POST- ESMO: From Barcelona to real world
Roma, 2-3 Dicembre 2019

TUMORI GINECOLOGICI: NUOVI DATI

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Modulo dichiarazione conflitto di interessi

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

☒ 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

Relationship	Company/Organization
/	/
/	/
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/	/

POST- ESMO: From Barcelona to real world

Global Cancer in Women: Burden and Trends - 2012

New cases annually

Cervix uteri: 527,600
- More developed nations: 83,100
- Less developed nations: 444,500

Corpus uteri: 319,600
- More developed nations: 167,900
- Less developed nations: 151,700

Ovary: 238,700
- More developed nations: 99,800
- Less developed nations: 139,000

Deaths annually

Cervix uteri: 265,700
- More developed nations: 35,500
- Less developed nations: 230,200

Corpus uteri: 76,200
- More developed nations: 34,700
- Less developed nations: 41,500

Ovary: 151,900
- More developed nations: 65,900
- Less developed nations: 86,000

Torre LA, Cancer Epidemiol Biomarkers Prev 2017

ESMO 2019 – Ovarian carcinoma

Vilnius

Ovarian cancer - maintenance therapy

Treatment-free interval following primary therapy

Previous critical points:

- Last dose of primary platinum agent (platinum free interval)
- Last dose of maintenance therapy with anti-angiogenic agents (bevacizumab)
- Response to platinum agent in recurrent platinum sensitive ovarian cancer
- Maintenance therapy with PARPi

SHIFT

Maintenance following primary therapy

New critical points:

- Last dose and response to primary platinum agent
- Maintenance therapy:
  - anti-angiogenic agents (bevacizumab)
  - PARPi

Ovarian cancer – maintenance therapy

Background

- Platinum and paclitaxel combination is a standard chemotherapy regimen for over 2 decades
- Bevacizumab as maintenance therapy (GOG 218; ICON 7) in first-line setting in stage III-IV has become a new standard of care (other standard of care platinum-based chemotherapies: intravenous 3-weekly carboplatin and paclitaxel without bevacizumab, intraperitoneal therapy, weekly intravenous paclitaxel plus carboplatin) [Fifth Ovarian Cancer Consensus Conference – Tokio]
- Maintenance treatments with PARPi (olaparib, niraparib, rucaparib, veliparib) in recurrent platinum sensitive high grade serous ovarian carcinoma have extended the progression-free survival
- Olaparib as maintenance therapy (SOLO-1) in first-line setting has become a new standard of care for patients with ovarian cancer BRCAm

Key questions

- How can we improve the standard of care and the outcomes (increasing survival), moving benefit derived from PARPi treatment, in first-line setting ?
- How can we select patients who will have greater benefit with these therapies ?
- The main goal of maintenance treatment in ovarian cancer is to avoid relapse after first-line therapy (converting ovarian cancer into a chronic disease, or hopefully, curing patients). What is the best way ?

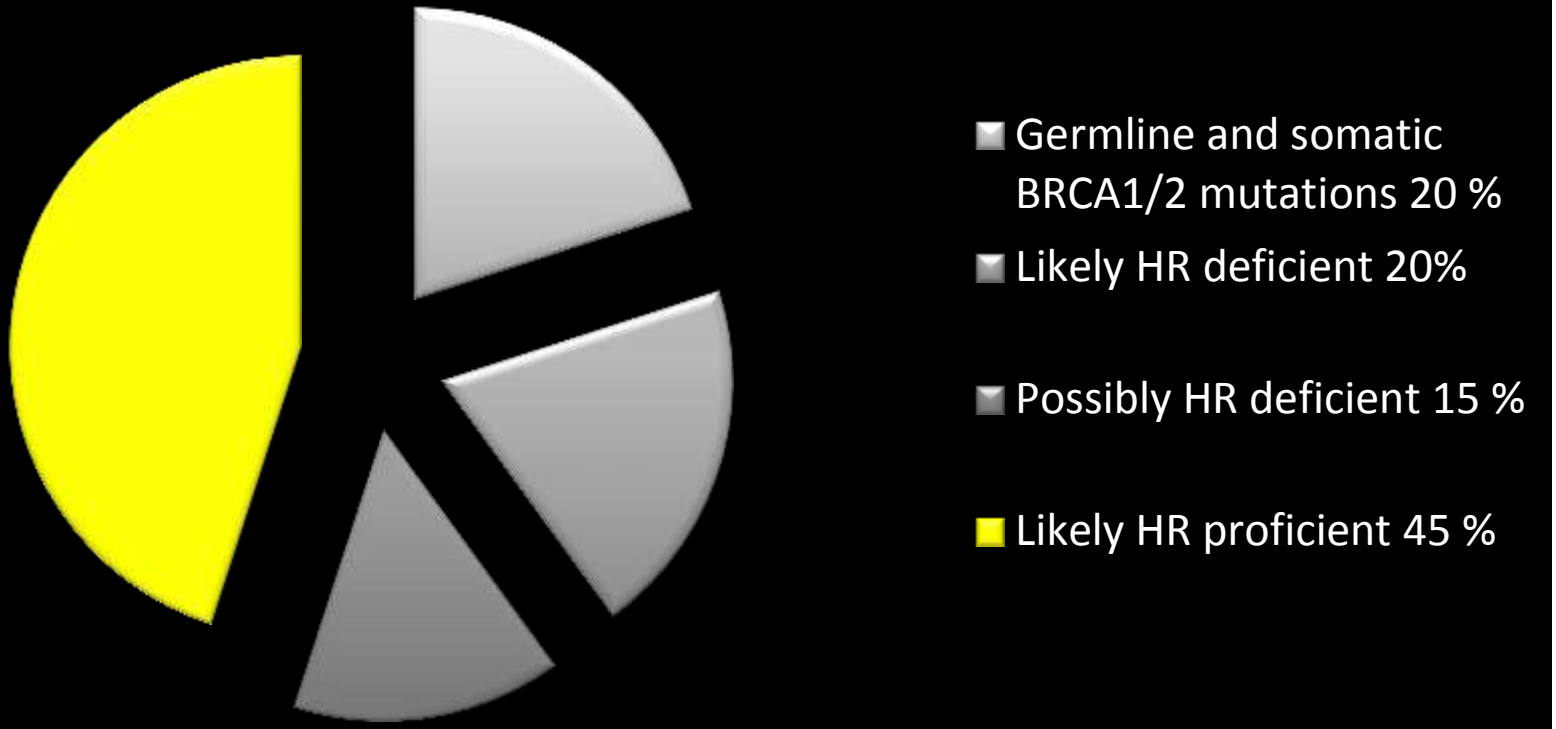
➢ PAOLA 1: Olaparib plus Bevacizumab

➢ PRIMA: Niraparib, in (very) high risk patients

➢ VELIA: Veliparib, concomitant /sequential with chemotherapy

Ovarian cancer

Genetic alterations responsible for homologous recombination (HR) pathway in Ovarian cancer



Kostantinopoulos PA, Cancer Discov 2015

ESMO 2019 - Ovarian cancer

European Network of Gynaecological Oncological Trial groups

PAOLA-1/ENGOT-OV25 trial

Ray-Coquard I.L.

Olaparib plus bevacizumab as maintenance therapy in patients with newly diagnosed, advanced ovarian, fallopian tube, primary peritoneal [high grade serous or high grade endometrioid or other epithelial non mucinous], with or without BRCAm/HRD, undergone upfront or interval surgery an advanced stage: FIGO stage IIIB, IIIC, or IV

Phase III
806 patients

RANDOM

2

tBRCAm	12 m = 94 % 24 m = 76 %	HR = 0,31
HRD positive (255) including tBRCAm	12 m = 89 % 24 m = 66 %	HR = 0,33
HRD positive (97) excluding tBRCAm	12 m = 83 % 24 m = 52 %	HR = 0,43

HRD (282) negative/unknown	No benefit vs standard (137)	HR = 0,92

Bevacizumab 15mg/kg q3w for 15 months

Within 9 weeks after completion of the last dose of platinum-based chemotherapy: Olaparib 300 mg BID for 24 months

ITT Population

PFS: 22,1

PFS: 16,6

HR: 0,59
p= < 0,00001

1

tBRCAm	12 m = 76 % 24 m = 39 %	
HRD positive (132) including tBRCAm	12 m = 71 % 24 m = 29 %	
HRD positive (55) excluding tBRCAm	12 m = 69 % 24 m = 26 %	

Bevacizumab 15mg/kg q3w for 15 months

Placebo for 24 months

- Carboplatin
- Paclitaxel
- Bevacizumab
- Olaparib

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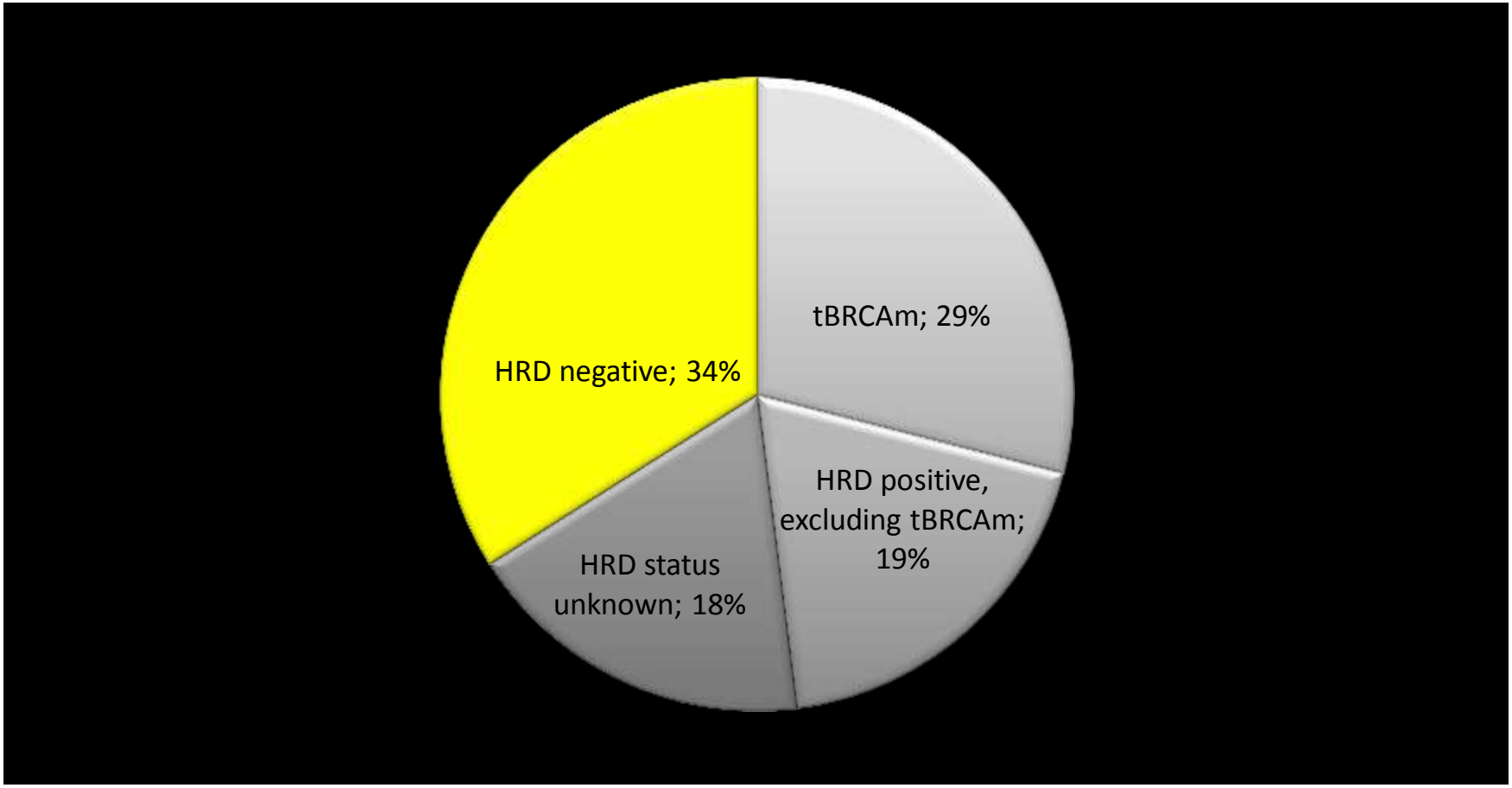
PAOLA-1/ENGOT-OV25 trial

Biomarker subgroups



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PAOLA-1/ENGOT-OV25 trial

- First randomized trial to explore the efficacy and safety of maintenance olaparib plus bevacizumab in newly diagnosed stage III-IV, high-grade serous or endometrioid ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, with or without BRCAm, undergone upfront or interval surgery, received platinum-taxane–based chemotherapy, and received at least three cycles of bevacizumab.

- Adding olaparib to bevacizumab as maintenance after first-line platinum-based chemotherapy for advanced ovarian cancer met its primary endpoint of a statistically significant improvement in PFS in the [intent-to-treat] population, in favor of the olaparib arm.

- This benefit was particularly relevant in patients with a tumor BRCAm and in those with HRD positive disease.

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PAOLA-1/ENGOT-OV25 trial

Adverse events

- Hypertension
- Anemia

	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)
New primary malignancies, n (%)	7 (1.3)	3 (1.1)
Acute lymphocytic leukaemia	1	0
Breast cancer	2	2
Lung cancer	1	0
Myeloma	1	0
Pancreatic cancer	1	0
Squamous skin cancer	1	0
Thyroid cancer	0	1
Pneumonitis/ILD, n (%)	6 (1.1)	0

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PRIMA/ENGOT-OV26/GOG-3012

González-Martín A

Niraparib or placebo as maintenance therapy in patients* with newly diagnosed, advanced had high-grade serous or endometrioid tumors ovarian, fallopian tube, primary peritoneal niraparib after a response to platinum-based chemotherapy

*with stage III disease with visible residual tumor after primary debulking surgery, inoperable stage III disease, or any stage IV disease, as well as those who had received neoadjuvant chemotherapy.

Phase III
733 patients

RANDOM

2 → Niraparib

1 → Placebo

Niraparib arm
Patients without PD or death (%):
At 6 months: 86 %
At 12 months: 72 %
At 24 months: 59 %

PFS:
Median in HRD pop.: 21,9 months
Median in int. to treat pop.: 13,8 months

MedianPFS in HRD pop.: p= < 0,001
Median PFS in int. treat pop.: p= < 0,001
HR= 0,43

Within 12 weeks after completion of the last dose of platinum-based chemotherapy:
Niraparib 300 mg/day
for 36 months or until disease progression.
[individualized starting dose of 200 mg once daily for patients with a baseline body weight of less than 77 kg]

Placebo arm
Patients without PD or death (%):
At 6 months: 68 %
At 12 months: 42 %
At 24 months: 35 %

PFS:
Median in HRD pop.: 10,4 months
Median in int. to treat pop.: 8,2 months

Placebo

Platinum-based Chemotherapy

Niraparib

Placebo

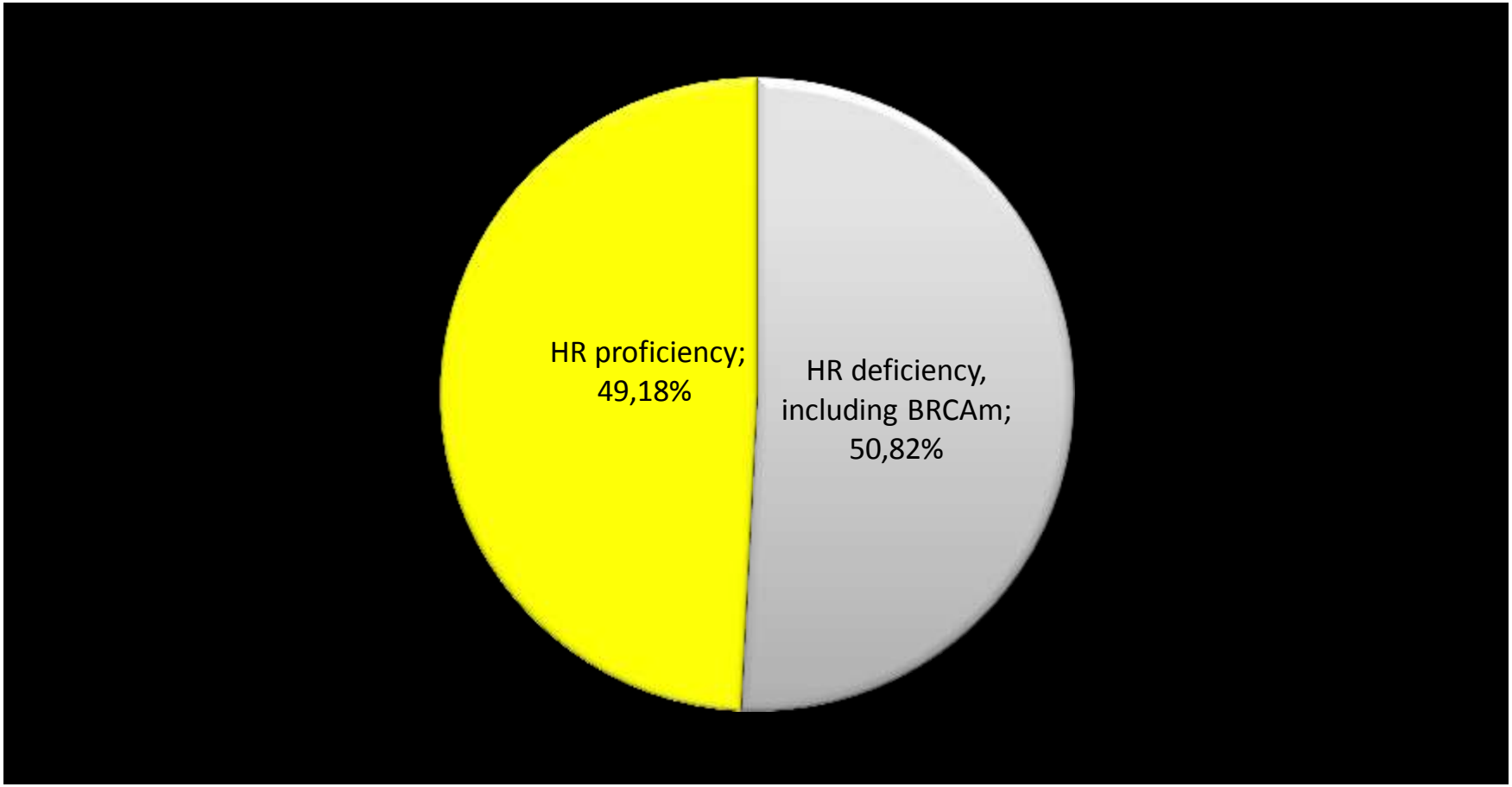
The primary end point was progression-free survival in patients who had tumors with homologous recombination deficiency and in those in the overall population

González-Martín A, NEJM 2019

ESMO 2019 - Ovarian carcinoma

PRIMA/ENGOT-OV26/GOG-3012

Biomarker subgroups



ESMO 2019 - Ovarian carcinoma

PRIMA/ENGOT-OV26/GOG-3012

- Adding niraparib as maintenance after first-line platinum-based chemotherapy for advanced ovarian cancer met its primary endpoint of a statistically significant improvement in PFS in the [intent-to-treat] population, in favor of the niraparib arm.

- This benefit was particularly relevant in patients with HRD positive (including tBRCAm) disease.

ESMO 2019 - Ovarian carcinoma

PRIMA/ENGOT-OV26/GOG-3012

Adverse events

Among the most common grade 3/4 or higher adverse events in the niraparib group were:

- anemia (31.0 %)
- thrombocytopenia (28.7 %)
- neutropenia (12.8 %)

Dose reductions

Dose reductions in 70.9% of the patients in the niraparib group.

Treatment discontinuation for toxicity: 12 %

Myelosuppressive adverse events were the main reason for discontinuation.

One case of myelodysplastic syndrome was identified in a patient in the niraparib group

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The primary end point was investigator-assessed progression-free survival in the veliparib-throughout group as compared with the control group, analyzed sequentially in the BRCA-mutation cohort, the cohort with homologous-recombination deficiency (HRD) (which included the BRCA-mutation cohort), and the intention-to-treat population.

VELIA (G 3OO5)

Coleman R

Chemotherapy plus placebo followed by placebo maintenance (control), chemotherapy plus veliparib followed by placebo maintenance (veliparib combination only), or chemotherapy plus veliparib followed by veliparib maintenance (veliparib throughout) in patients with previously untreated stage III or IV high-grade serous ovarian carcinoma

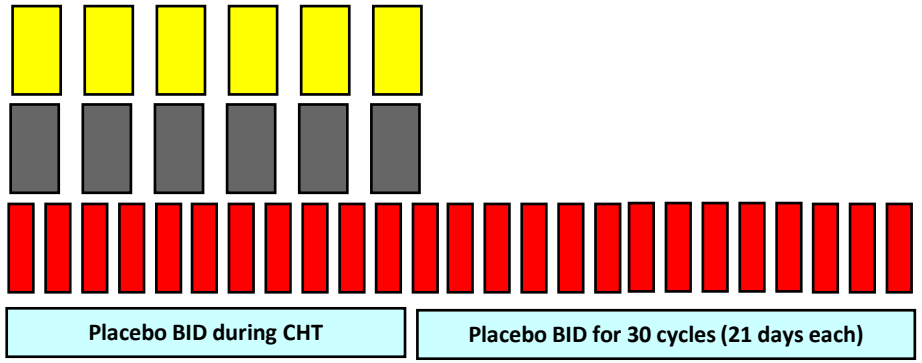
Phase III
1140 patients

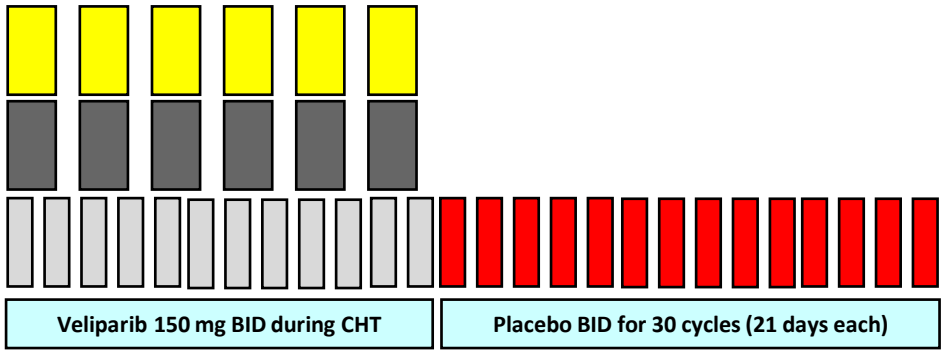
RANDOM

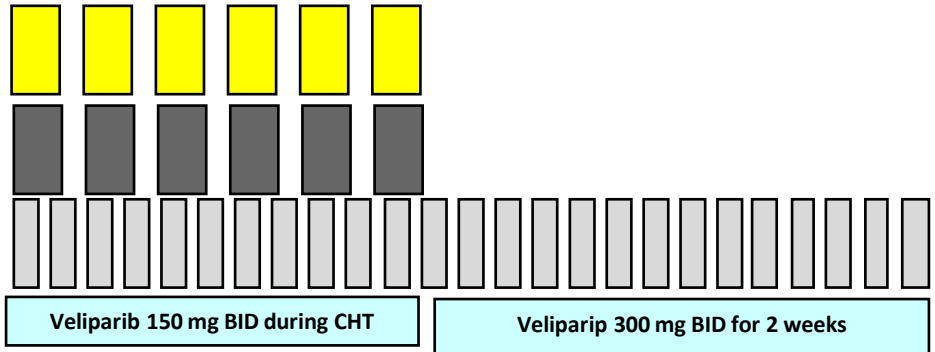
1

1

1







Carboplatino

Paclitaxel

Veliparib

Placebo

Coleman R, NEJM 2019

Ovarian carcinoma

Oza AM, Lancet Oncol 2015

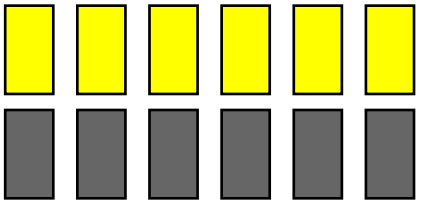
Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer
with or without BRCA mutation

≤ 3 lines of platinum-based chemotherapy

Phase II randomized
162 patients

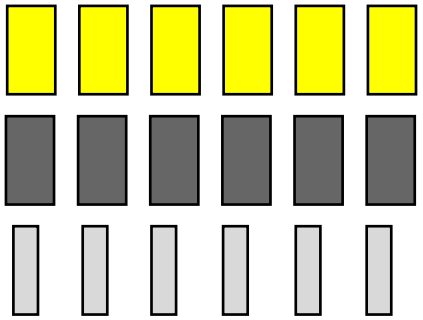
RANDOM

- Carboplatin AUC 6 , d1 q 21
- Paclitaxel 175 mg/m2, d1 q 21



PFS: 9,6 months

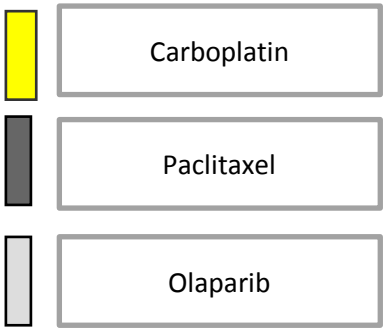
- Carboplatin AUC 4, d1 q 21
- Paclitaxel 175 mg/m2, d1 q 21
- Olaparib 200 mg BID x 10 days q 21



PFS: 12,2 months

p: 0,0012

Olaparib 400 mg x 2/die



Primary endpoint was progression-free survival (PFS)

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VELIA (G 3OO5)

Chemotherapy plus placebo followed by placebo maintenance (control), chemotherapy plus veliparib followed by placebo maintenance (veliparib combination only), or chemotherapy plus veliparib followed by veliparib maintenance (veliparib throughout) in patients with previously untreated stage III or IV high-grade serous ovarian carcinoma

Phase III
1140 patients

- Carboplatino
- Paclitaxel
- Veliparib
- Placebo

Median PFS (months)	Veliparib throughout	Control
BRCAm	34,7	22,0
HR= 0,44 p < 0,001		
HRD positive	31,9	20,5
HR= 0,57 p < 0,001		
Intention to treat population	23,5	17,3
HR= 0,68 p < 0,001		

Data about arm with Veliparib together chemotherapy without Veliparip maintenance

Not presented

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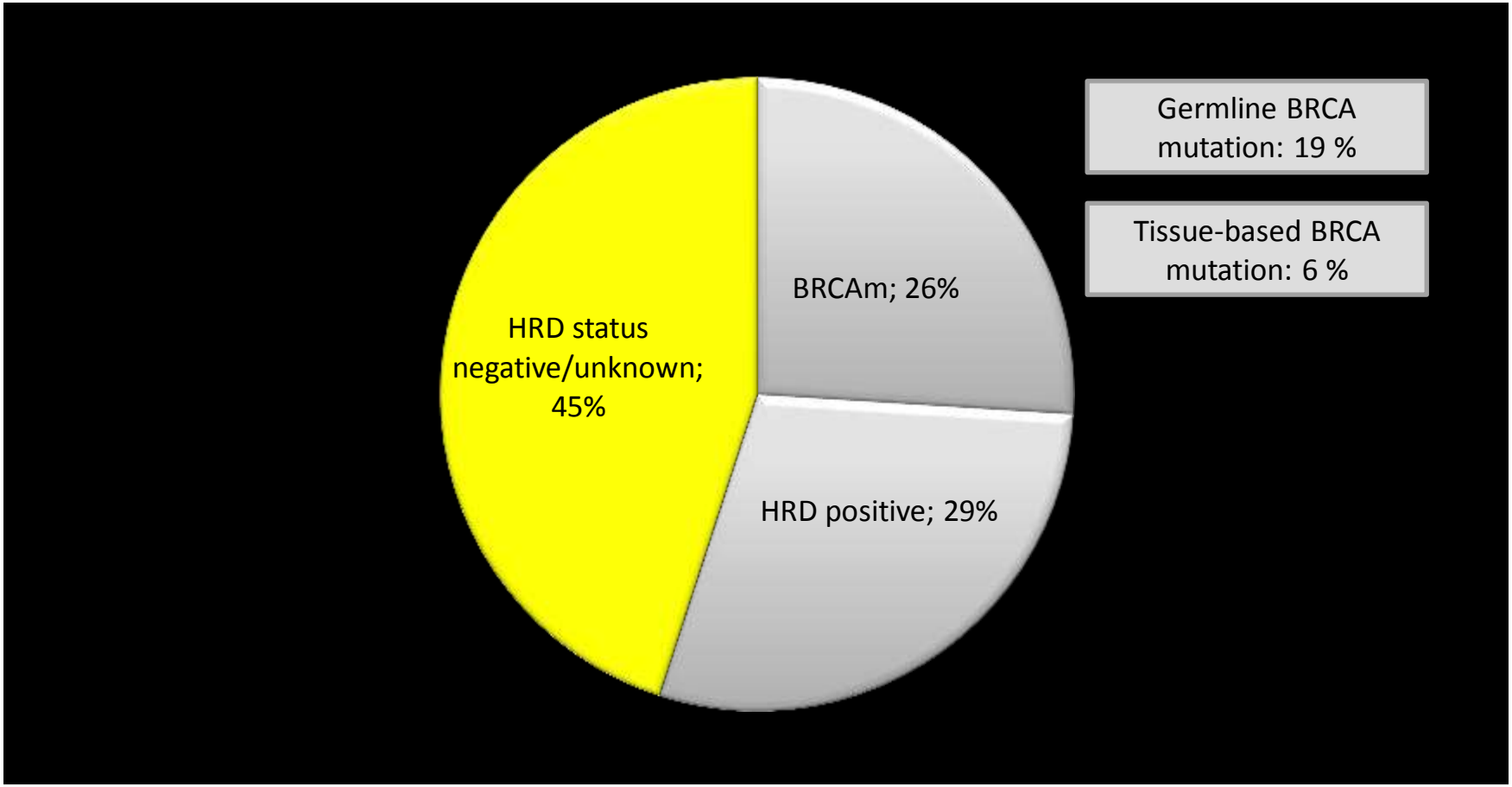
VELIA trial

Biomarker subgroups



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VELIA (G3005)

Adverse events

Among the most common grade 3/4 or higher adverse events in the veliparib combination-only group and in the veliparib throughout group were:

- **Anemia**:
  - veliparib combination-only group 41.0 %
  - veliparib throughout group 38.0 %
- **Thrombocytopenia**:
  - veliparib combination only group 31.0 %
  - veliparib throughout group 28.0 %
- **Neutropenia**
  - veliparib combination-only group 62.0 %
  - veliparib throughout group 58.0 %

- One event of myelodysplastic syndrome in the veliparib-combination-only group (patient with a germline BRCA1 mutation)
- One event of acute myeloid leukemia in the veliparib-throughout group

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VELIA (G3005)

Dose reductions

The percentages of patients who had a reduction in the dose of veliparib or placebo or an interruption because of an adverse event were higher in the veliparib-throughout group than in the control group

during the combination phase:
dose reductions in
- 6% of the patients of veliparib group
- 2% of the patients of placebo group

interruptions in
- 58% of the patients of veliparib group
- 39% of the patients of placebo group

during the maintenance phase
dose reductions in
- 24% of the patients of veliparib group
- 4% of the patients of placebo group

interruptions in
- 41% of the patients of veliparib group
- 19% of the patients of placebo group

In the combination phase, 11% or less of the patients had an adverse event leading to the discontinuation of veliparib or placebo in any group.

In the maintenance phase, the percentage of patients who discontinued veliparib or placebo owing to an adverse event was:
- 19% in the veliparib-throughout group
- 6% in the control group.

The most common adverse event leading to the discontinuation of veliparib therapy was nausea (in 8% of patients).

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Fluzoparib

Li N

Efficacy and safety of oral poly (ADP-ribose) polymerase inhibitor fluzoparib in patients with germline BRCA1 or BRCA2 mutations and platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with two or more previous platinum-based chemotherapy regimens were enrolled

Phase II
113 patients

Adverse events

The most common (≥20%) TRAE:

- nausea (55.8%)
- fatigue (47.8%)
- white blood cell count decreased (44.2%)
- anemia or decreased hemoglobin (42.5%)
- neutrophil count decreased (31.9%)
- decreased appetite (30.1%)
- thrombocytopenia (29.1%)
- vomiting (23.9%).

Treatment-emergent AEs led to treatment interruption and dose reduction in 31.0% and 21.1% of patients, respectively.

After completion of the last dose of platinum-based chemotherapy:

fluzoparib 150 mg BID until PD or intolerable toxicity

ORR	64,0 %
CR	8,7 %
DCR (disease control rate)	95,1 %

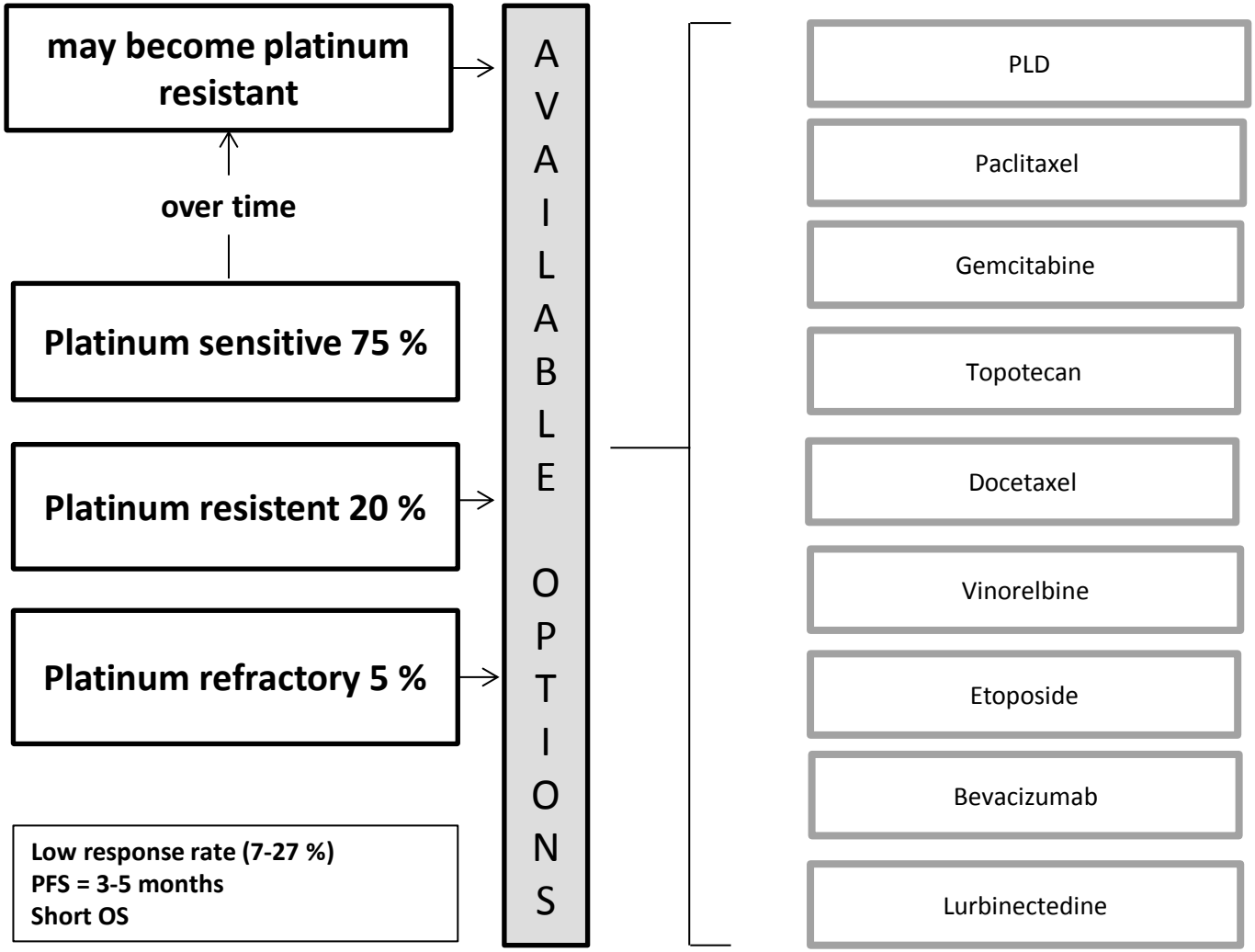
Platinum based chemotherapy

Fluzoparib

From April 4 2018 to March 21 2019, 113 pts at Chinese national-wide 26 sites received fluzoparib

From april 2019, phase 3 randomized, double-blind, placebo-controlled, multicenter trial of maintenance treatment with fluzoparib capsules versus placebo in patients with platinum-sensitive recurrent ovarian cancer

Platinun resistent/refractory ovarian cancer



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Ngoi NYL

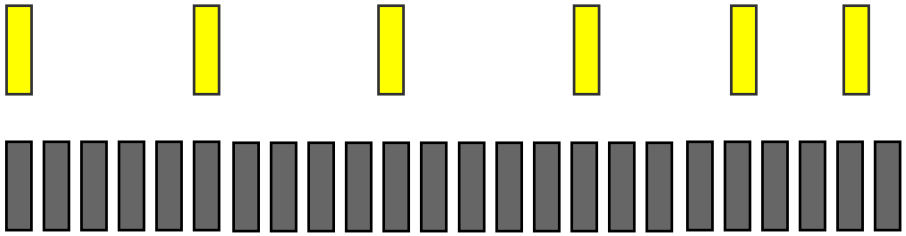
Low dose whole abdominal radiation therapy (LDWART) in combination with weekly paclitaxel for platinum resistant ovarian cancer

Phase I
10 patients

Weekly paclitaxel

Weekly paclitaxel at a pre specified dose of 80 mg/m2, 70 mg/m2, 60mg/m2 or 50 mg/m2.

Cycles of chemotherapy will be administered weekly without interruption on Days 1,8,15,22,29,36 for a total of 6 weekly cycles in combination with LDWART.



LDWART

LDWART will be given at 60 cGy fractions, twice daily for two days, with a minimum of 4 hours inter fraction interval, starting on day 1 of each cycle of weekly paclitaxel for 6 weeks..

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GAS6/AXL signaling pathway – AVB-500

Bonifacio L, Clin Transl Sci 2019

TAM family: Tyro3, **AXL**, Mer

AXL is activated by a single ligand, growth-arrest specific 6 (GAS6)

Strong binding affinity between AXL and GAS6

AXL is overexpressed in ovarian cancer (and in other cancers)

AXL overexpression linked to:

- Cancer cell survival
- Metastasis
- Poor survival
- Drug resistance
- Immune suppression
- Fibrogenesis

Experimental models:

- AXL inhibition decreases tumor
- AXL inhibition decreases tumor invasion/migration
- AXL inhibition improve sensitivity to platinum and taxane therapies

- **AVB-500 is an ultra-high affinity decoy protein**
- **AVB-500 binds circulating and bound GAS6 (blocking GAS6/AXL signaling)**
- **AVB-500 has better than 200-fold tighter affinity for GAS6 compared to the natural affinity of the ligand and the receptor**
- **AVB-S6-500 is not expected to have drug-drug interactions with cancer therapies metabolized by CYP450**

Target-mediated drug disposition (TMDD) pharmacokinetic/pharmacodynamic (PK/PD) model

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GAS6/AXL signaling pathway – AVB-500

Bonifacio L, Clin Transl Sci 2019

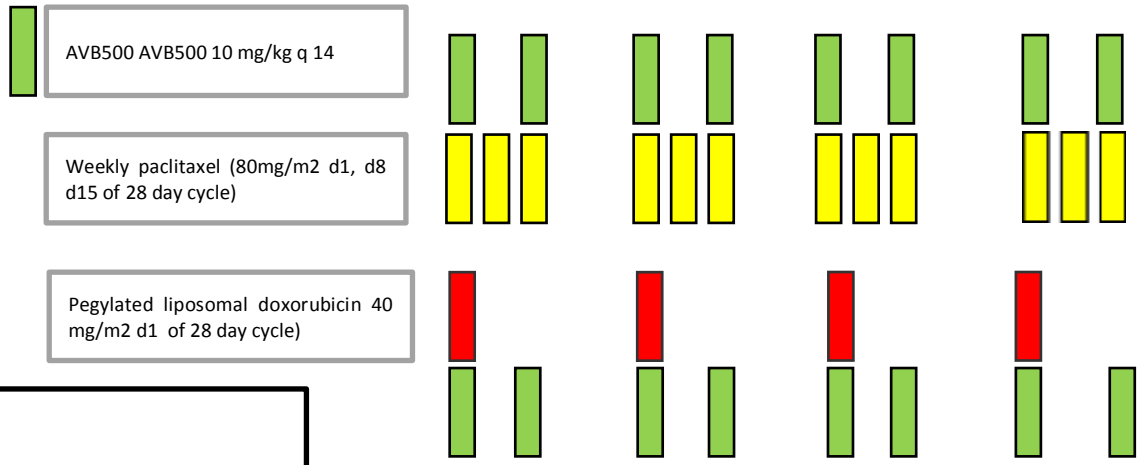
First-in-human (FIH) doses for AVB-S6-500 based on predicted target (GAS6) suppression in the clinic

1 mg/kg → 2.5 mg/kg → 5 mg/kg → 10 mg/kg → GAS6 suppression duration of 14 days

Monk B

AVB500 (high affinity inhibitor of GAS6/AXL Path) in combination with paclitaxl and PLD in platinum resistant recurrent ovarian cancer

Phase I B/II
12 patients



- **No severe adverse events**
- **No dose limiting toxicity**
- **Long lasting response**
- **Dose that is tolerated and has a optimal PK/Pdwill be investigated in pahse II trial**

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OCTOPUS trial

Banerjee S

Randomised, multi-centre phase ii umbrella trial of weekly paclitaxel +/- novel agents in platinum-resistant ovarian cancer vistusertib
Vistusertib

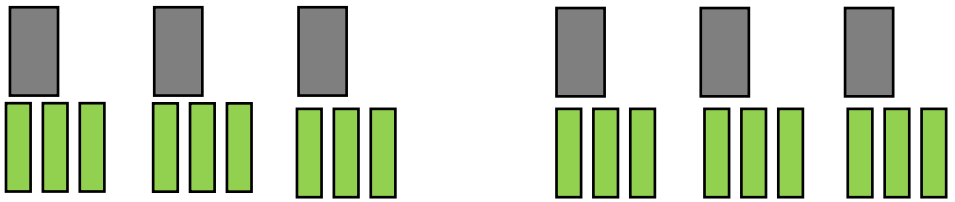
Vistusertib: dual mTORC1/mTORC2 inhibitor

Phase II randomized
140 patients

RANDOM

1

- Weekly paclitaxel (80mg/m2 d1, d8 d15 of 28 day cycle)
- Placebo (50mg BD) (D1-3, D8-10, D15-17) of 28 day cycle)



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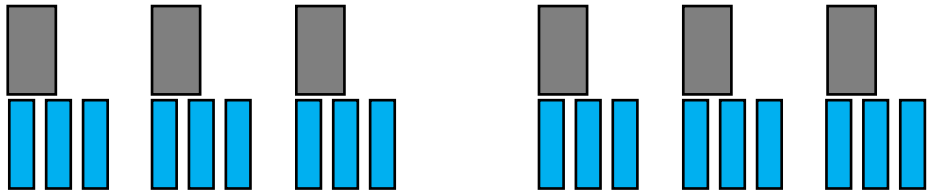
- Weekly paclitaxel (80mg/m2 d1, d8 d15 of 28 day cycle)
- Vistusertib (50mg BD) (D1-3, D8-10, D15-17) of 28 day cycle)



paclitaxel

Placebo

Vistusertib

Primary endpoint was progression-free survival (PFS)
Secondary endpoints:

- Toxicity, safety
- Overall survival (OS)
- Objective response rate (ORR)
- Qol

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Best response	Paclitaxel + vistutertib	Paclitaxel + placebo
Complete response	0 %	1 %
Partial response	29 %	30 %
Stable disease	20 %	19 %
Progressive disease	20 %	19 %
Unevaluable	21 %	23 %

	Paclitaxel + vistutertib	Paclitaxel + placebo
Median PFS (months)	4,5	4,2
HR		0,84
p		0.18
Median OS (months)	9,7	11,1
HR		1,21
p		0.80

OCTOPUS trial

- No increased Grade 3 / 4 toxicity with the addition of vistusertib to weekly paclitaxel
- No evidence of improvement in Progression-free Survival
- No evidence of improvement in Overall Survival
- No evidence of improvement in Response Rate
- BRCA n/tested: Paclitaxel + vistutertib: 6/54
  Paclitaxel + vistutertib: 12/48
- PTEN loss may preditc activity of vistusertib

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BAROCCO Trial

Colombo N

Weekly paclitaxel vs. cediranib-olaparib combination given with continuous or intermittent schedule in patients with resistant high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer

*any line of treatment
*any BRCA status

Phase III Randomized
123 patients

Paclitaxel

Olaparib

Cedinarib

RANDOM

1

1

1

Paclitaxel 80 mg/m2 weekly up to 24 weeks or PD

Olaparib 300 mg BID 7 days/week until PD

CONTINUOUS SCHEDULE - Cediranib 20 mg/D 7 days/week until PD

Olaparib 300 mg BID 7 days/week until PD

INTERMITTENT SCHEDULE - Cediranib 20 mg/D 5 days/week until PD

Primary endpoint were:

- Efficacy: progression-free survival (PFS)
- Safety: compare the safety of olaparib and cediranib as continuous vs intermittent schedule

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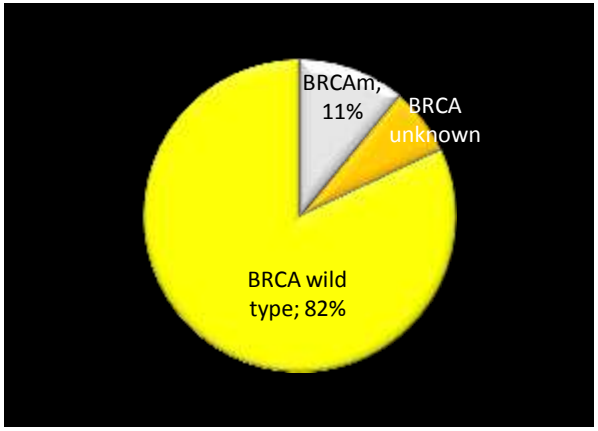
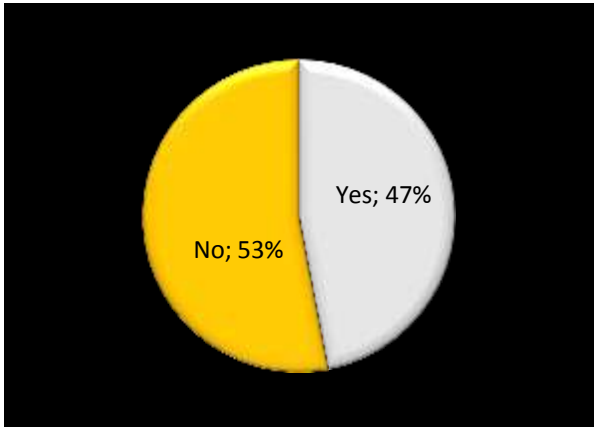
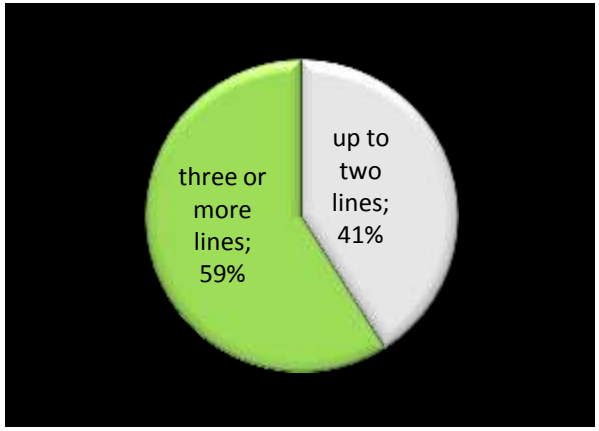
Biomarker subgroups



Previous antiangiogenic treatment subgroups



Previous chemotherapy subgroups



Treatment related discontinuation

Paclitaxel: 1

- **neurotoxicity G2**

Olaparib + Cediranib continuous schedule: 3

- **myelodisplastic syndrome G5**
- **pneumonitis G3**
- **fatigue G3**

Olaparib + Cediranib intermittent schedule: 1

- **fatigue G2**

Dose reduction

Paclitaxel:

- **7 pts (24,1 %)**

Olaparib + Cediranib continuous schedule:

- **16 pts (39 %)**

Olaparib + Cediranib intermittent schedule:

- **10 pts (24,4 %)**

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Drug related adverse events	Paclitaxel (28 pts) Any G/≥ G3	Olaparib + Cediranib continuous schedule (41 pts) Any G/≥ G3	Olaparib + Cediranib intermittent schedule (40 pts) Any G/≥ G3
Neutopenia	11 % / 7 %	7 %b / 2 %	5 % / 3 %
Anemia	18 % / -	17 % / 10 %	18 % / 13 %
MDS	- / -	2 % 2 % **(G5)**	- / -
Diarrhoea	4 % / -	51 % / 5 %	58 % / 3 %
Mucositis oral	7 % / -	12 % / 2 %	- / -
Nausea	18 % / -	51 % / 2 %	50 % / 8 %
Vomiting	- / -	37 % / -	38 % / 5 %
Per. Neurotox.	14 % / -	- / -	- / -
Fatigue	25 % / -	46 % / 10 %	40 % / 10 %
Sepsis	4 % / 4 % **(G5)**	- / -	- / -
Alopecia	18 %/ -	- / -	- / -
Rash maculo-papular	11 / -	5 % / -	5 % / -
Hypertension	- / -	29 % / 12 %	18 % / 13 %

BAROCCO trial

- First trial with the combination olaparib – cediranib in platinum resistant ovarian cancer
- Oral chemotherapy-free regimen
- Interesting PFS with the continuous schedule vs weekly paclitaxel (particularly in gBRCA wild-type population)
- Clinical benefit observed in 85 % of patients with the continuous schedule
- Continuous schedule is feasable
- The interruptionof two days of cediranib may have detrimental effect on PFS with no benefit of toxicity
- PFS and ORR data for BRCAm pupulation not provided
- 12/41 randomized patients to weekly paclitaxel refused to receive treatment after randomization

Best response	Paclitaxel	Olaparib + Cediranib continuous schedule	Olaparib + Cediranib intermittent schedule
Complete response	2 (8.3 %)	0 (0 %)	0 (0 %)
Partial response	6 (25 %)	7 (17.9 %)	4 (11.4 %)
Stable disease	5 (20.8 %)	26 (66.7 %)	18 (51.4 %)
Clinical benefit (CR + PR + SD)	54.1 %	84.6 %	62.8 %
Progressive disease	11 (45.8 %)	6 (15.4 %)	13 (37.1 %)

	Paclitaxel	Olaparib + Cediranib continuous schedule	Olaparib + Cediranib intermittent schedule
Duration of response Months)	4.4	6	2,7
Median PFS (months)	3.1	5.7	3.8
HR		0.76	1.08
p		0.29	0.76
Median PFS BRCA wt/uk (months)	2.1	5.8	3.8
HR		0.63	0.96
p		0.1	0.87

ESMO 2019 - Ovarian carcinoma

NCT02595892 trial

Konstantinopoulos PA

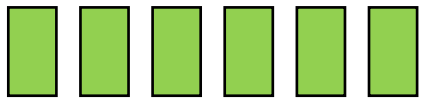
ATR inhibitor M6620 in combination with gemcitabine versus gemcitabine alone in platinum-resistant* high grade serous ovarian cancer

*no more than 1 prior regimen in the platinum resistant setting
* no prior ATR/CHK1 inhibitors and no prior gemcitabine as single agent

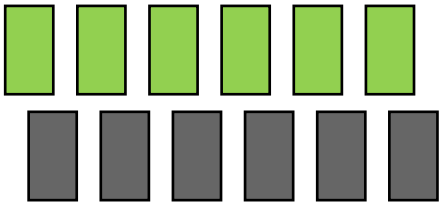
Phase II randomized
70 patients

RANDOM

- Gemcitabine 1000 mg/m2 IV on days 1 and 8 of a 21-day cycle



- Gemcitabine 1000 mg/m2 IV on days 1 and 8
- M6620 210 mg/m2 IV on days 2 and 9 of a 21-day cycle



Gemcitabine

ATR inhibitor M6620

Primary endpoint was progression-free survival (PFS)
Secondary endpoints:

- Toxicity, safety
- Overall survival (OS)
- Objective response rate (ORR)

ESMO 2019 - Ovarian carcinoma

NCT02595892 trial

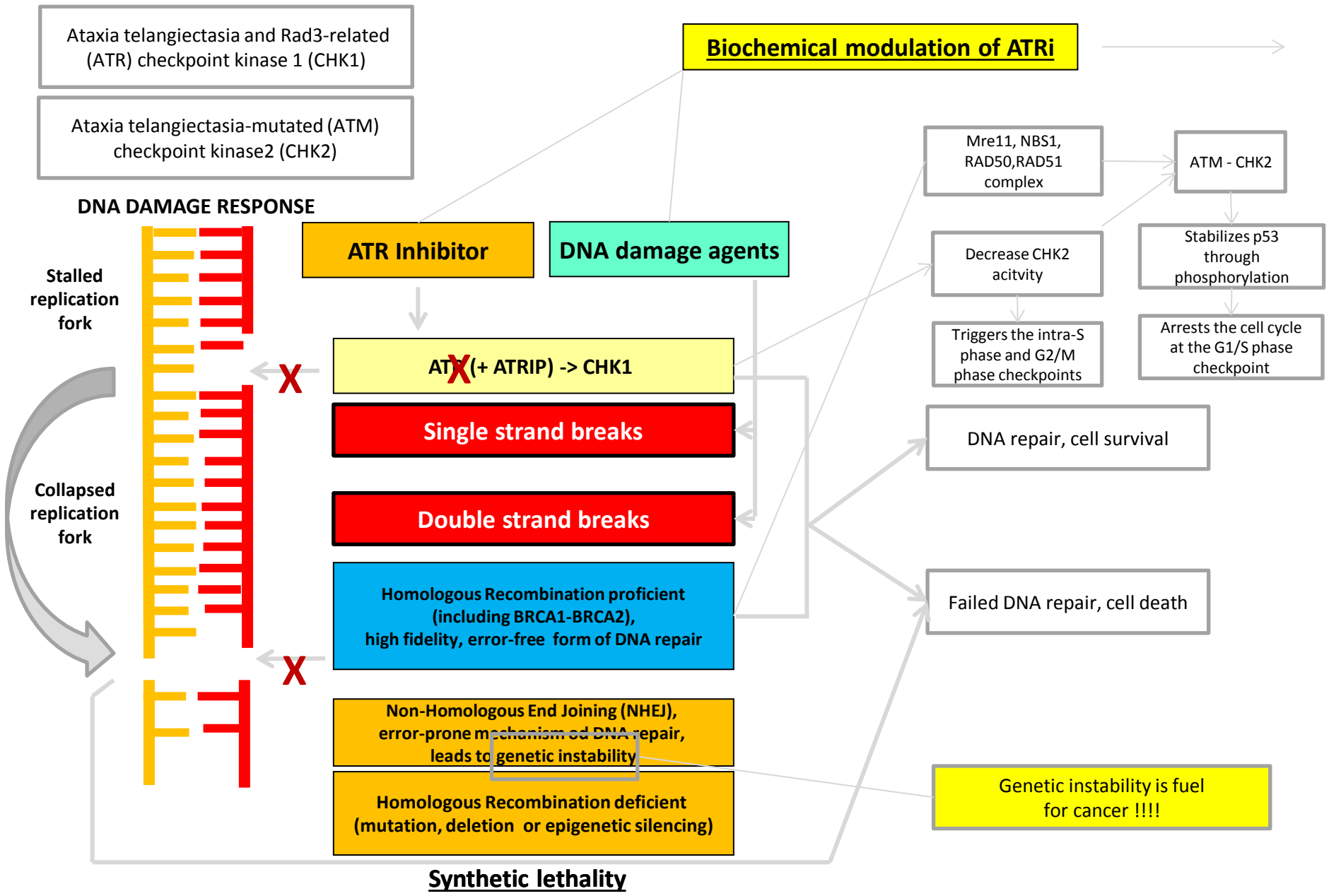
ATR inhibitor M6620 in combination with gemcitabine versus gemcitabine alone in platinum-resistant high grade serous ovarian cancer

Ongoing correlative studies

- TP53 mutations
- HRR pathway alterations
- Nucleotide excision repair pathway alterations
- ATM mutations
- CCNE1, MYC amplification
- CDKN2A, RB1 alterations
- Mutational signatures

- Almost universal loss of G1/S checkpoint (via deleterious TP53 mutations)
- Premature entry into S phase of the cell cycle due to CCNE1 amplification (about 20 % of tumors) or RB1 loss (about 11 % of tumors) or CDKN2A mRNA downregulation (about 32 % of tumors)
- Presence of homologous recombination repair alterations (about 50 % of tumors)
- Induction via amplification of various oncogenes as MYC (about 40 % of tumors)

ATR inhibitors mechanism of action



ATR inhibitors mechanism of action

5-fluorouracile in colorectal cancer

- tale of two drugs:

implications for biochemical modulation

AF Sobrero, Carlo Aschele, JR Bertino

JCO 1997

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Adverse events	M6620 in combination with gemcitabine	Gemcitabine alone
Dose reduction	13	13
Discontinuated treatment	7/34 (20.6 %)	4/36 (11,1 %)
Treatment related death **Pneumonitis** **Trombocytopenia** **Infusion related reactions**	1 (pneumonitis)* 3 (2 G2 – 1 G5)* 24 % (G3/G4) 3 (2 G1 – 1 G2)	1 (sepsis) 2 (2 G2) 6 % 0

Best response	M6620 in combination with gemcitabine	Gemcitabine alone
Complete response	0 (0 %)	1 (3 %)
Partial response	1 (3 %)	3 (8 %)
Stable disease	21 (62 %)	19 (53 %)
Progressive disease	7 (21 %)	12 (33 %)
Unvaluable* **patients who never received on-treatment scan**	5 (15 %)	1 (3 %)
Total	34 (100 %)	36 (100 %)

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	M6620 in combination with gemcitabine	Gemcitabine alone
PFS (weeks) HR = 0.57 p = 0.0491	22.8	14.7
STRATUM PFI < 3 months HR = 0.31 p = 0.0173	27.7	9.0
STRATUM PFI > 3 months < 6 months HR = 0.95 p = 0.45	Insignificant PFS difference	Insignificant PFS difference
OS (weeks) (crossover subjects censored at the time of crossover) HR = 0.82 p = 0.278	47	40.4
OS (weeks) (including subjects who crossed over) HR = 1.17 p = 0.32	47	49.1

ESMO 2019 - Ovarian carcinoma

FORWARD I (GOG 3011)

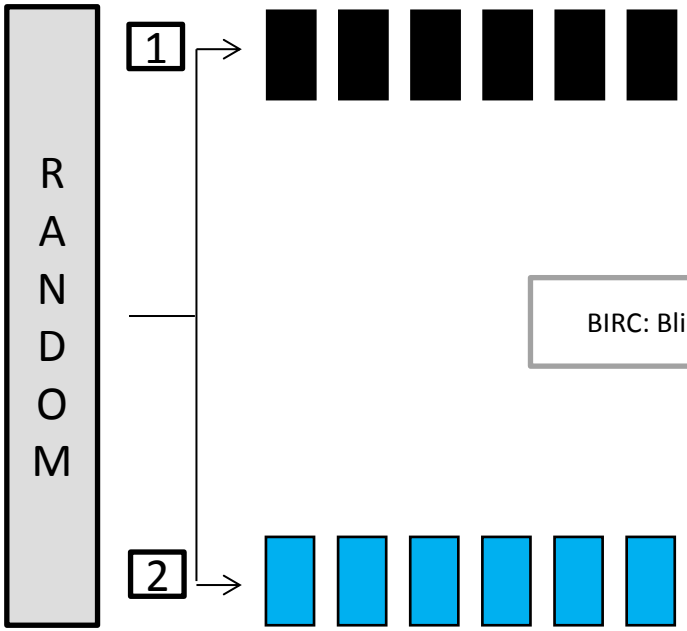
Moore KN

Mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer

Phase III
366 patients

Investigators' choice chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan).

Mirvetuximab soravtansine



BIRC: Blinded Independent Review Committee

*__Mirvetuximab soravtansine__: it is an antibody-drug conjugate that targets the FRα (folate receptor α) to microtubule –disrupting agent DM4 directly to the tumor

Primary endpoint: progression-free survival (PFS):
- for intention-to-treat (ITT) population (medium and high FRα expression)
- separately, for patients with high FRα

Secondary endpoints included objective response rate (ORR) overall survival (OS), patient reported outcomes (PRO)

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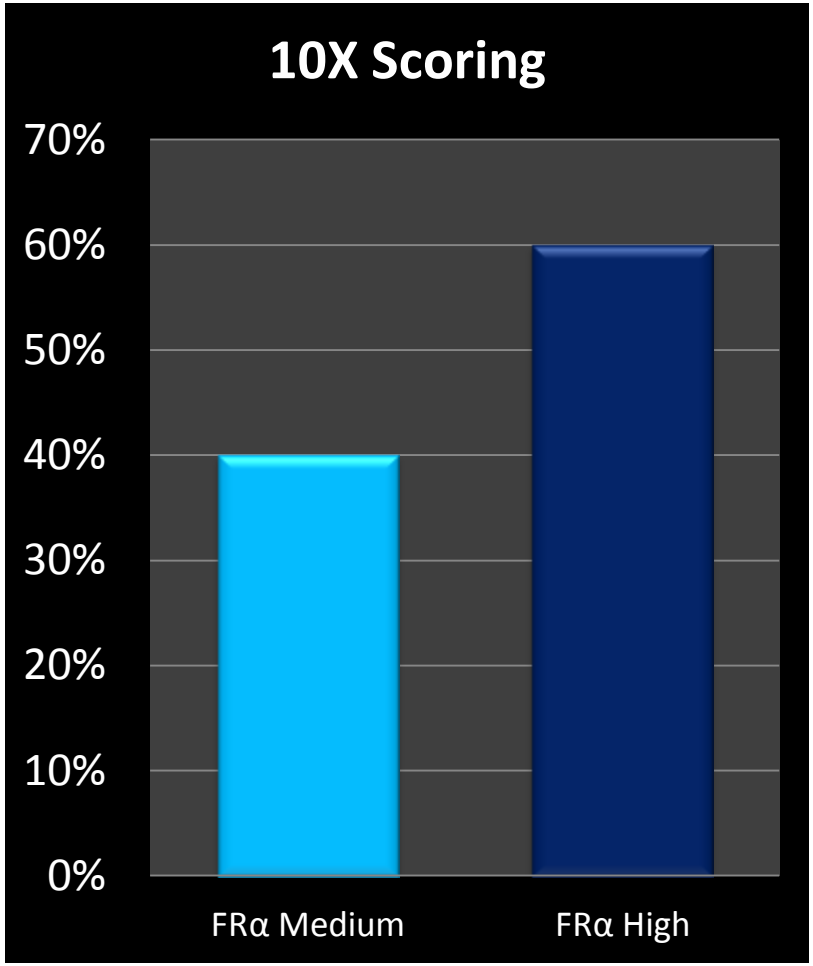
X10 SCORING

ITT Population		
Endpoint	**Treatment effect size Mirv vs Chemot**	**P value**
PFS (by BIRC) months	HR= 0.981 mPFS : 4.1 vs 4.4	0.897
ORR (by BIRC)	22 % vs 12 %	0.015
OS months	HR= 0.846 mOS : 15.6 vs 13.9	0.278
PRO	32 % vs 14 %	0.011

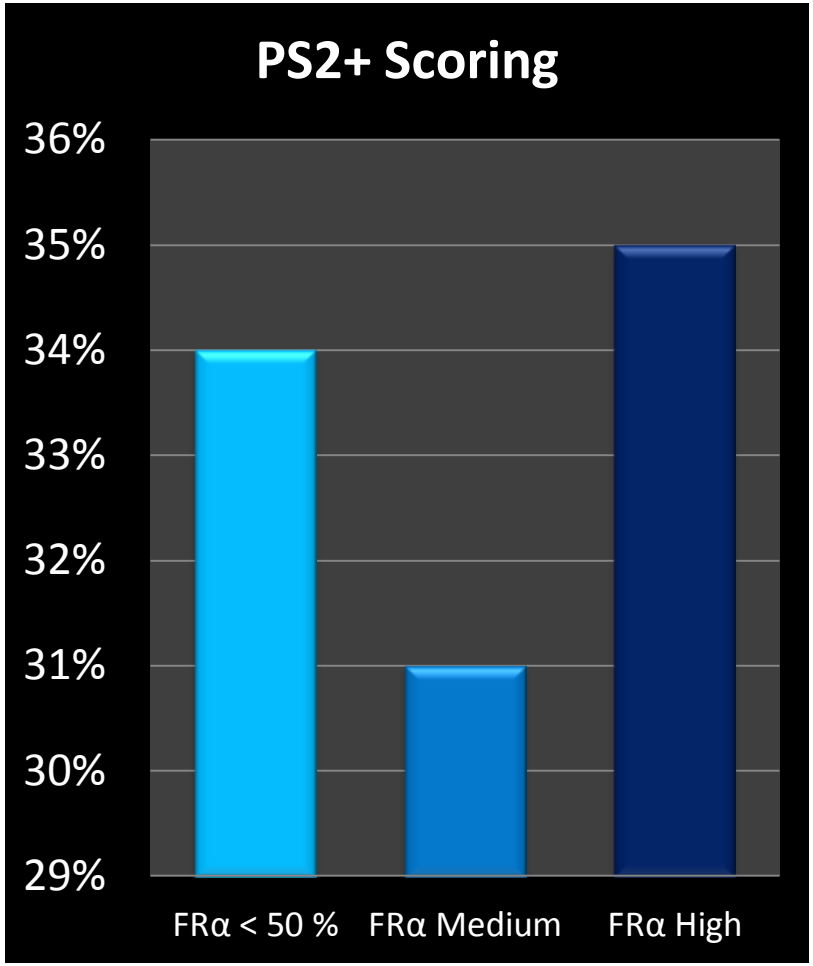
FRα population		
Endpoint	**Treatment effect size Mirv vs Chemot**	**P value**
PFS (by BIRC) months	HR= 0.693 mPFS : 4.8 vs 3.3	0.049
ORR (by BIRC)	24 % vs 10 %	0.014
OS months	HR= 0.678 mOS : 16.4 vs 12.0	0.048
PRO	28 % vs 13 %	0.096



ESMO 2019 - Ovarian carcinoma

PS2+ SCORING

	FRα < 50 %	FRα Medium	FRα high
Endpoint	**Treatment effect size Mirv vs Chemot**	**Treatment effect size Mirv vs Chemot**	**Treatment effect size Mirv vs Chemot**
PFS (by BIRC) months	HR= 1.458 mPFS : 3.8 vs 5,5	HR= 1.015 mPFS : 4.3 vs 5.6	HR= 0.549 mPFS : 5,6 vs 3.2
ORR (by BIRC)	16 % vs 16 %	28 % vs 18 %	29 % vs 6 %
OS months	HR= 0.923 mOS : 14.0 vs 13.4	HR= 0.936 mOS : 15.9 vs 20,7	HR= 0.678 mOS : 16.4 vs 11.4



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FORWARD I trial

A)

- Mirvetuximab soravtansine was well tolerated
- FORWARD I trial did not meet the PFS primary endpoint in the Intention to treat or FRα populations

B)

- 10X: wrong test
- Correct analysis of predictive markers of benefit is crucial

C)

- Exploratory analyses suggest that the change in scoring method from PS2+ to 10X introduced a population of patients into FORWARD I trial with lower levels of FRα expression than intended
- Re-analysis of the FRα high population (by PS2+ scoring) demonstrated improved outcomes correlated with FRα expression, with the strongest treatment effects for all efficacy endpoints in this population

D)

- Mirvetuximab soravtansine warrants further study

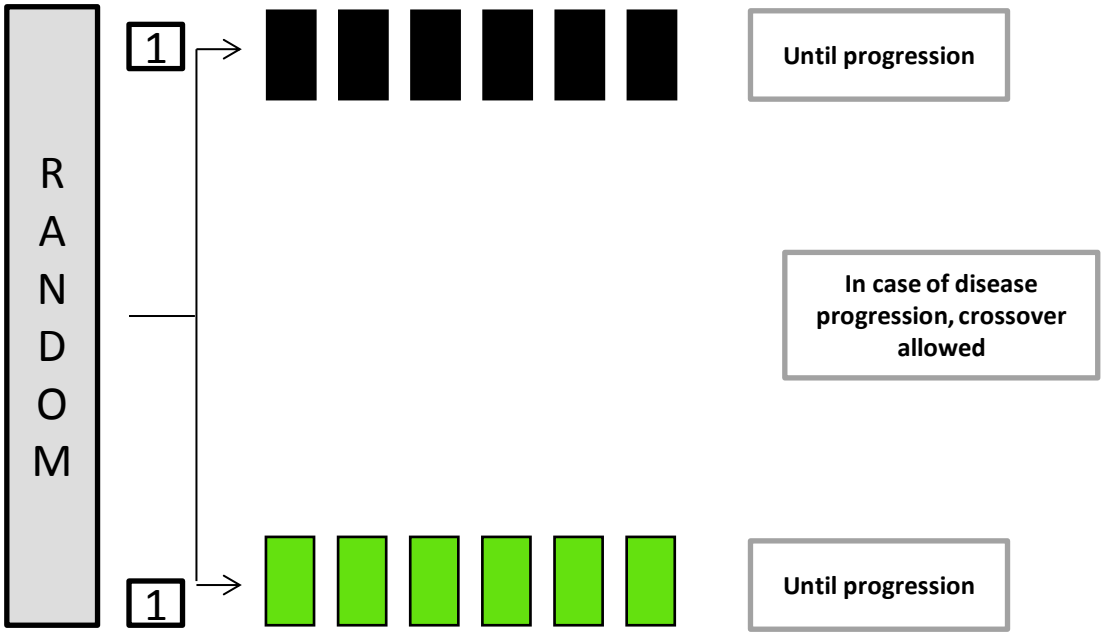
ESMO 2019 - Ovarian carcinoma

Gershenson D

Efficacy of Trametinib in patients with recurrent or progressive low-grade serous ovarian or peritoneal cancer

- At least 1 prior platinum regimen
- Unlimited n° prior therapies

Phase II/III
260 patients



Investigators' choice therapy (weekly paclitaxel, PLD, topotecan, letrozole, or tamoxifen).

Trametinib 2mg daily

Trametinib: oral MEK inhibitor

Primary endpoint: progression-free survival (PFS)
Secondary endpoints included objective response rate (ORR), toxicity, Qol

ESMO 2019 - Ovarian carcinoma

Arm	N° Patients CR + PR/ Treated	Objective response rate	Stable disease rate	Response duration (months)	Odds ratio for ORR	P value
Trametinib	34/130	26.2 %	59 %	13.6		
					5.44	< 0.0001
SOC	8/130	6.2 %	70.8 %	5.9		
Letrozole	6/44	13.6 %	70.5 %			
Tamoxifen	0/27	0 %	66.7 %			
Paclitaxel	1/11	9.1 %	63.6 %			
PLD	1/40	2.5 %	80 %			
Topotecan	0/8	0 %	50 %			

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Most common adverse events

Drug related adverse events	Trametinib Any G/≥ G3	SOC Any G/≥ G3
Skin rush	92.1 % / 15.0 %	48.5 % / 3.9 %
Fatigue	72.5% / 7.9 %	57.8 % / 3.9 %
Diarrhoea	72.4 % / 10.2 %	33.6 % / 3.1 %
Nausea	60.6 % / 9.4 %	50.8 % / 10.9 %
Anemia	51.9 % / 12.6 %	43.0 / 9.4 %
Vomiting	45.7-/ 7.1 %	34.4 % / 7.9 %
Abdominal pain	44.0 % / 5.5 %	-46.9 % / 17.2 %
Constipation	42.6 %/ 2.4 %	38.3 % / 2.3 %
Hypertension	38.6 % / 11.8 %	21,2 %-/ 4.7 %

Adverse events of special interest

Drug related adverse events	Trametinib	SOC
Retinal tear	1 (0.8 %)	0 (0 %)
Retinal vascular disorder	2 (1.6 %)	0 (0 %)
LV systolic dysfunction	2 (1.6 %)	1 (0.8 %)
Decreased ejection fraction	10 (7.9 %)	1 (0.8 %)
QTc polongation	2 (1.6 %)	0 (0 %)
Pneumonitis	3 (2.4 %)	0 (0 %)

35 % of patients discontinuated therapy for adverse events

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PFS

	Trametinib	SOC (Control)
Median PFS (months)	13.0	7.2
Hazard Ratio	0.48	
One-sided p-value	< 0.0001	

Trametinib on Crossover

	Trametinib on Crossover
Median PFS (months)	10.8
ORR	15 %
Response duration (months)	15.9

OS

	Trametinib	SOC (Control)
Median OS (months)	37.0	29.2
Hazard Ratio	0.75	
One-sided p-value	0.054	

ESMO 2019 - Ovarian carcinoma

Trametinib:

- Improved progression-free survival (PFS)
- Improved overall response rates (ORRs)
- Improved duration of response
- Improved median overall survival (mOS)

Principal grade $\geq$ 3 adverse events are haematological, gastrointestinal, skin and vascular toxicities

Trametinib represents a new potential standard-of-care treatment option for women with recurrent low-grade serous ovarian carcinoma

ESMO 2019 – Cervical carcinoma

Vilnius

ESMO 2019 – Cervical carcinoma

Multidisciplinary session

Young patients with stage IB2 cervical cancer

- Is there a place for conservative surgery ?

Sven Mahner

- Is there a place for neoadjuvant chemotherapy ?

Mary Mc Cormack

- Can modern tecniques reduce the burden of toxicity ?

Remy A. Nout

ESMO 2019 – Cervical carcinoma

ESMO Guidelines - Cervical cancer

FIGO stage IB1 < 2cm

Radical trachelectomy is considered a standard fertility-sparing procedure in patients with early cervical cancer and tumours < 2cm".

FIGO stage IB> 2cm

For tumours > 2cm, NACT followed by conisation or trachelectomy may also be a valid choice, but downstaging by NACT in IB1 and IB2 cervical cancer before fertility-sparing surgery is still an experimental procedure

Locally advanced cervical cancer (bulky IB2–IVA disease)

CRT is considered the standard of care for patients with bulky IB2–IVA disease

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Cervical cancer

40 % diagnosis of cervical cancer before 40 years

Increasing mean age of women at birth of first child

Criteria for performing a conservative surgery:

- A desire for future fertility
- Proven diagnosis of invasive squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, not unfavorable histology
- Stage IA1 with lymphovascular space invasion, stage IA2 o IB1
- Tumor size $\leq$ 2 cm
- Tumor limited to the cervix
- No evidence of pelvic and/or other distant metastases

ESMO 2019 – Cervical carcinoma

FIGO staging for carcinoma of the cervix uteri

Stage IB: clinical visible lesion confined to the cervix or microscopic lesion greater than IA2

- stage IB1: clinical visible lesion ≤ 4 cm in greatest dimension
- stage IB2: clinical visible lesion > 4 cm in greatest dimension

Revised FIGO staging for carcinoma of the cervix uteri

Stage IB: invasive carcinoma with measured deepest invasion ≥ 5 mm (greatest than stage IA), lesion limited to the cervix uteri

- stage IB1: invasive carcinoma ≥ 5 mm depth of stromal invasion and < 2 cm in greatest dimension
- stage IB2: invasive carcinoma ≥ 2 and < 4 cm in greatest dimension
- stage IB3: invasive carcinoma ≥ 4 in greatest dimension

Bhatla N, Gyn Obstet 2019

ESMO 2019 – Cervical carcinoma

Multidisciplinary session

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Remy A. Nout

ESMO 2019 – Cervical carcinoma

Multidisciplinary session

Young patients with stage IB2 cervical cancer
Is there a place for conservative surgery ?
Conclusion - Sven Mahner

Yes, but:

- If surgery only, open abdominal trachelectomy is probably b
- If NACT, vaginal trachelectomy or cone biopsy appear f
  - Unclear , whether lymph node staging bett

Oncololgic outcome unclear

- Early stage cervical cancer curable

Obstetric outcome

- If pregnancy occurs, goo
- Live birth/healthy f elivery)

Patients treat ge stage IB cervical cancer should be treated at tertiary cancer centersan registry

EXPERIMENTAL

ESMO 2019 – Cervical carcinoma

Multidisciplinary session

Young patients with stage IB2 cervical cancer

- Is there a place for conservative surgery ?

Sven Mahner

- Is there a place for neoadjuvant chemotherapy

Mary Mc Cormack

- Can modern tecniques reduce the burden of toxicity ?

Remy A. Nout

ESMO 2019 – Cervical carcinoma

Neoadjuvant chemotherapy

Rationale for neoadjuvant chemoterapy:
- shrinkage of primary tumor
- treatment of locoregional and distant micrometastases
- reduced risk factors and improved negative surgical margins
- reduced needs for adjuvant treatments
- better disease control
- increased overall survival ?

Adverse events any grade occurring or persisting more than 90 days after completion of treatment

Nodal points:
- lack of RT resources
- RT long waiting times
- great surgical expertise

Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial

Site	NACT – Surgery (n=316)	CTRT (n=317)	All (n=633)	P value
Rectal	18 (5,7 %)	42 (13,3 %)	60 (9,5 %)	0,002
Bladder	9 (2,8%)	27 (7,3 %)	32 (5,1 %)	0,017
Vaginal	63 (19,9 %)	117 (36,9 %)	180 (28,4 %)	< 0,001
Other	30 (9,5 %)	17 (5,4 %)	47 (7,4 %)	0,068

Gupta S, JCO 2018

ESMO 2019 – Cervical carcinoma

Multidisciplinary session

Young patients with stage IB2 cervical cancer
Is there a place for neoadjuvant chemotherapy
Conclusion - Mary Mc Cormack

Recent studies of NACT/RS vs CRT:

- Better DFS with CRT but no difference in OS
- < 20 % had IB disease (under represented)
- About 25 % in NACT/RS group had postoperative RT
- Appears to be a correlation between response to NACT and outcome
- Only consider NACT/RS if RT resources are lacking and were surgical expertise available-otherwise no advantage over CRT
- In future may be a role for NACT before CRT in this patient group

ESMO 2019 – Cervical carcinoma

Multidisciplinary session

Young patients with stage IB2 cervical cancer

- Is there a place for conservative surgery ?

Sven Mahner

- Is there a place for neoadjuvant chemotherapy

Mary Mc Cormack

- Can modern tecniques reduce the burden of toxicity ?

Remy A. Nout

ESMO 2019 – Cervical carcinoma

Multidisciplinary session

Young patients with stage IB2 cervical cancer
Can modern tecniques reduce the burden of toxici
Conclusion - Remy A. Nout

Integration of modern imaging in pre-treatment wo ing) and response evaluation

Dose and volume matter; increased confor cision reduce morbidity

Future developments:

- MRI guidance; proton t
- Ultrasound guidan g; individualized applicators

Impact of /s rogrammes

Cost- vailability on a global level

... new indications ?

ESMO 2019 - Ovarian carcinoma

CheckMate 358

Nauman RW

Efficacy and safety of nivolumab (Nivo) + ipilimumab (Ipi) in patients with recurrent / metastatic cervical cancer

Open-label, multi-cohort
Phase I/II
91 patients

RANDOM

1

Nivolumab + Ipilimumab regimen

Nivo3 + IPI1 (n = 45)
- Nivolumab 3 mg/kg q2w
- Ipilimumab 1 mg/kg q6w

1

Nivo1 + IPI3 (n = 46)
- Nivolumab 1 mg/kg + Ipilimuma b 1 mg/kg q3w x 4 followed by Nivolumab 240 mg q2w

Ongoing trial

Primary endpoint: objective response rate (ORR)

Secondary endpoints: progression-free survival (PFS), overall survival (OS), duration of response

ESMO 2019 - Ovarian carcinoma

Tumor response

	NIVO3 + IPI1		NIVO1 + IPI3	
Response in all treated patients	NO prior systemic therapy for R/M disease (n = 19)	Prior systemic therapy for R/M disease (n = 26)	NO prior systemic therapy for R/M disease (n = 24)	Prior systemic therapy for R/M disease (n = 22)
ORR (%)	31.6	23.1	45.8	36.4
Clinical benefit rate (%)	63.2	53.8	70.8	72.7
Best overall response				
Complete response	3 (15.8)	1 (3.8)	1 (4.2)	3 (13.6)
Partial response	3 (15.8)	5 (19.2)	10 (41.7)	5 (22.7)
Stable disease	6 (31.6)	8 (30.8)	6 (25.0)	8 (36.4)
Progressive disease	7 (36.8)	11 (42.3)	6 (25.0)	5 (22.7)
Duration of response, median (months)	NR	14.6	NR	9.5
ORR by tumor cell PD-L1 expression				
PD-L1 ≥ 1 %, responder (%)	4/13 (30.8)	4/10 (40.0)	4/11 (36.4)	2/12 (16.7)
PD-L1 ≤ 1 %, responder (%)	1/3 (33.3)	1/11 (9.1)	0/4 (0.0)	4/7 (57.1)

ESMO 2019 - Ovarian carcinoma

Safety

	NIVO3 + IPI1		NIVO1 + IPI3	
Events, n (%)	Any grade	Grade 3-4)	Any grade	Grade 3-4)
TRAEs	36 (80)	13 (28.9)	38 (82.6)	17 (37.0)
Treatment related SAEs	12 (26.7)	8 (17.8)	16 (34.8)	10 (21.7)
TRAEs leading to treatment discontinuation	6 (13.3)	2 (4.4)	9 (19.6)	6 (13.0)
Treatment related SAEs leading to treatment discontinuation	2 (4.4)	1 (2.2)	5 (10.9)	5 (10.9)

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TRAEs with incidence ≥ 5 %

	NIVO3 + IPI1		NIVO1 + IPI3	
	Any grade	Grade 3-4)	Any grade	Grade 3-4)
Generaladministration site	17 (37.8)	0 (0.0)	20 (43.5)	0 (0.0)
Gastrointestinal	16 (35.6)	4 (8.9)	26 (56.5)	6 (13.0)
Skin	16 (35.6)	0 (0.0)	16 (34.8)	2 (4.3)
Laboratory investigations	15 (33.3)	5 (11.1)	17 (37.7)	9 (19.6)
Endocrine	13 (28.9)	2 (4.4)	20 (43.5)	0 (0.0)
Pulmonary	6 (13.3)	1 (2.2)	6 (13.0)	1 (2.2)
Metabolism	5 (11.1)	1 (2.2)	5 (10.9)	0 (0.0)
Nervous system	4 (8.9)	0 (0.0)	6 (13.0)	0 (0.0)
Musculoskeletal	2 (4.4)	1 (2.2)	9 (19.6)	0 (0.0)
Hepatobiliary	2 (4.4)	2 (4.4)	3 (6.5)	2 (4.3)

ESMO 2019 - Ovarian carcinoma

Survival

	NIVO3 + IPI1		NIVO1 + IPI3	
	NO prior systemic therapy for R/M disease (n = 19)	Prior systemic therapy for R/M disease (n = 26)	NO prior systemic therapy for R/M disease (n = 24)	Prior systemic therapy for R/M disease (n = 22)
Median PFS (months)	13.8	3.6	8.5	5.8
PFS 6 months (%)	57.9	26.9	60.9	47.6
PFS 12 months (%)	52.6	17.9	43.5	38.1
Median OS (months)	NR	10.3	NR	25.4
OS 6 months (%)	89.5	64.6	91.7	90.0
OS 12 months (%)	83.5	37.5	78.0	84.7

ESMO 2019 – Endometrial carcinoma

Kernavè

The Cancer Genome Atlas (TCGA)

The Cancer Genome Atlas (TCGA): four molecular subgroups of endometrial cancer [exome sequence analysis: somatic copy number alterations (SCNAs) plus tumour mutation burden] - Comprehensive, multiplatform analysis of 373 endometrial carcinomas (307 endometrioid, 66 serous, 13 mixed; fully evaluted cases: 232) **:**

1. polymerase E catalytic subunit (POLE) ultra-mutated (232 × 10^{-6} mutations/Mb), unique nucleotide change spectrum [patients: 17/232 = **7,327** %]
2. MSI hyper-mutated (18 × 10^{-6} mutations/Mb), MSI tumors, most with MLH1 promoter methylation [patients: 65/232 = **28,017** %]
3. copy number low, lower mutation frequency (2.9 × 10^{-6} mutations/Mb), most of the microsatellite stable (MSS) endometroid subtype [patients: 90/232 = **38,793** %]
4. copy number high, low mutation rate (2.3 x 10^{-6} mutations per Mb), primarily serous-like cancers with extensive SCNA [patients: 60/232 = **25,862** %]

Endometrioid: 307 (82,3 %)
Serous/other: 66 (17,7%)

Kandoth, Nature 2013

ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer)

ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) - Vancouver team (primary ECs from the Vancouver General Hospital cases banked in the OVCARE Tissue Bank Repository, Vancouver, BC, Canada) - analysis of 152 high-risk endometrial (endometrioid, serous clear cell) carcinomas (fully evaluted cases: 143) [Talhouk, Br J Cancer 2015]**:**

1. MMR abn [patients: 41/143= **29** %]
2. POLE EDM [patients: 12/143= **9** %]
3. p53 wt [patients: 63/143 = **45** %]
4. p53 abn [patients: 25/143 = **18** %]

Vancouver General Hospital cases banked in the OVCARE Tissue Bank Repository: analysis of low, intermediate, high risk endometrial carcinoma

Endometrioid: (83 %)
Serous/other: (17 %)

ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) – TransPORTEC team (PORTEC 1 - 2) - analysis of 947 endometrial carcinomas (fully evaluated cases: 834) [Stelloo, Clin Cancer Res 2016]:

1. MMR abn [patients: 219/834 = **26** %]
2. POLE EDM [patients: 49/834 = **6** %]
3. p53 wt [patients: 492/834 = **59** %]
4. p53 abn [patients: 74/834 = **9** %]

PORTEC 1: endometrial adenocarcinoma stage I, grade 1 with deep (>50%) myometrial invasion [ESMO 2016 Intermediate risk]; grade 2 with any invasion [ESMO 2016 Low-Intermediate risk] ; or grade 3 with superficial (<50%) [ESMO 2016 High-Intermediate risk]
PORTEC 2: endometrial adenocarcinoma stage I or IIA endometrial carcinoma with features of high-intermediate risk (age 60 years and stage IC, grade 1 or 2[ESMO 2016 Intermediate risk]; or stage IB, grade 3 disease)[ESMO 2016 High-Intermediate risk; ESMO 2016 High risk]; or any age and stage 2A disease, except grade 3 disease with >50 % myometrial invasion)[ESMO 2016 High risk]

ProMisE (Proactive Molecular Risk Classifier for Endometrial Cancer) – TransPORTEC team (PORTEC 3) - analysis of 116 high-risk endometrial carcinomas using inclusion criteria of the PORTEC3 study [Stello, Modern Patol 2015]:

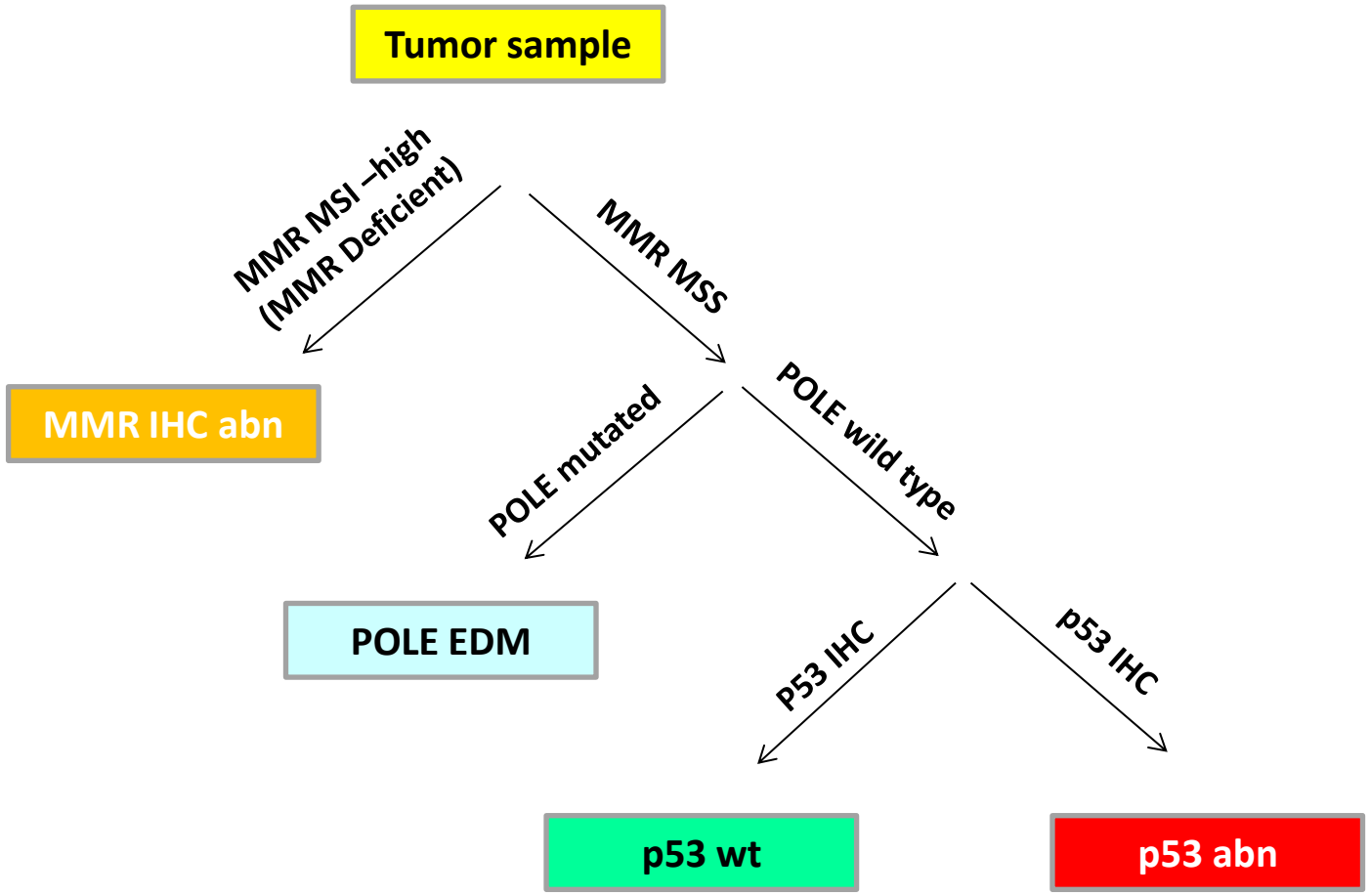
1. MMR abn [patients: 19/116 = **16** %]
2. POLE EDM [patients: 14/116 = **12** %]
3. p53 wt [patients: 44/116 = **38** %]
4. p53 abn [patients: 39/116 = **34** %]

Endometrioid: 74,1 %
Serous/other: 25,8 %

PORTEC 3: stage 1A endometrioid endometrial cancer grade 3 with documented LVSI [ESMO 2016 High-Intermediate risk]; stage IB endometrioid endometrial cancer grade 3 [ESMO 2016 High-Intermediate risk]; stage II endometrioid endometrial cancer [ESMO 2016 risk]; stage IIIA, IIIB (parametrial invasion), or IIIC endometrioid endometrial cancer [ESMO 2016 High risk]; or serous or clear-cell histology endometrial cancer with stages IA (with invasion), IB, II, or III. [ESMO 2016 High-risk]

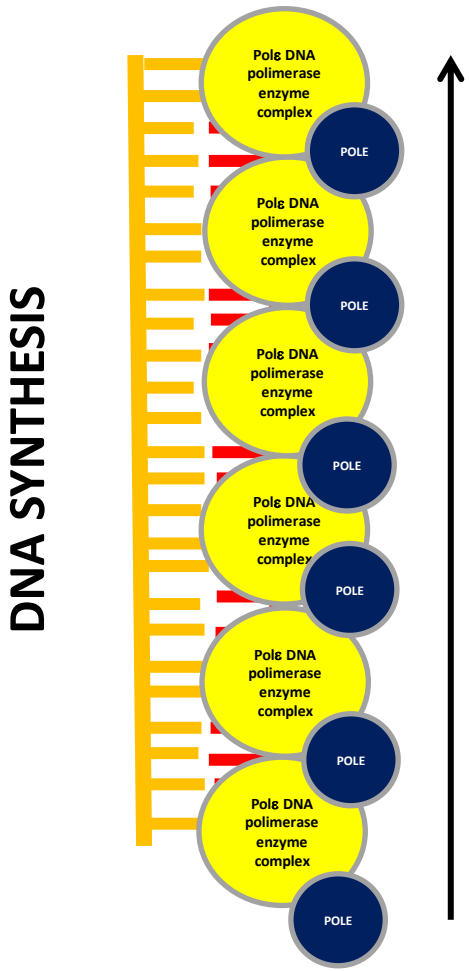
Steps in molecular classification with Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE)

Model: MMR IHC/POLE mut/p53 IHC

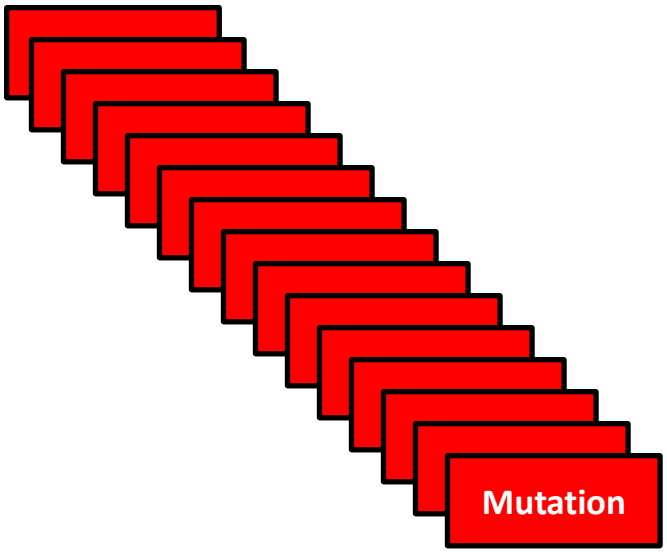


Thalouk, Br J Cancer 2015

Endometrial cancers - POLE



POLE: catalytic and proofreading subunits of the Polε DNA polymerase enzyme complex; exonuclease function



POLE exonuclease domain mutations (EDMs)

↓

Increase of spontaneous mutation rate

↓

Tumorigenesis

The Cancer Genome Atlas (TCGA): endometrial carcinoma - polymerase E catalytic subunit (POLE) ultra-mutated

p53 in human cancers

The TP53 gene is the most frequently mutated (or inactivated) gene in human cancers (> 50 %) [Freed – Pastor WA, Gene Dev 2012]

TP53: Discover as Proto-Oncogene [Kress, 1979 J Virol; Linzer 1979, Cell]

TP53: Considered as Tumor Suppressor Gene [Wolf 1984, Mol Cell Biol; Baker 1989, Science]

p53: "**The Guardian of the Genome**" [Lane, Nature 1992]

p53 activities:

- DNA repair process regulation
- Apoptotic or survival cell regulation
- Tissue renewal
- Cell adhesion regulation
- Eptithelial to mesenchimal transition inhibition
- Differentiation regulation
- Migration regulation
- Inflammation regulation
- Wound healing
- Homeostatic regulation of metabolism

The new concept of p53 as a "**Super Hub**" [Aylon 2015, Cold Spring Harb Perpect Med]

p53 mutation or inactivation causes **"Gain of function"** (GOF)

DNA Damage
p53 Wild type
→ • p53 level rises • G1 arrest
→ Repair before cell division
→ Programmed cell death (apoptosis)

DNA Damage
p53 mutated (or inactivated)
→ • No p53 • No G1 arrest
→ Division with damage (anueuploidy, mutation)
→ Tumor mitotic failure and cell ceath

Functional flexibility of p53 (wild type)

p53 family members: p53, p63, p73
How do they interact ?

p53 Isoforms ?

p53 mutated tumor cells acquire:
- genomic instability
- proangiogenic properties
- invasive and metastatic properties
- metabolic adaptations
- stemness

Mutated p53: reprogramming stem cell differentiation

ESMO 2019 – Endometrial carcinoma

NCT02501096

Patients wiith Advanced Endometrial Cancer

Phase II Study
108 patients

Pembrolizumab

Lenvatinib

Treatment:
- Pembrolizumab 200 mg day 1 q3w
- Lenvatinib 20 mg administered orally, once daily continuously

Vs
- Paclitaxel 80 mg /m2 days 1,8,18 q 4w

or
- Doxorubicin 60 mg /m2 day 1 q 3w

Primary Outcome Measures :
- Overall response rate at 24 weeks

Secondary Outcome Measures
- Duration of progression-free survival (PFS)
- Health-Related Quality of Life (HRQoL)
- Safety and tolerability
- Overall Survival (OS)

Inclusion criteria:
- Histologically confirmed diagnosis of endometrial carcinoma
- Evidence of advanced, recurrent or metastatic
- Evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC
- Historical or fresh tumor biopsy specimen for determination of mismatch repair (MMR) status.
- Measurable disease
- performance status ECOG 0-1

ESMO 2019 – Endometrial carcinoma

Tumor response

Response in all treated patients (24 weeks)	Total (n = 108)	Not MSI –H or dMMR (n = 94)	MSI –H or dMMR (n = 11)
ORR (%), complete + partial response)	41 (38.0 %)	34 (36.2 %)	7 (63.6)
Duration of response		NE	
> 6 months	87 %	85 %	
> 12 months	63 %	60 %	

Critical points

- Grade 3/4 adverse ev3ents in 69, 4 % of patients (hypertension 32.4 %)
- Most frequent adverse events of any grade: hypetension, diarrhoea, decrease appetite, fatigue, hypothyroidism, nausea
- Study drug discontinuation in 20 % of patients, interruption in 72 %, reduction of 65 %
- No information about grade G5 toxicity

ESMO 2019 – Endometrial carcinoma

Keynote 775 - Ongoing

Phase III Study

Patients wiith Advanced Endometrial Cancer

RANDOM

- **Pembrolizumab**
- **Lenvatinib**
- **Paclitaxel** or **Doxorubicin**

Treatment:
- Pembrolizumab 200 mg day 1 q3w
- Lenvatinib 20 mg administered orally, once daily continuously

Vs
- Paclitaxel 80 mg /m2 days 1,8,18 q 4w

or
- Doxorubicin 60 mg /m2 day 1 q 3w

Primary Outcome Measures :
- Duration of progression-free survival (PFS)
- Overall survival (OS)

Secondary Outcome Measures :
- Objective response rate by RECIST 1.1
- Health-Related Quality of Life (HRQoL)
- Frequency and severity of adverse events

Inclusion criteria:
- Histologically confirmed diagnosis of endometrial carcinoma
- Evidence of advanced, recurrent or metastatic
- Evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen for EC
- Historical or fresh tumor biopsy specimen for determination of mismatch repair (MMR) status.
- Measurable disease
- performance status ECOG 0-1

ESMO 2019 – Endometrial carcinoma

GARNET

Patients wiith Advanced Endometrial Cancer

Phase I/II Study
125 patients

Dostarlimab

Dostarlimab 500 mg once every 3 weeks x 4 doses, then 1000 mg once every 6 weeks until disease progression

Dostarlimab is a humanized monoclonal antibody that binds with high affinity to PD-1 resulting in inhibition of its binding to programmed death receptor ligands 1 and 2 (PD-L1 and PD-L2).

Other Name: TSR-042

Primary Outcome Measures :
- Objective response rate

Secondary Outcome Measures :
- Duration of response
- PFS
- OS
- Safety

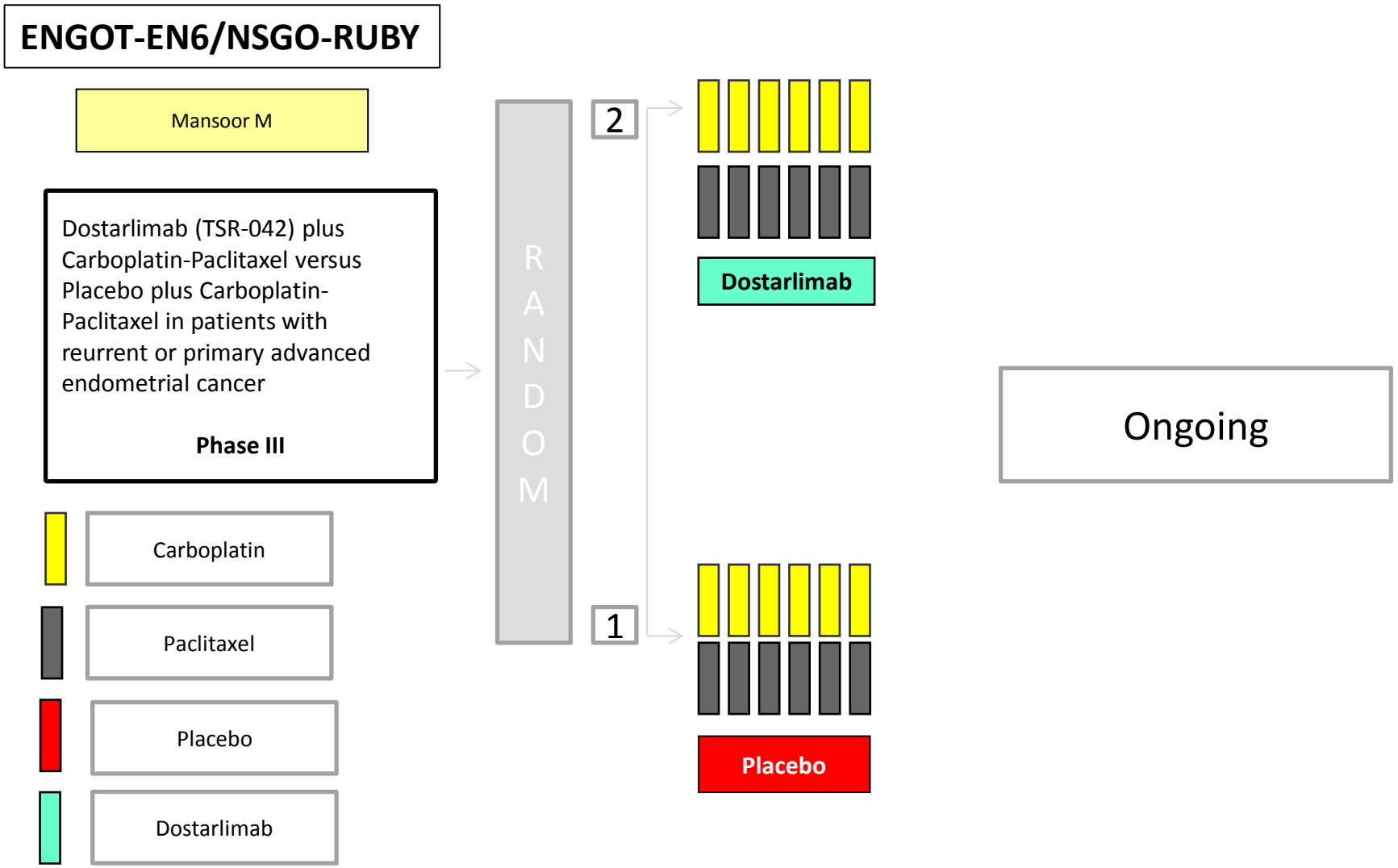
ESMO 2019 – Endometrial carcinoma

Tumor response

Response in all treated patients (24 weeks)	Total (n = 125)	MSS (n = 41)	MSI (n = 79)	MSI unknown (n = 5)
ORR (%), complete + partial response)	30 %	49 %	20 %	
Disease control rate	53 %	63 %	47 %	

- 84/125 (70.4%) patients had at least 1 treatment-emergent adverse event (TEAE)
- The most commonly reported TEAEs related to dostarlimab were fatigue (14.4%), diarrhea (12.8%), and nausea (12.0%).
- Adverse events of low grade, with only 13.6% of patients experiencing grade 3 or higher adverse events
- No deaths occurred due to a treatment-related adverse event.
- 5.6% of all patients experienced a grade 3 or higher immune related, treatment-related adverse event.

ESMO 2019 – Endometrial carcinoma



ESMO 2019 – Gynecologic tumors

Thank you for your attention …

Jurmala

… and Lithuania and Latvia for their wonderful landscapes