3, 2017 — Indicated as single agent

# Choice of treatment: What did we know?

## The *platinum free interval* dogma




# Choice of treatment: What do we know today?

**1.** Importance of **BRCA** mutation status as **biomarker**

# Choice of treatment: What do we know today?

**1.** Importance of **BRCA** mutation status as **biomarker**

**Well established**

- ✓ Risk-reducing salpingo-oophorectomy
- ✓ PARP inhibitors in women with recurrent ovarian cancer

**Advances**

SOLO1 trial: Olaparib maintenance moves to first line Maintenance

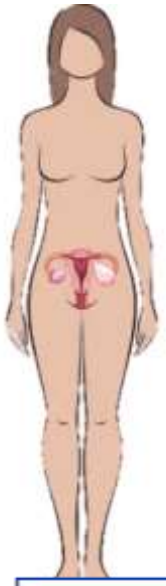

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. González-Martín, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, and P. DiSilvestro

# Ovarian Cancer Medical Treatment: Advances



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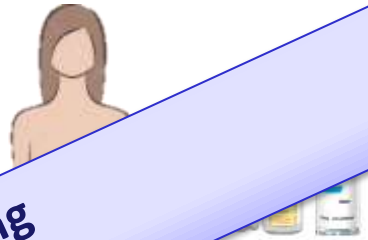


Practice-changing advances

Diagnosis

Recurrent Disease

Upfront debulking **surgery**

3-weekly **carboplatin-paclitaxel**

Olaparib

Platinum-based 2nd-line chemotherapy

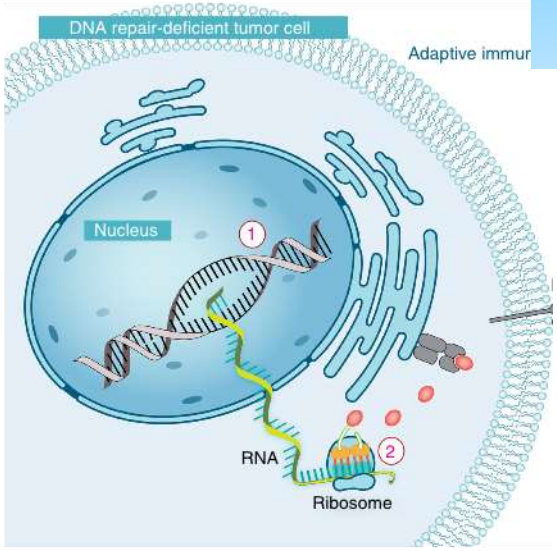
Olaparib

# 3) Ovarian Cancer Medical Treatment: Where to go next?

# 3) Ovarian Cancer Medical Treatment

## Where to go next?

**Predictive biomarkers for treatment stratification**

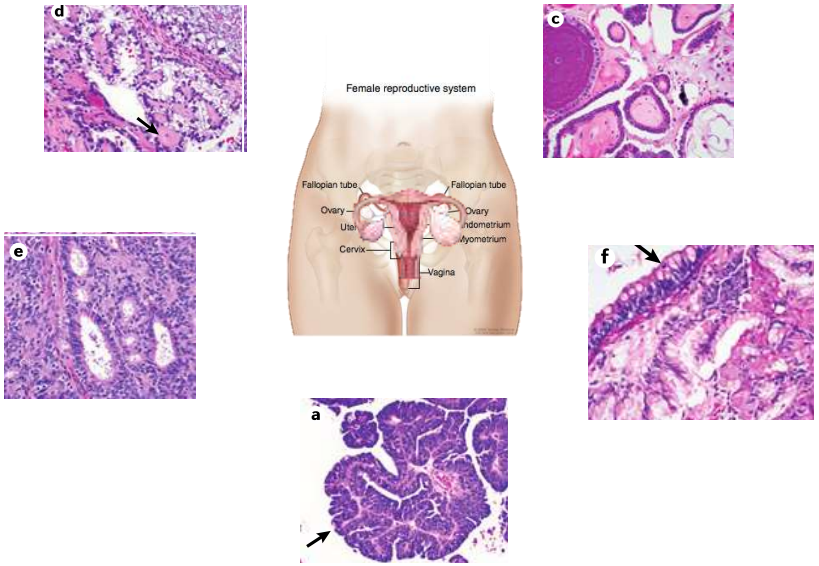


# Choice of treatment: What do we know today?

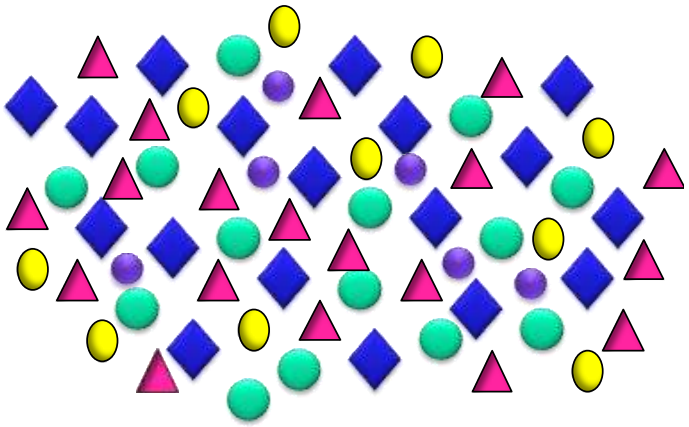
**2.** The power of using **genomics** to improve patient selection and precision medicine

**Well established**

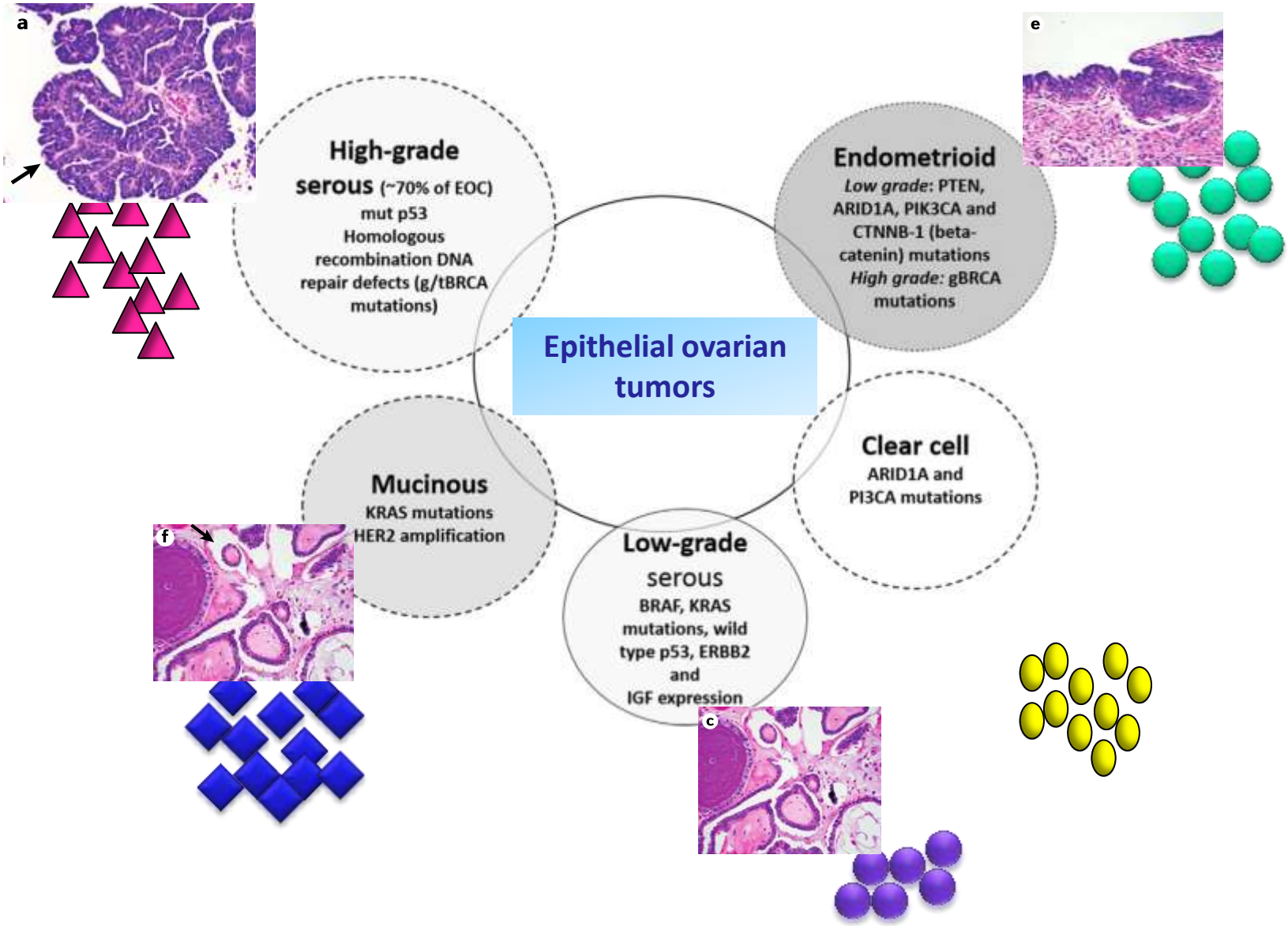
**Epithelial Ovarian cancer is not a unique disease**



# Epithelial Ovarian cancer is not a unique disease
# From singular to plural….



# Epithelial ovarian tumors: broad range of genomic variability with different histological subtypes

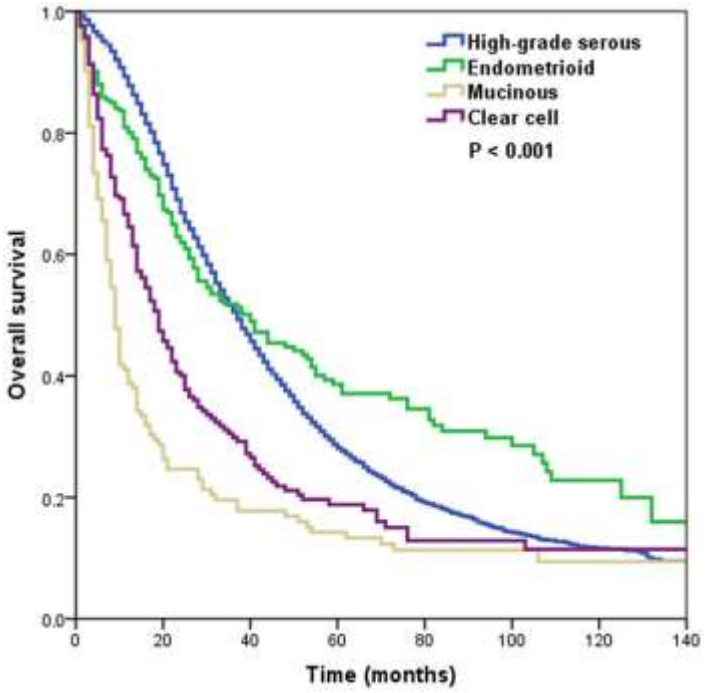


frontiers in Oncology

# The Effect of Histological Subtypes on Outcomes of Stage IV Epithelial Ovarian Cancer

ORIGINAL RESEARCH
published: 04 December 2018
doi: 10.3389/fonc.2018.00577

*Juan Zhou[1†], San-Gang Wu[2†], Jun Wang[2], Jia-Yuan Sun[3], Zhen-Yu He[3], Xin Jin[4*] and Wen-Wen Zhang[3*]*




*Zhou J Front. Oncol, 2018*


HGSOCs

| | | | | | |
|---|---|---|---|---|---|
| Tothill's | C1/MES | C2/IMM | | C5/PRO | C4/DIF |
| TCGA | MES | IMM | | PRO | DIF |
| *De novo* | s1.MES Mesenchymal | s2.IMM Immunoreactive | s3.PRO Proliferative | s4.DIF Differentiated | s5.ANM Anti-mesenchymal |
| Clinical outcomes | Lowest RD0 rate Higher SCS Worst prognosis | Better prognosis | Worse prognosis | Intermediate prognosis | Better prognosis |
| Genes | ↑ *COL11A1, POSTN, VCAN, CXCL14, ZEB1, SNA/2* | ↑ *CXCL11, CXCL10, TAP1, PSMB8, PSMB9* | ↑ *TCF7L1, HMGA2, SALL2, SOX11* | ↑ *COLEC11, STAR, ITGB4, MGLL,MLPH, DEFB1* | ↓ *COL11A1, POSTN, VCAN, DCN, ZEB1, FAP* |
| ...lated pathways | Focal adhesion ECM-receptor interaction Jak-STAT signaling | Antigen presentation Toll-like receptor T-cell receptor signaling | Cell cycle Notch signaling MMR/NER/BER | Ribosome Metabolism cytochrome P450 | Oxidative phosphorylation Peroxisome Butanoate metabolism |

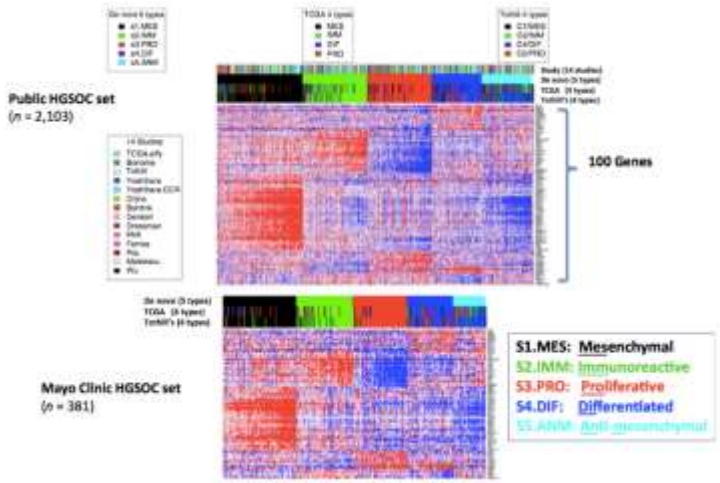
Gene expression classification of HGSOCs

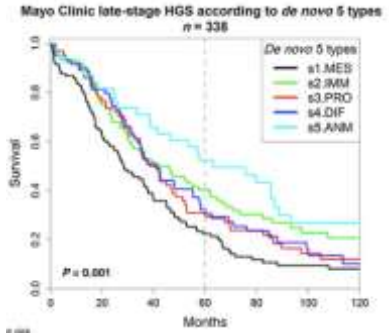
Cancer Therapy: Clinical

Clinical Cancer Research

# Pooled Clustering of High-Grade Serous Ovarian Cancer Gene Expression Leads to Novel Consensus Subtypes Associated with Survival and Surgical Outcomes

Chen Wang[1], Sebastian M. Armasu[1], Kimberly R. Kalli[2], Matthew J. Maurer[1], Ethan P. Heinzen[1], Gary L. Keeney[3], William A. Cliby[4], Ann L. Oberg[1], Scott H. Kaufmann[2], and Ellen L. Goode[1]




Clin Cancer Res; 23(15) August 1, 2017

# Characteristics of ovarian cancer by histology, genomic profile and active therapies

| Histological subtype | Clinical findings | Genetic characteristics | T |
|---|---|---|---|
| High-grade serous carcinoma and high-grade endometrioid carcinoma | • Can present with peritoneal carcinomatosis, ascites and/or pelvic mass<br>• Typically advanced stage at presentation | • Deficiencies in homologous recombination (50% of<br>• Associated with *P*<br>mutations | hemotherapy<br>-ribose) polymerase<br>tors<br>umours are initially sensitive to platinum-based chemotherapy, but most patients with advanced-stage cancer will recur |
| Low-grade serous carcinoma | • Presents in younger patients (<br>reported age: 43–55 ye<br>• Can be early or la | with *KRAS* and *BRAF*<br>ions<br>umours have genomic stability | • MEK inhibitors (currently being tested in clinical trials) and hormonal therapies |
| Low-grade endometrioid carcinoma | • Can be a | • Associated with *PTEN*, *ARID1A* and *PIK3CA* mutations<br>• Can have microsatellite instability | • Possible hormonal therapies (not yet established) |
| Clear-cell carci | parenchymal<br>s (in the liver and the lungs)<br>be associated with hypercoagulability and hypercalcaemia | • Associated with *ARID1A* and *PIK3CA* mutations | • Immunotherapy agents<br>• Can be resistant to platinum-based chemotherapy |
| Mucinous oma | • Presents in younger patients and is typically early stage at presentation | • Associated with *KRAS* mutations | • Tends to be insensitive to chemotherapy but is still treated initially with cytotoxic chemotherapy |

Potentially Practice-changing Advances

*The current standard-of care, including the definition of platinum-resistant disease, is not based on molecular signatures*

# Choice of treatment: What do we know today?

**2.** The power of using **genomics** to improve patient selection and precision medicine

**Well established**

→ **Epithelial Ovarian cancer is not a unique disease**


**Advances**

→ **Translational findings demonstrated the importance of testing tissues before therapy**

ARTICLES
https://doi.org/10.1038/s41588-018-0179-8
nature genetics

**Copy number signatures and mutational processes in ovarian carcinoma**

Geoff Macintyre[1,24], Teodora E. Goranova[1,24], Dilrini De Silva[1], Darren Ennis[2], Anna M. Piskorz[1], Matthew Eldridge[1], Daoud Sie[3], Liz-Anne Lewsley[4], Aishah Hanif[4], Cheryl Wilson[4], Suzanne Dowson[2], Rosalind M. Glasspool[5], Michelle Lockley[6,7], Elly Brockbank[8], Ana Montes[9], Axel Walther[10], Sudha Sundar[11], Richard Edmondson[12,13], Geoff D. Hall[14], Andrew Clamp[15], Charlie Gourley[16], Marcia Hall[17], Christina Fotopoulou[18], Hani Gabra[18,19], James Paul[4], Anna Supernat[1], David Millan[20], Aoisha Hoyle[20], Gareth Bryson[20], Craig Nourse[2], Laura Mincarelli[2], Luis Navarro Sanchez[2], Bauke Ylstra[3], Mercedes Jimenez-Linan[21], Luiza Moore[21], Oliver Hofmann[2,22], Florian Markowetz[1*], Iain A. McNeish[2,5,18*] and James D. Brenton[1,21,23*]

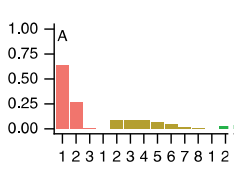
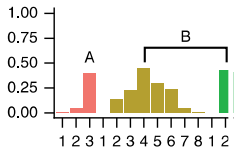
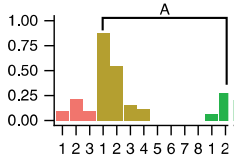
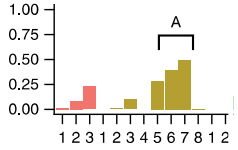
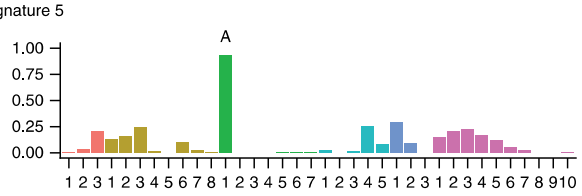
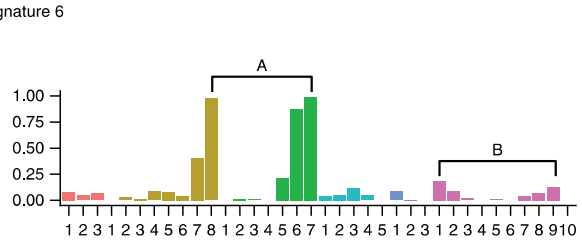
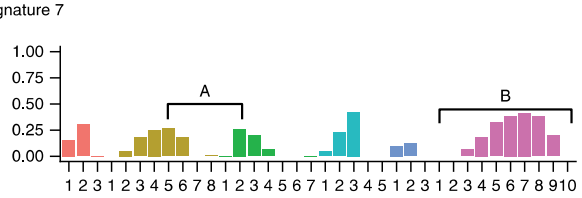
Identification of copy number variation (CNV) signatures as indicators of outcome

ARTICLES
https://doi.org/10.1038/s41588-018-0179-8
nature genetics

# Copy number signatures and mutational processes in ovarian carcinoma

Geoff Macintyre[1,24], Teodora E. Goranova[1,24], Dilrini De Silva[1], Darren Ennis[2], Anna M. Piskorz[1]
Matthew
Suzanne
Axel Wa
Charlie C
David M
Luis Nav
Florian M

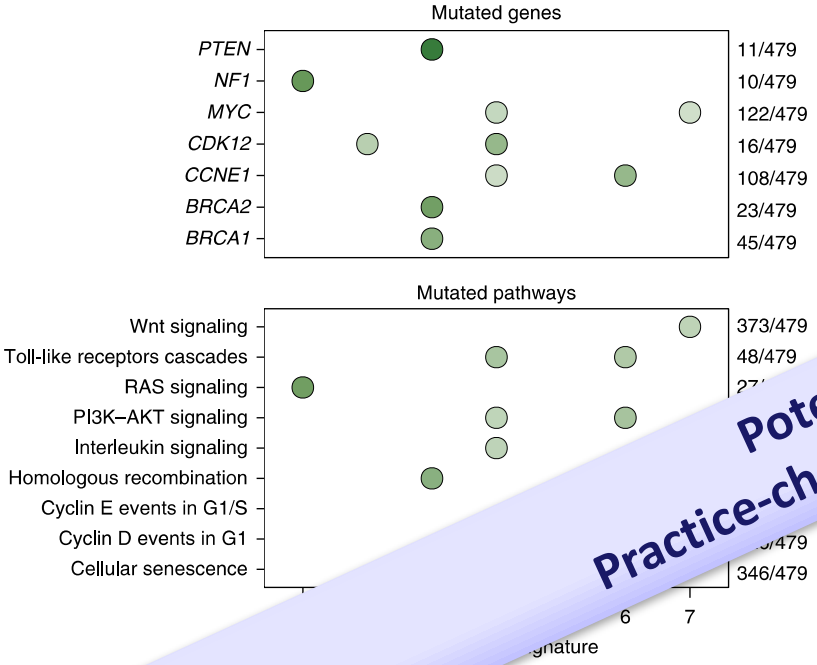
Seven copy number signatures in HGSOC

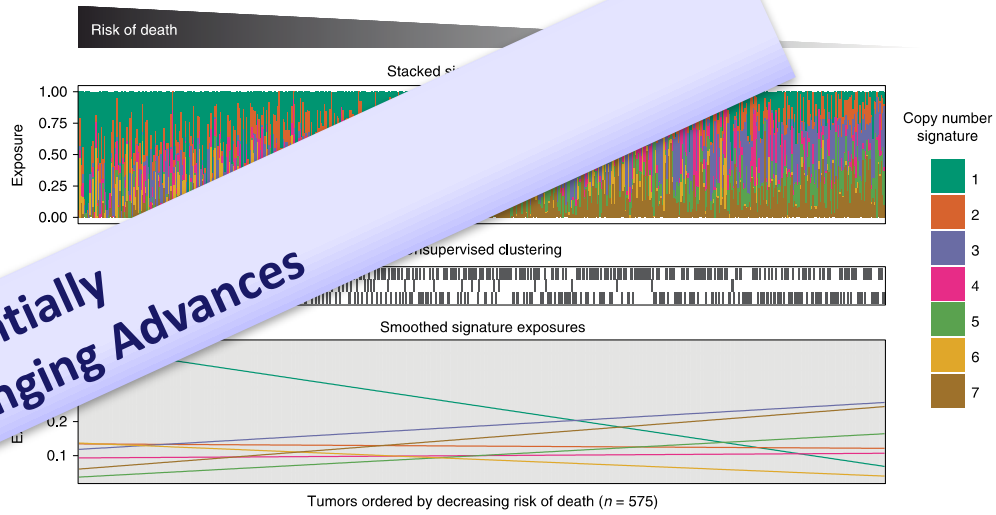
| Copy number signature component weights | Important components | Key associations | Proposed mechanism |
|---|---|---|---|
| Signature 1  | (A) Low number of breakpoints (<1 break per 10 Mb)<br>(B) 0 or 2 breakpoints | • Poor overall survival<br>• Higher in cases with mutated NF1 and RAS signaling pathway:<br>*NF1, KRAS, RASA1, RASA2, CUL3, NRAS* | Oncogenic RAS–MAPK signaling and telomere |
| Signature 2  | | | |
| Signature 3  | | | |
| Signature 4  | | | |
| Signature 5  | (A) Subclonal copy number changes (~0.5 copies) | • Correlated with number of chromothriptic-like events<br>• Anti-correlated with SNV signature 16 | Subclonal catastophic chromothriptic-like events through unknown mechanisms |
| Signature 6  | (A) Large copy number changes (6–28) resulting in high copy number states (8–30 copies)<br>(B) Short segments interspersed with long segments | • Higher in cases with mutated *CCNE1*, and mutations in the TLR cascade, PI3K–AKT signaling, CCNE1- and CCND1-associated events and cellular senescence pathways:<br>*AKT2, RICTOR, MET, JUN, MAP2K4, PPP2R1A, MYC, CCNE1, CCND2, CCND3, CDK6, MDM4*<br>• Correlated with age at diagnosis; age-related SNV signature 1; APOBEC SNV signature 13<br>• Anti-correlated with tandem-duplication score; HRD-associated SNV signature 3 | Focal amplification due to failure of cell cycle control |
| Signature 7  | (A) Copy number changes from tetraploid to 3 copies<br>(B) Breaks distributed evenly across genome | • Good overall survival<br>• Higher in cases with mutated MYC and mutations in the Wnt signaling and interleukin signaling pathways:<br>*MYC, SOX2, TERT, AKT2, JAK2*<br>• Correlated with HRD-associated SNV signature 3 | Non-BRCA1/2 related HRD |

Features
- Breakpoint count per 10 Mb
- Copy number
- Copy number change point
- Breakpoint count per chromosome arm
- Length of chains of oscillating copy number
- Segment size

## Linking copy number signatures with mutational processes

## Association of survival with copy number signatures




Potentially Practice-changing Advances

# HGSOC: a continuum of genomes

- ✓ Copy number signature exposures at diagnosis predict both overall survival and the probability of platinum-resistant relapse.
- ✓ Measurement of signature exposures provides a rational framework to choose combination treatments that target multiple mutational processes.

# 4) What’s next after PARP-inhibitors?

# The challenges of combining **DNA damaging agents** with **immune checkpoint inhibitors**

VOLUME 33 · NUMBER 34 · DECEMBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Safety and Antitumor Activity of Anti–PD-1 Antibody, Nivolumab, in Patients With Platinum-Resistant Ovarian Cancer

*Junzo Hamanishi, Masaki Mandai, Takafumi Ikeda, Manabu Minami, Atsushi Kawaguchi, Toshinori Murayama, Masashi Kanai, Yukiko Mori, Shigemi Matsumoto, Shunsuke Chikuma, Noriomi Matsumura, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Akihiko Ueda, Yuko Hosoe, Satoshi Morita, Masayuki Yokode, Akira Shimizu, Tasuku Honjo, and Ikuo Konishi*

**Anti PD1/PDL1**

**-ORR 15%**

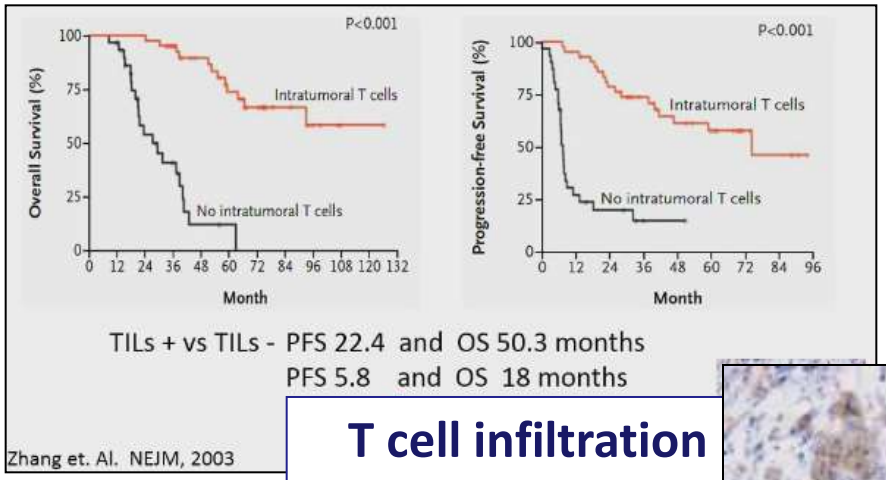
**-Very rarely long lasting responses**

**Other Studies**

**-Disis et Al, Avelumab: ORR 9.7%**

**-Brahmer et al, Nivolumab: 17 pts, 1 PR, 2 SD**

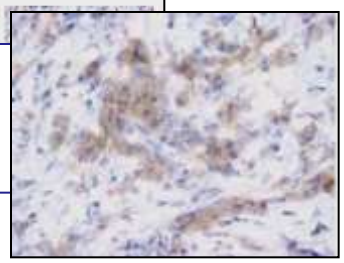
# Why combine DDR inhibitors + immunotherapy?



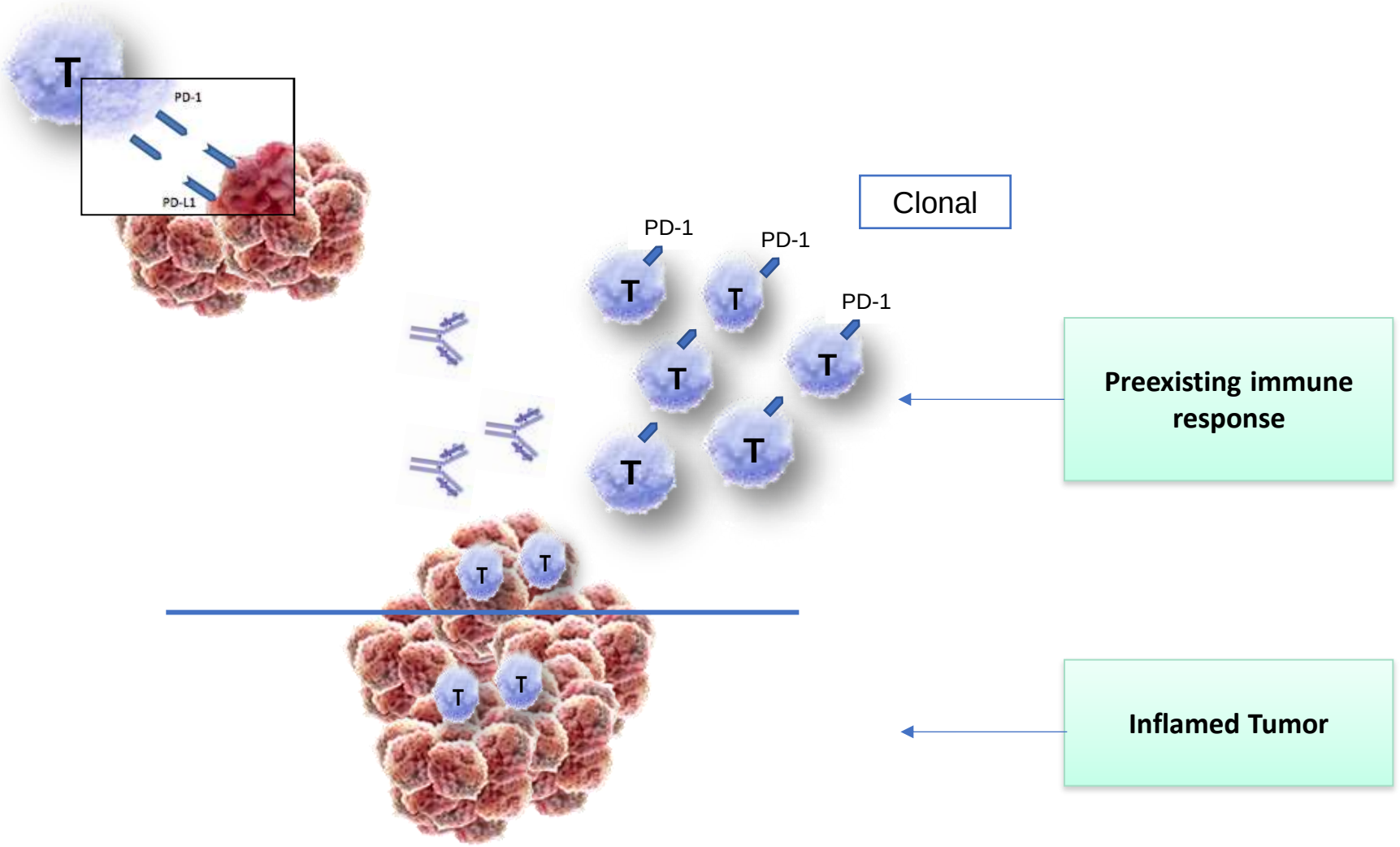

TILs + vs TILs - PFS 22.4 and OS 50.3 months
PFS 5.8 and OS 18 months

Zhang et. Al. NEJM, 2003

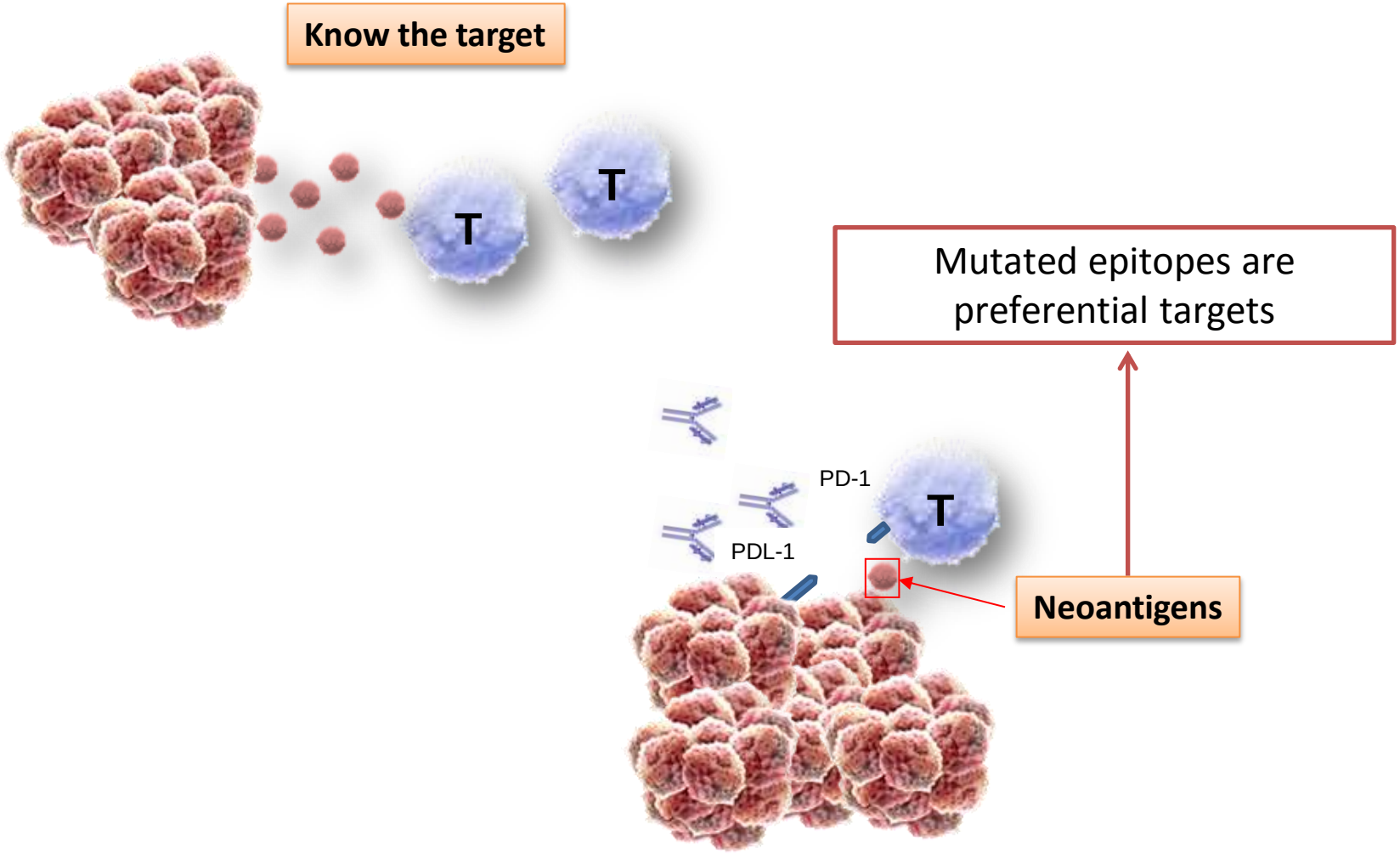
**T cell infiltration affect outcome**



# Response to immunotherapy: T lymphocytes



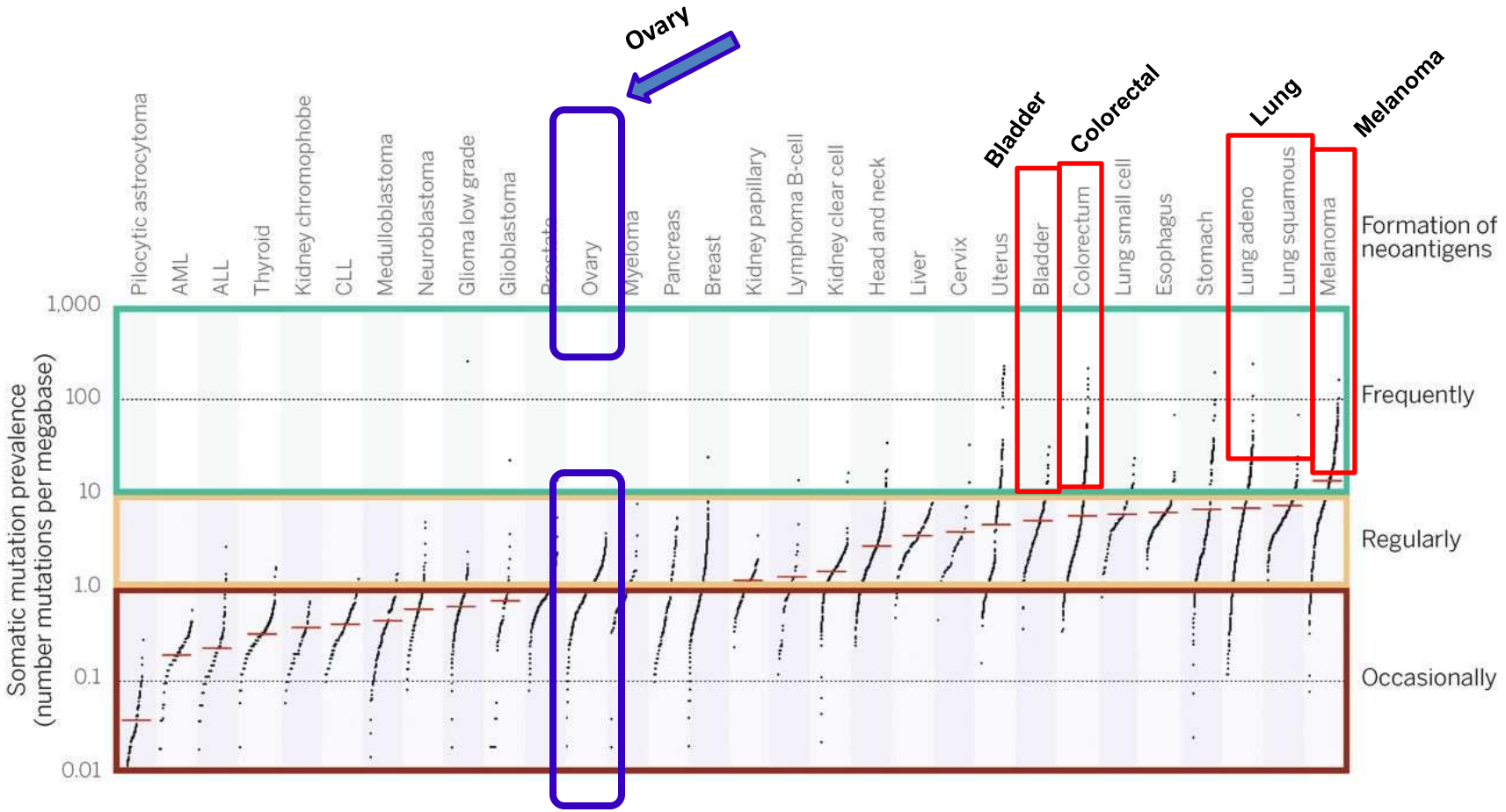
# Response to immunotherapy: T lymphocytes




**The increased presence of tumor-specific neoantigens makes the tumor more immunogenic**, leading to an increased number of tumor-infiltrating immune cells.

# Ovarian Cancer: Immunogenic?

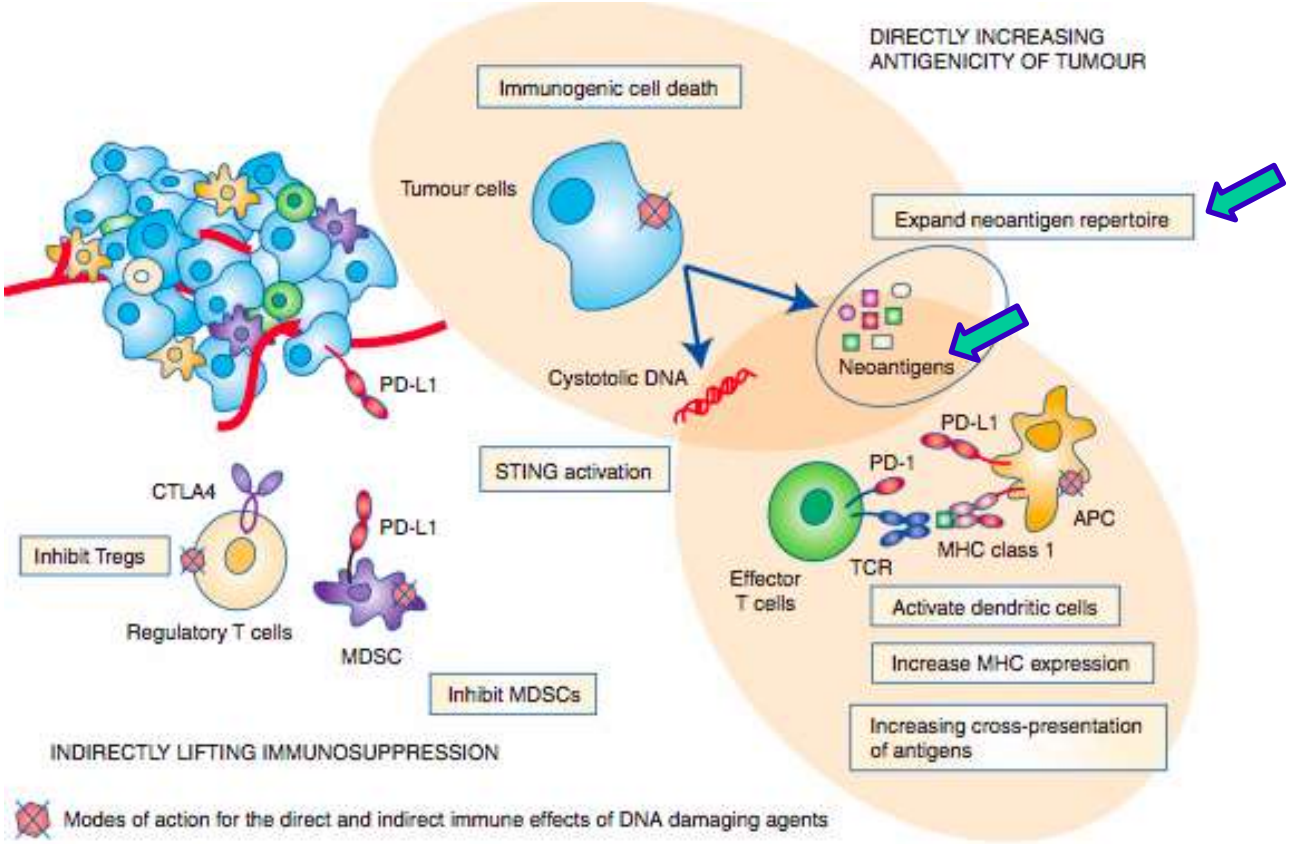
## Estimate of neo-antigen repertoire in human cancer



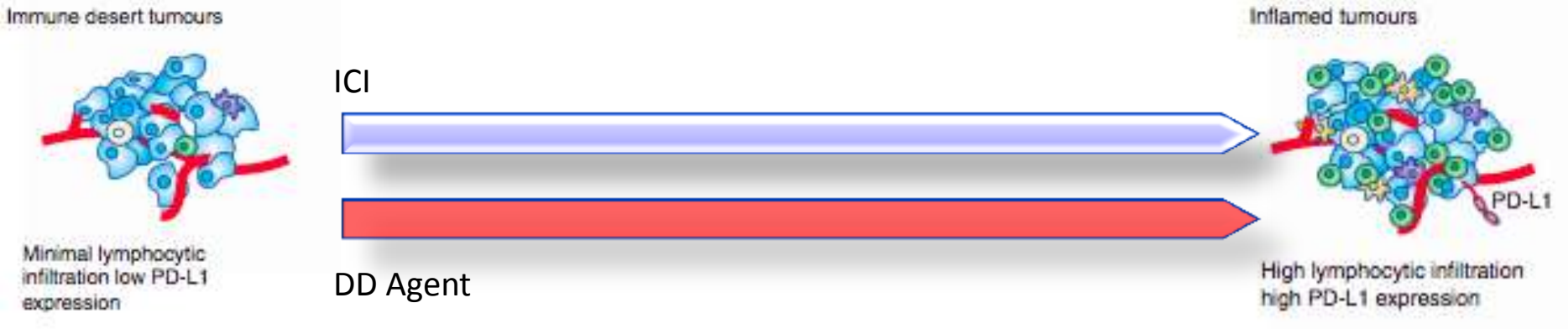

*Shumacher T et al Science 2015*

# Why combine DDR inhibitors + immunotherapy

- **HGSOC has intermediate mutational load (surrogate of neoantigen production)**
- **Inhibition of DDR pathways would be expected to propagate DNA damage and thus increase neoantigen potential**




J. S Brown, British Journal of Cancer (2018)




| Trial | Agent | Phase | Population | Response rate |
|---|---|---|---|---|
| Ovarian cancer | | | | |
| Brahmer et al. [9] | Pembrolizumab | I | 207 patients; 17 recurrent ovarian | PR 6%<br>SD 18% |
| Hamanishi et al. [16] | Nivolumab | II | 20 platinum-resistant ovarian | CR 10%<br>PR 5%<br>SD 30% |
| JAVELIN [27] | Avelumab | I | 124 recurrent ovarian | PR 9.7%<br>SD 44% |
| KEYNOTE-028 [28] | Pembrolizumab | Ib | 26 PD-L1-positive recurrent ovarian | ORR 11.5% |
| TOPACIO [29] | Niraparib + pembrolizumab | I/II | 60 recurrent ovarian | ORR 25%<br>DCR 68% |
| MEDIOLA [29] | Olaparib + durvalumab | I/II | 34 recurrent, platinum-sensitive, BRCA mutant | ORR 72%<br>12 week DCR 81% |
| Matulonis et al. [29] | Pegylated liposomal doxorubicin + pembrolizumab | II | 26 recurrent, platinum-resistant ovarian | 11% PR<br>0% CR |

Trials of PD-1/PD-L1 inhibitors in ovarian cancers

# Ongoing comination immunotherapy trials in ovarian cancer

| Treatment | Mechanism | Phase |
|---|---|---|
| Ovarian | | |
| *Upfront* | | |
| Carboplatin/paclitaxel with or without avelumab (JAVELIN) | Chemo/PD-L1 | III |
| Carboplatin/paclitaxel/bevacizumab/atezolizumab vs. placebo (IMAGYN50) | Chemo/VEGF/PD-L1 | III |
| Maintenance rucaparib + nivolumab vs. rucaparib vs. nivolumab vs. placebo (ATHENA) | PARP/PD1 following chemo | III |
| *Relapsed/refractory* | | |
| Carboplatin/paclitaxel/bevacizumab/atezolizumab vs. placebo (ATALANTE) | Chemo/VEGF/PD-L1 | III |
| Nivolumab/ipilimumab vs. nivolumab (NRG) | PD1/CTLA-4 | II |
| PLD + avelumab vs. avelumab vs. PLD (JAVELIN Ovarian 200) | Chemo/PD-L1 | III |
| PLD + durvalumab | Chemo/PD-L1 | I/II |
| Chemo/bevacizumab/atezolizumab vs. placebo | Chemo/VEGF/PD-L1 | III |
| PLD/bevacizumab/atezolizumab vs. PLD/atezolizumab vs. PLD/bevacizumab | Chemo/VEGF/PD-L1 | II/III |

# Conclusions

- *Ovarian cancers include a number of distinct tumor types with a unique pattern of alterations*
- *Options likely will increase in tandem with our understanding*
- *Intoduction of PARPi into the I line changes the therapeutic paradigm and paves the way for biomarker-based patient selection*
- *Identifying predictors of response and resistance to CT and PARPi remain an active area of research.* ***Need for Biomarkers!***
- *Medical Treatment according to histotype and molecular profile is the future!*

*Thanks!*