The 4th MEMAGO Annual Congress
in Association with the 1st Emirates
Gynecological Oncology Conference

Medical Treatment for Advanced Endometrial Cancer

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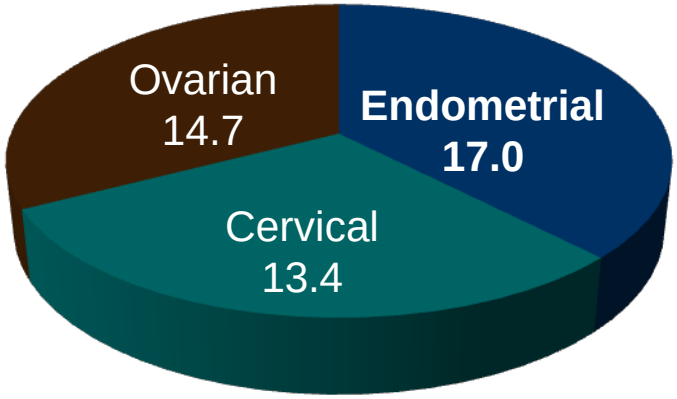
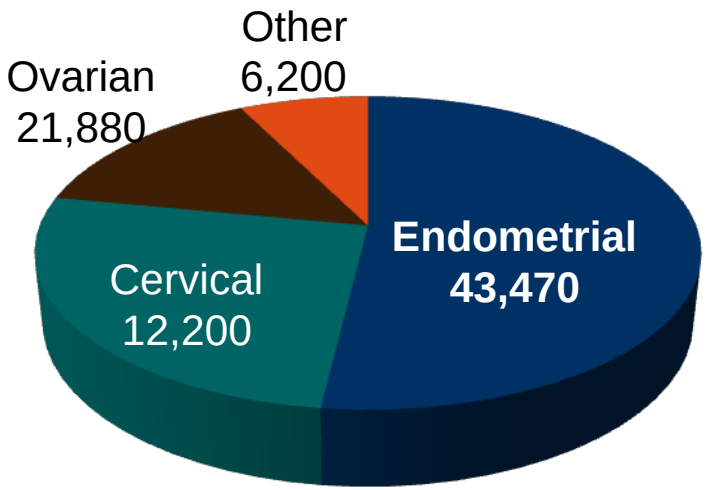
Endometrial Cancer Epidemiology

- Endometrial cancer is most common gynaecologic malignancy in Europe and US
  - US: 22 per 100,000 women
  - Europe: 17 per 100,000 women
  - South East Asia/Africa: each <3.5 per 100,000 women

EU age-adjusted standardized gynecologic cancer incidence rates per 100,000 women, 2000



US estimated new gynecologic cancer cases, 2010



Histology Subtype in endometrial cancer

	Type I	Type II
Clinical, endocrinological, and morphological components (Bokhman classification[5])		
Distribution	60–70%	30–40%
Reproductive function	Decreased	No disturbances
Onset of menopause	After age 50 years	Younger than age 50 years
Background endometrium	Hyperplasia	Atrophy
Oestrogen associated	Yes	No
Associated obesity, hyperlipidaemia, and diabetes mellitus	Yes	No
Tumour grade	Low (grades 1–2)	High (grade 3)
Myometrial invasion	Superficial	Deep
Potential for lymphogenic metastatic spread	Low	High
Prognosis	Favourable	Unfavourable
Sensitivity to progestagens	High	Low
Outcome (5-year survival)	86%	59%
Prototypical histological type	Endometrioid	Serous
Oestrogen-receptor or progesterone-receptor expression	High	Low
Stage at diagnosis	Early (FIGO stage I–II)	Advanced (FIGO stage III–IV)

Murali R, Lancet Oncol, 2014

Molecular alterations in endometrial cancer

	Type I	Type II
PTEN mutation	52–78%	1–11%
PIK3CA mutation	36–52%	24–42%
PIK3R1 mutation	21–43%	0–12%
KRAS mutation	15–43%	2–8%
ARID1A mutation	25–48%	6–11%
CTNNB1 mutation	23–24%	0–3%
TP53 mutation	9–12%	60–91%
PPP2R1A mutation	5–7%	15–43%
HER2 amplification	0	27–44%
Microsatellite instability	28–40%	0–2%

FIGO=International Federation of Gynaecology and Obstetrics.

Murali R, Lancet Oncol, 2014

Cancer Genome Atlas Research Network

Comprehensive genomic and transcriptomic analysis of endometrial cancer

Four genomic classes

	POLE (ultramutated)	MSI (hypermutated)	Copy-number low (endometrioid)	Copy-number high (serous-like)
Copy-number aberrations	Low	Low	Low	High
MSI/*MLH1* methylation	Mixed MSI high, low, stable	MSI high	MSI stable	MSI stable
Mutation rate	Very high (232×10^{-6} mutations/Mb)	High (18×10^{-6} mutations/Mb)	Low ($2{\cdot}9\times10^{-6}$ mutations/Mb)	Low ($2{\cdot}3\times10^{-6}$ mutations/Mb)
Genes commonly mutated (prevalence)	*POLE* (100%) *PTEN* (94%) *PIK3CA* (71%) *PIK3R1* (65%) *FBXW7* (82%) *ARID1A* (76%) *KRAS* (53%) *ARID5B* (47%)	*PTEN* (88%) *RPL22* (37%) *KRAS* (35%) *PIK3CA* (54%) *PIK3R1* (40%) *ARID1A* (37%)	*PTEN* (77%) *CTNNB1* (52%) *PIK3CA* (53%) *PIK3R1* (33%) *ARID1A* (42%)	*TP53* (92%) *PPP2R1A* (22%) *PIK3CA* (47%)
Histological type	Endometrioid	Endometrioid	Endometrioid	Serous, endometrioid, and mixed serous and endometrioid
Tumour grade	Mixed (grades 1–3)	Mixed (grades 1–3)	Grades 1 and 2	Grade 3
Progression-free survival	Good	Intermediate	Intermediate	Poor
	7%	28%	39%	26%

Murali R, Lancet Oncol, 2014

Endometrial Cancer: FIGO Staging

Surgical & Pathological

Old FIGO staging (1988)

Stage	
IA	Tumour limited to endometrium
IB	Invasion to <50% of the myometrium
IC	Invasion to >50% of the myometrium
IIA	Endocervical glandular involvement only
IIB	Cervical stromal invasion
IIIA	Tumour invades serosa and/or adnexa and/or positive peritoneal cytology
IIIB	Vaginal metastases
IIIC	Metastases of pelvic and/or para-aortic lymph nodes
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph nodes

New FIGO staging (2009)

Stage	
I	Tumour confined to the corpus uteri
IA	No or <50% of the myometrium
IB	Invasion ≥50% of the myometrium.
II	Tumour invades cervical stroma but does not extend beyond the uterus
III	Local and/or regional spread of the tumour
IIIA	Tumour invades serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC1	Positive pelvic lymph nodes
IIIC2	Positive para-ortic lymph nodes with or without pelvic nodes
IV	Tumour invades bladder/bowel mucosa, and/or distant metastases
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases including intra-abdominal and/or inguinal lymph nodes

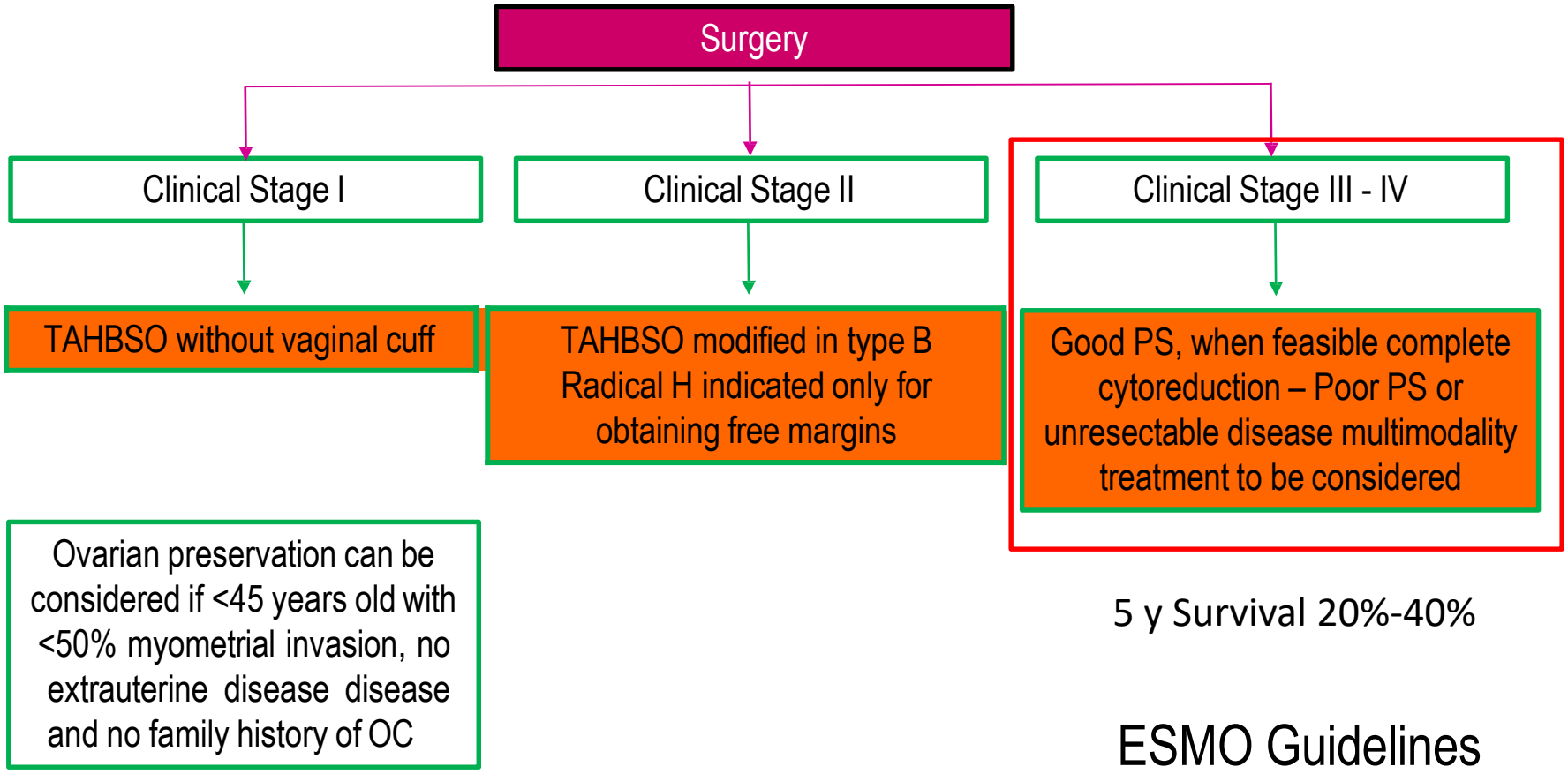
Pathological assessment includes: Myometrial invasion, cervical involvement, tumor size and location, extension to fallopian tubes and ovaries, grade and histological subtypes, lymphovascular space invasion (LVSI), nodal status

75% stage I

ENDOMETRIAL CANCER

Surgical management algorithms

Surgery is the cornerstone of treatment



5 y Survival 20%-40%

ESMO Guidelines

Medical Treatment for advanced disease

Hormone therapy in advanced and recurrent endometrial cancer: Type I a systematic review

- Four randomized studies comparing progestogens, TAM and aminogluthetimide with similar results.
- In Phase III and Phase II studies the duration of response was of 3-6 months, the response rate in Grade 1 or Grade 2 tumors was almost double that achieved in Grade 3 and was higher in ER+ and PR+ tumors.
- Progestogens are indicated for first-line treatment, tamoxifen in progestogens failures.
- ORR: 20%-50%
- ER and PR status have prognostic and predictive values.

Decruze, Int J Gynecol Cancer, 2007

Phase III Trials in Advanced/Metastatic Disease Chemotherapy

	RT agent vs. Doublet	*Single agent vs. Doublet*		*Doublet vs. Doublet*	*Doublet vs. Triplet*	*TAP vs. TC*
	GOG Randall et al. JCO '06	*EORTC55872 Van Wijk Ann Onc '03*	GOG107 Thigpen JCO '04	*GOG Fleming. Ann Onc '04*	*GOG Fleming JCO '03*	*GOG209 Miller SGO '12*
Population (Stage)	**III-IV**	**Stage 3-4 & Relapsed**	Stage 3-4 & Relapsed	**Stage 3-4 & Relapsed**	**Stage 3-4 & Relapsed**	**Stage 3-4**
n	**396**	**177**	299	**317**	**273**	
Regimen	**WART A^{60} P^{50} x 8**	**Dox vs. Dox-Cisplat**	Dox vs. Dox-Cisplat	**Dox-Cisplat vs. Dox-Paclitax**	**Dox-Cisplat vs. Dox-Cisplat-Tax**	**Carbo-Tax vs. Dox-Cisplat-Tax**
PFS	**Signif *HR 0.71***	**NS**	Signif HR 0.73	**NS**	**Signif *P < 0.01***	***Equall***
OS	**Signif *HR 0.68***	**NS**	NS	**NS**	**Signif *P < 0.037***	***Equall***

Adding Radiotherapy?

PORTEC 3

Phase III trial comparing concurrent chemo radiation (CTRT) and adjuvant CT with pelvic RT alone in high-risk and advanced stage endometrial carcinoma (EC) S. de Boer et al.

Question

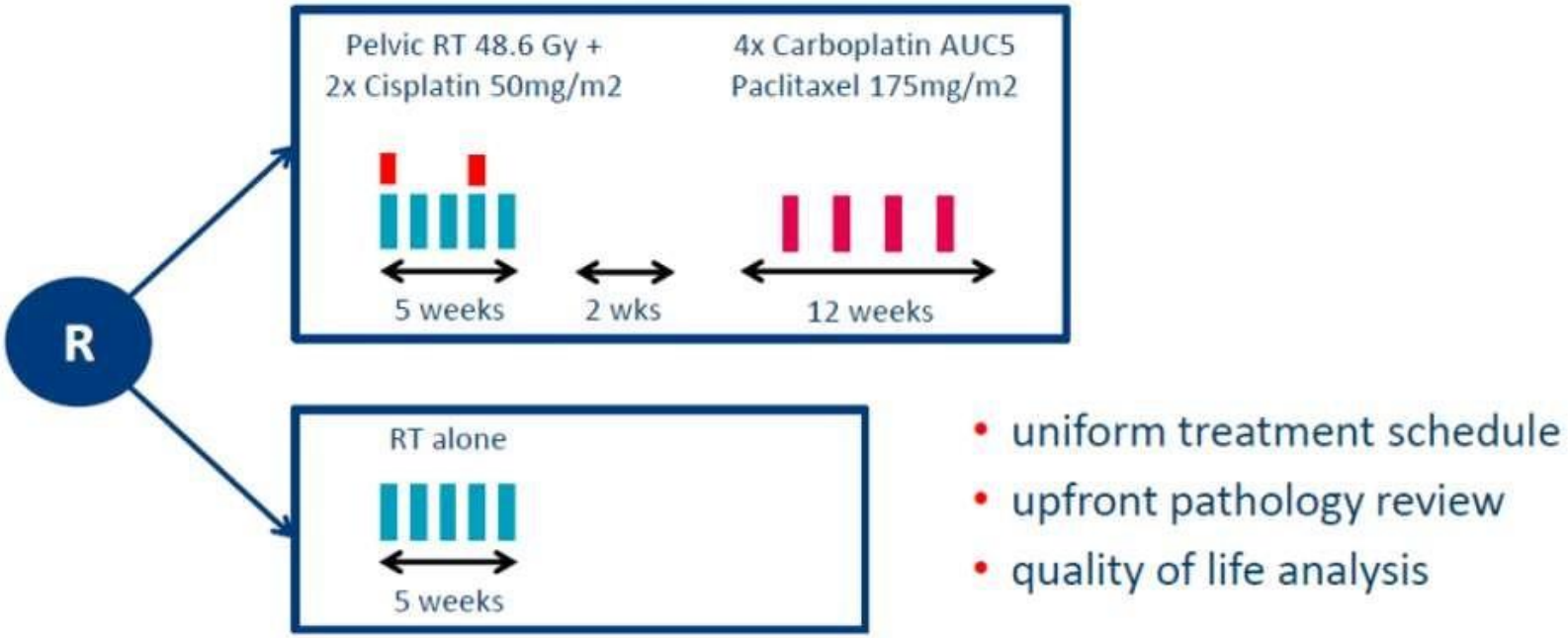
Is the combination of RT and CT better than RT alone in improving PFS and OS in high-risk EC patients?

ASCO 2017

PORTEC 3

Trial design

- **High risk Endometrial Cancer (HREC)**



- uniform treatment schedule
- upfront pathology review
- quality of life analysis

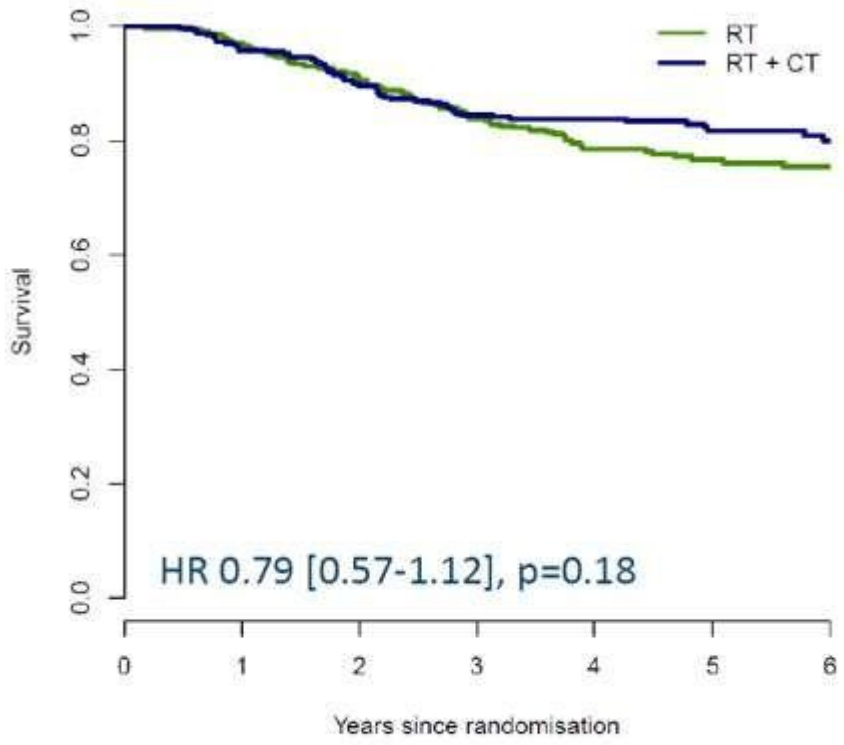
PORTEC 3

Tumour characteristics

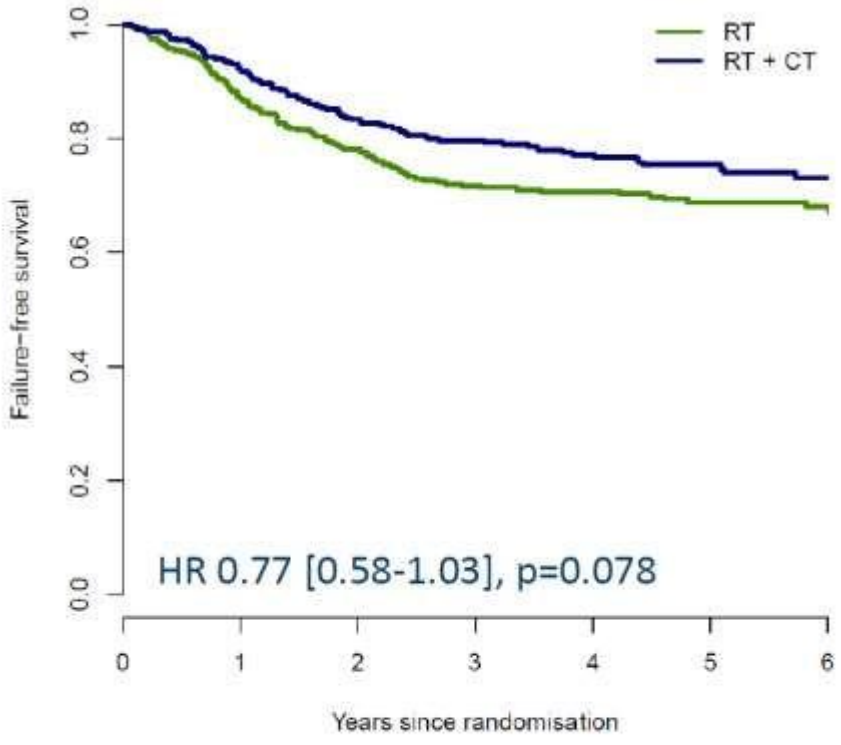
Tumour characteristics	RT alone	CTRT
Histology		
Endometrioid grade 1-2	39.7%	38.5%
Endometrioid grade 3	32.1%	32.4%
Serous/ clear cell/ other	28.2%	29.1%
LVSI		
Yes	58.2%	59.7%
No	41.8%	40.3%
Stage (%)		
I	29.4%	29.7%
II	27.3%	24.2%
III	43.3%	46.1%

PORTEC 3

Survival (Os and FFS)



5 yr OS: 82% (CTRT) versus 77% (RT)



5 yr FFS: 76% (CTRT) versus 69% (RT)

PORTEC 3

Survival results per stage

Patients with stage III EC:

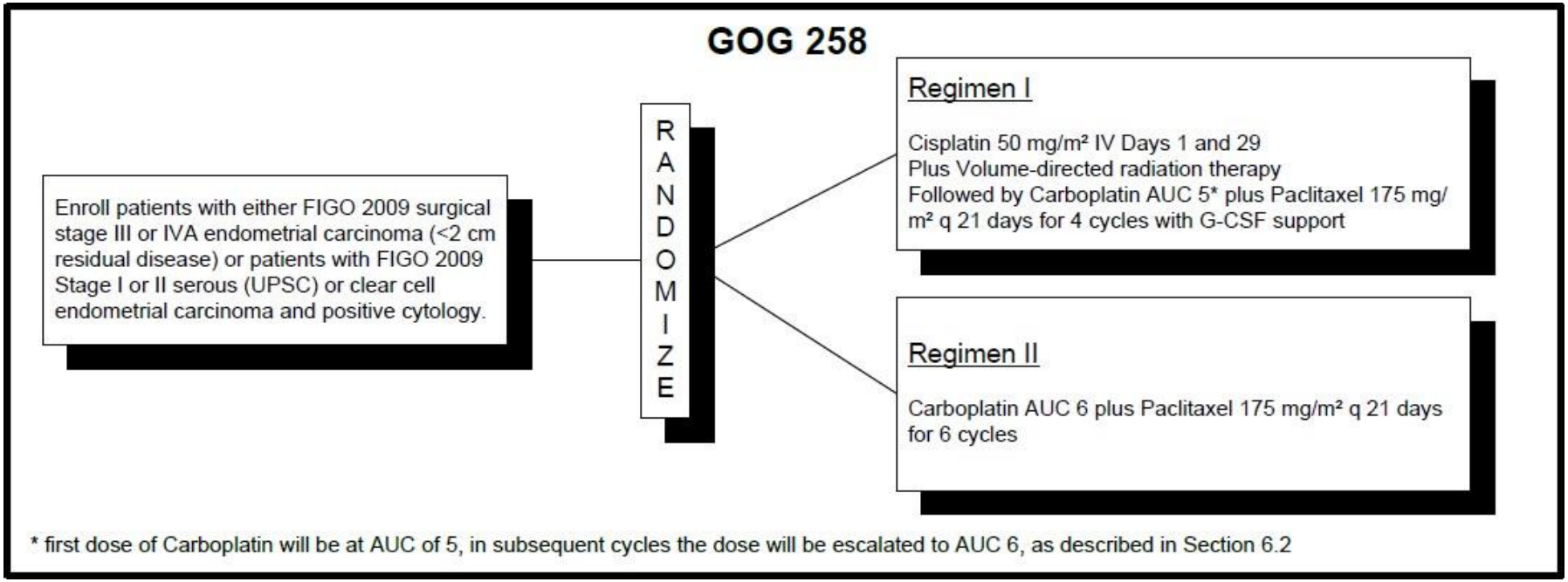
- Lower 5-year FFS and OS:
  - FFS: 64% stage III versus 79% for stage I-II (p<0.001)
  - OS: 74% vs 83% (p=0.003)
- Greatest benefit of CTRT
  - 5-year FFS 69% for CTRT vs 58% for RT
    [HR 0.66, 95% CI 0.45-0.97, **p=0.032**]
  - 5-year OS 79% vs 70%
    [HR 0.69, 0.44-1.09, p=0.114]

PORTEC 3

Conclusions

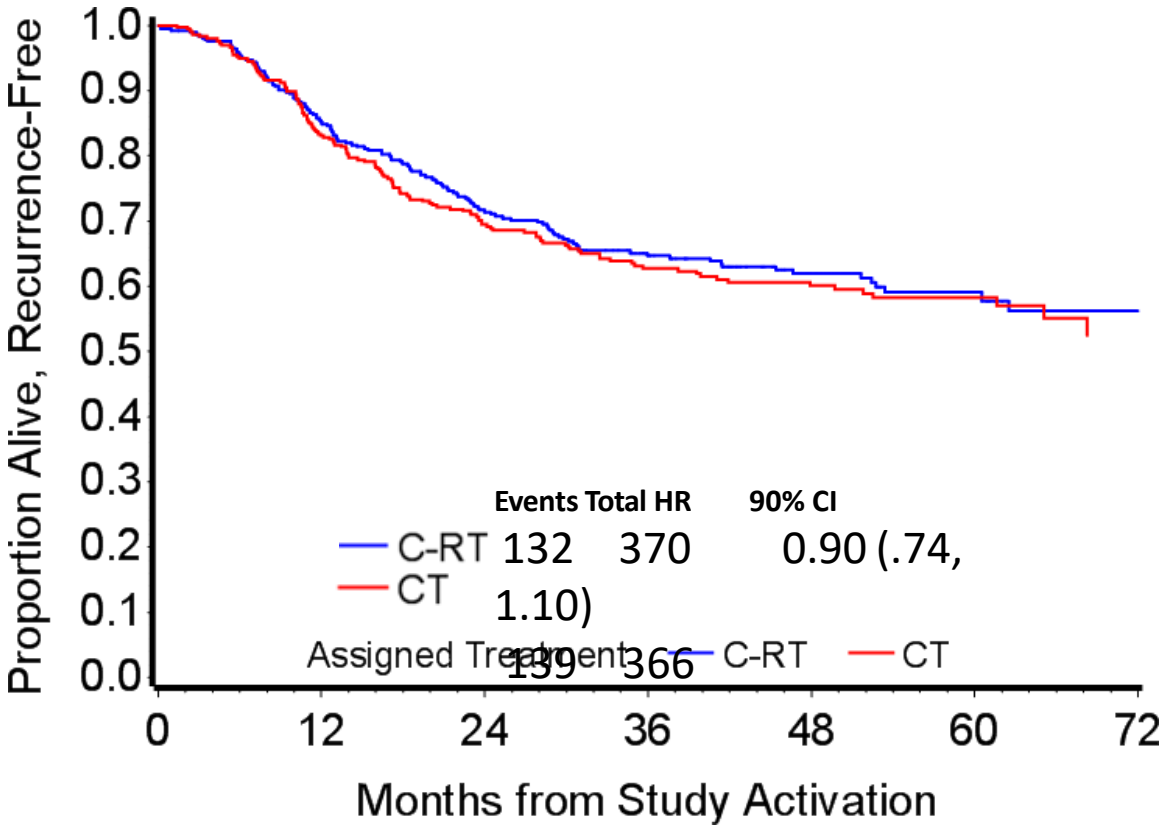
- Risk reduction of 7% (FFS) and 5% (OS)
- Significant 11% FFS benefit with CTRT for stage III → Recommended
- Significant more toxicity with CTRT in the first 12 mos
- Good pelvic control with RT alone
- OS analysis may need a longer follow up

GOG-258: Randomized Phase III Trial of Cisplatin and Tumor Volume–Directed Irradiation Followed by Carboplatin and Paclitaxel vs Carboplatin and Paclitaxel for Optimally Debulked, Advanced EC



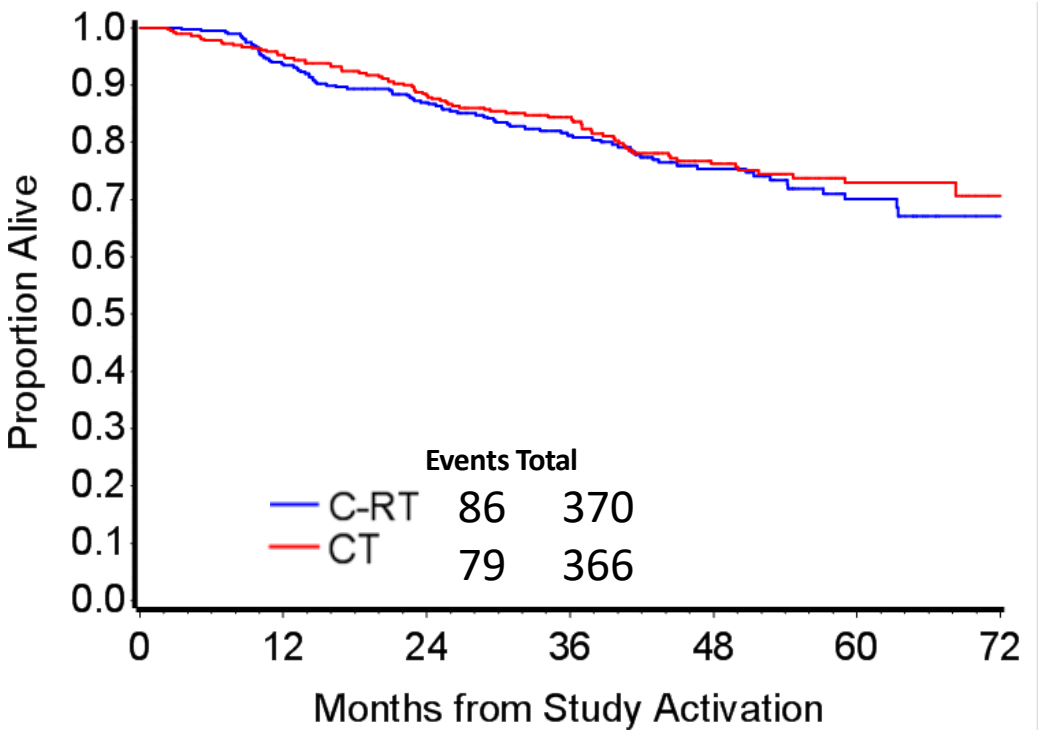
Matei D, et al. *J Clin Oncol*. 2017;35(suppl): Abstract 5505.

GOG-258 Recurrence-Free Survival



Matei D, et al. *J Clin Oncol*. 2017;35(suppl): Abstract 5505.

GOG-258 Overall Survival



5-year OS estimates
C-RT: 70%
CT: 73%

Data cut-off 03/09/2017 Data not mature for final analysis

OS, overall survival

Matei D, et al. *J Clin Oncol*. 2017;35(suppl): Abstract 5505.

Target therapy:

Anti-angiogenic therapy

MITO-END-2

Randomized Phase II Trial of Carboplatin-Paclitaxel compared to Carboplatin-Paclitaxel Bevacizumab in advanced or recurrent endometrial cancer

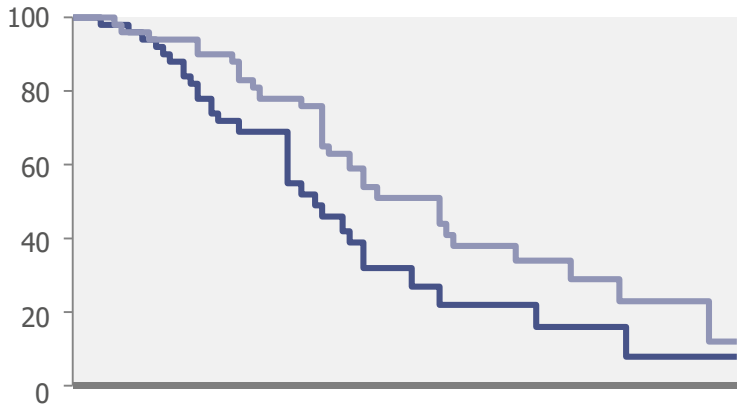
Patients with advanced (stage III-IV) or recurrent type 1 or type 2 (no carcinosarcoma) endometrial cancer; 0-1 previous CHT lines; Measurable or evaluable disease (n~108)

R

1:1

Carboplatin AUC 5 + Paclitaxel 175 mg/mq d1 q 21 x 6-8 cycles

Carboplatin AUC 5 + Paclitaxel 175 mg/mq d1 q 21 x 6-8 cycles
+
Bevacizumab 15 mg/kg in combination
with chemotherapy and maintenance until PD



	CT (N=54)	CT-B (N=54)
Events, n	34	32
Median PFS, months **(95% CI)**	8.7 (6.3-11.2)	13 (9.2-16.8)
HR (stratified) (95% CI) 2-sided log-rank p-value	0.59 (0.35–0.98) 0.036	

EUDRACT 00330116
Phase 2

Lorusso et al. ASCO 2015
n = 108

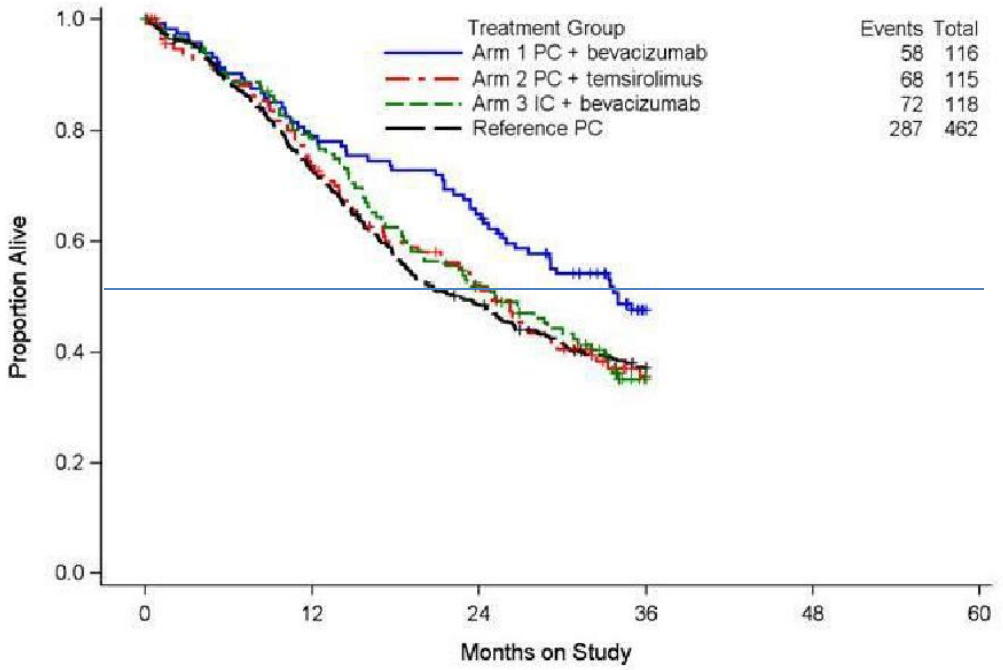
GOG-86-P

GOG86P: OS

ARM 1:
Paclitaxel
Carboplatin
Bevacizumab

ARM 2:
Paclitaxel
Carboplatin
Temsirolimus

ARM3:
Ixabepilone
Carboplatin
Bevacizumab



Arm	*Median Point Estimate*
1	**34.0 (p<0.039)**
2	25.0
3	25.2
Reference	22.7

NCT00977574

Phase 3

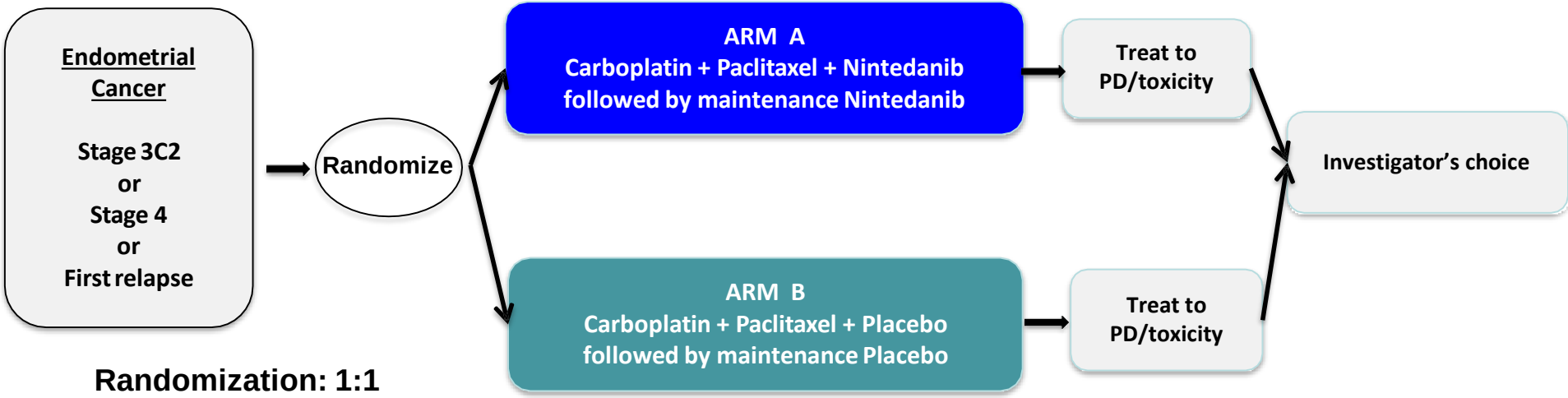
Aghaganian et al. ASCO 2015

n = 349

ENGOT-EN1 / FANDANGO

A randomized double-blind placebo-controlled phase II trial of first-line combination chemotherapy with Nintadenib for patients with advanced or recurrent endometrial cancer

Recruitment Completed



Randomization: 1:1

NCT02730416
Phase 2

Study Chair: Mirza MR
n = 148

PI3K/AKT pathway

Metabolic pathways

mTOR and PI3K i

Drug		N	RR	SD	PFS> 6 Months	PFS
mTOR inhibitors						
Temsirolimus (Oza 2011)	Chemo-naïve	29	**14%**	69%	-	7.3 months
	Chemo-treated	25	**4%**	48%	-	3.2 months
Ridaforolimus (Colombo 2013)	Chemo-treated	45	**11**%	18%	18%	
Ridaforolimus (Tsoref 2014)		31[a]	**8.8%**	52.9%	-	-
Ridaforolimus vs progestin or investigator choice chemotherapy (Oza 2015)		64 vs 66	**4.6% vs 3% (*P* = NS)**	56.3 vs 27.7 (*P* = .003)	-	5.6 months vs 1.9 months (HR, 0.39; 95% CI, 0.23 to 0.66; *P*<.001)
Everolimus (Slomovitz 2010)		28	**0%**	43%	-	-
PI3K inhibitors						
Pilasarilib (XL147) (Matulonis 2014)		67	**6%**	37.3%	11.9%	-
BKM120 NCT01289041		71	**2.8%**	36%	-	1.9 months

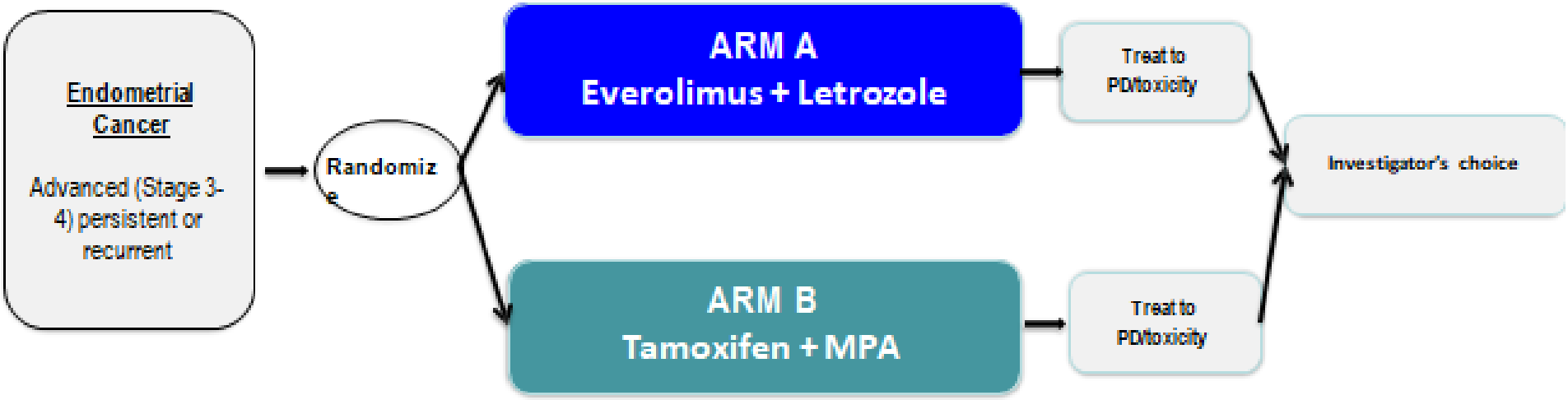
Oza AM, et al. *J Clin Oncol.* 2011;29(24):3278-3285, Colombo et al. Br J Cancer. 2013 Mar 19;108(5):1021-6 . Tsoref D, et al. G*ynecol Oncol*. 2014;135(2):184-189. Oza AM, et al. *J Clin Oncol.* 2015;33(31):3576-3582. Slomovitz BM, et al. *Cancer.* 2010;116(23):5415-5419. Matulonis U, et al. *Gynecol Oncol.* 2015;136(2):246-253.

GoG 3007

A randomized phase II trial of Everolimus and Letrozole or hormonal therapy for patients with advanced, persistent or recurrent endometrial cancer

GOG 3007

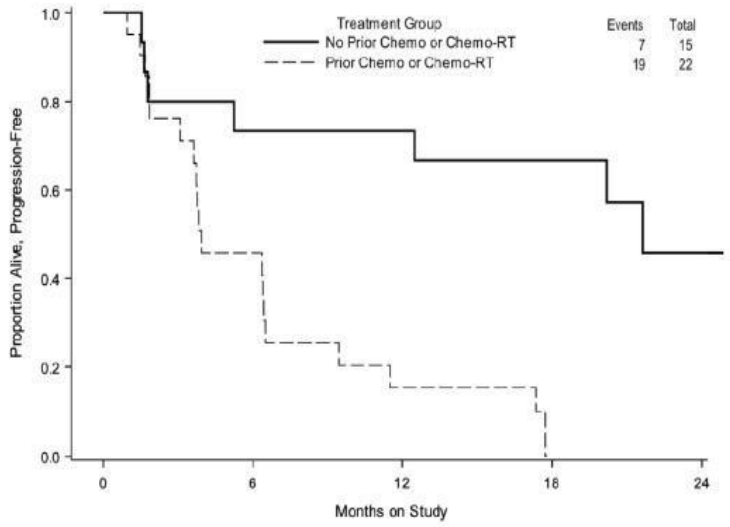
NCT02228681

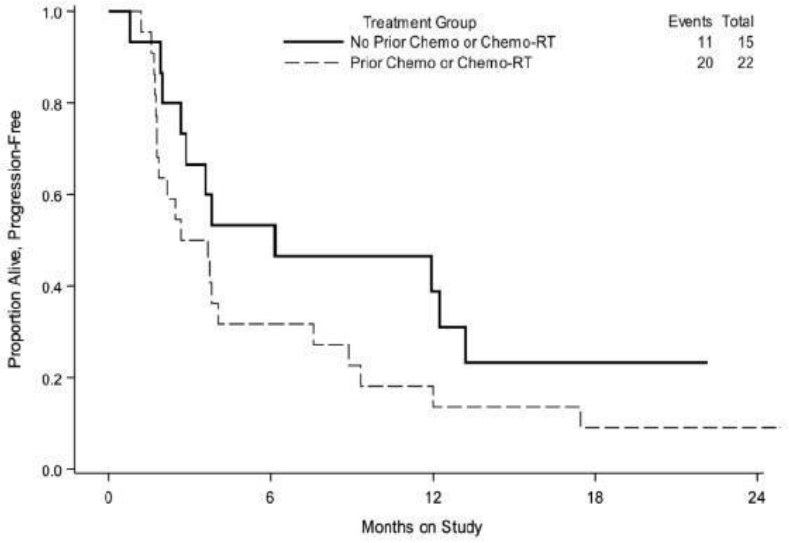


Slomovitz et al.

GOG 3007

PFS by prior treatment





Everolimus/Letrozole – NPC	PFS 21.6 mos.
Everolimus/Letrozole – Prior chemo	PFS 3.3 mos.

HT – NPC	PFS 6.6 mos.
HT– prior ctx	PFS 3.2 mos.

Slomovitz et al.

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NSGO

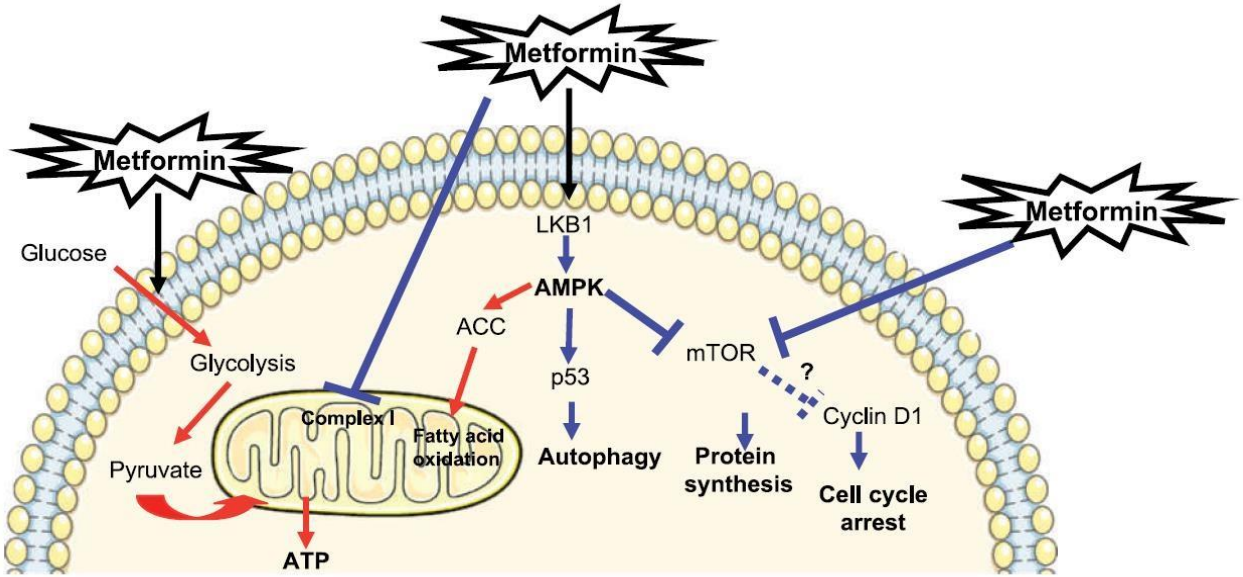
THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

A Phase II, Single-Arm Study of Everolimus, Letrozole, and Metformin in Patients With Advanced or Recurrent Endometrial Carcinoma

NCT01797523

Metformin in endometrial cancer

- Increased risk of endometrial cancer in diabetic patients
- Decreased risk of death in metformin users versus non users endometrial cancer patients
- Improved recurrence free survival and overall survival but not time to recurrence in a retrospective analysis of diabetic patients with endometrial cancer
- Antiproliferative effect in endometrial cancer cell lines



Mechanism of action and sensitivity dependent on tumor cell lines

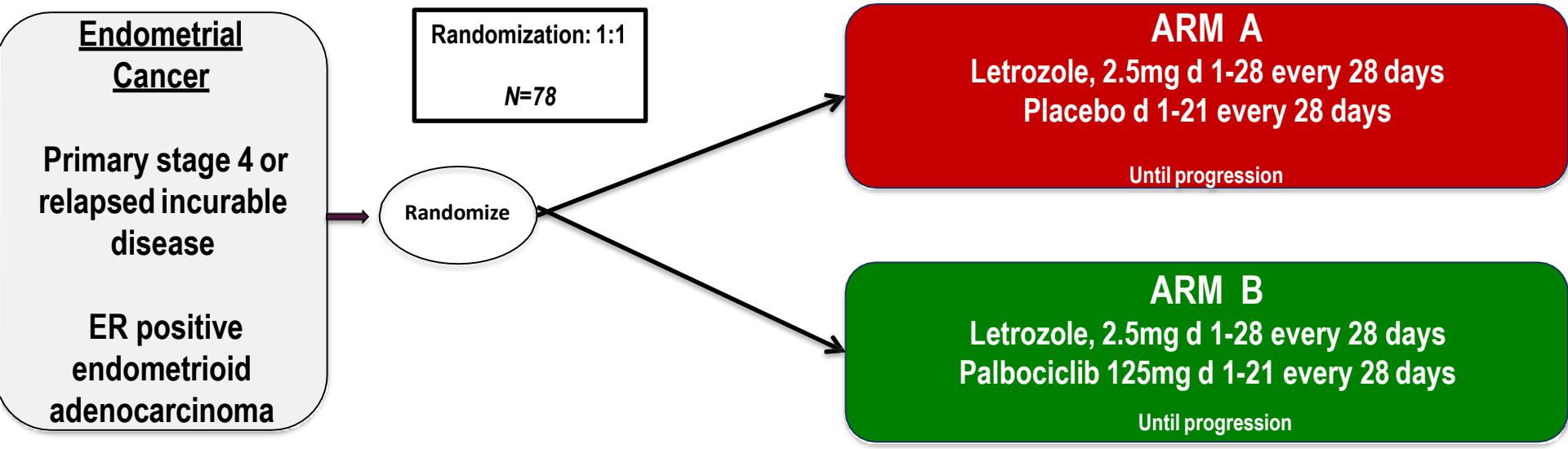
Bahra I.B., Mol Cancer Ther, 2010

Cyclin-Dependent Kinase (CDK) Inhibitors

The 4th MEMAGO Annual Congress in Association with the 1st Emirates Gynecological Oncology Conference

A randomized phase II trial of Palbociclib in combination with letrozole versus letrozole for patients with oestrogen receptor positive recurrent endometrial cancer.

ENGOT-EN3-NSGO/PALEO



NCT02730429

Recruitment Completed

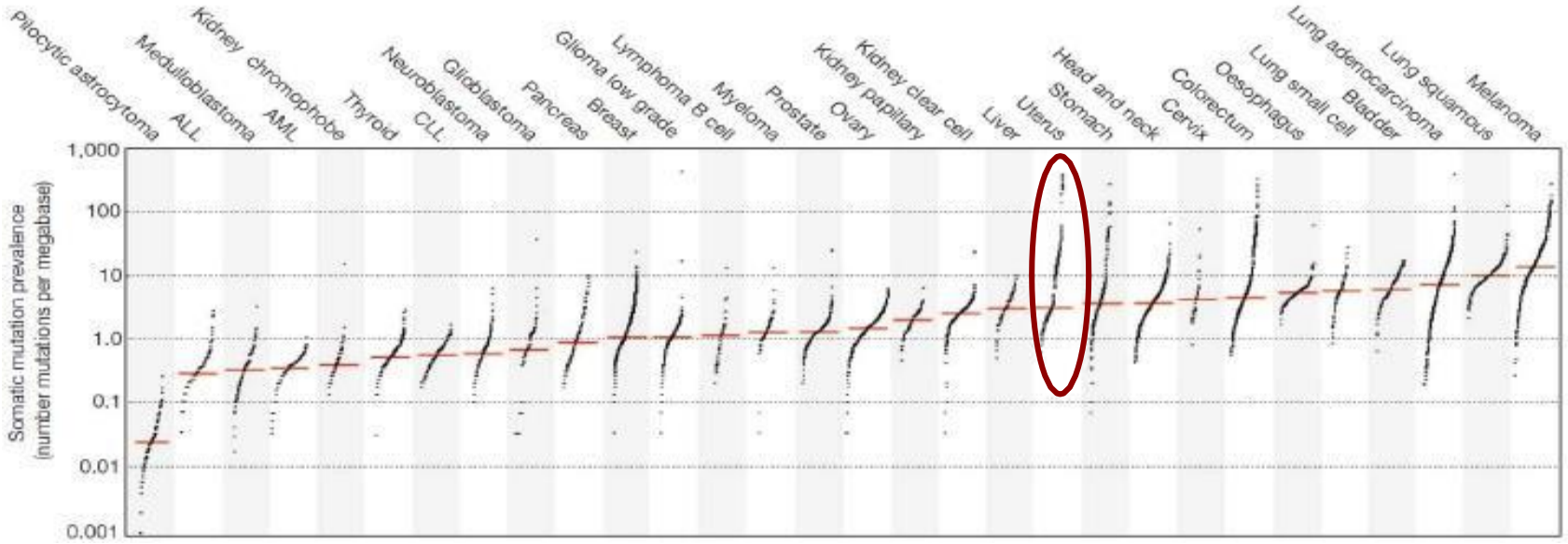
Stratification:

- Number of prior lines of therapy (primary advanced disease vs. 1st relapse vs. ≥2 relapses)
- Measurable vs. evaluable disease
- Prior use of MPA/Megace (prior MPA/Megace use capped to a maximum of 50%)

Novel Agents
Immune Check-Point Inhibitors

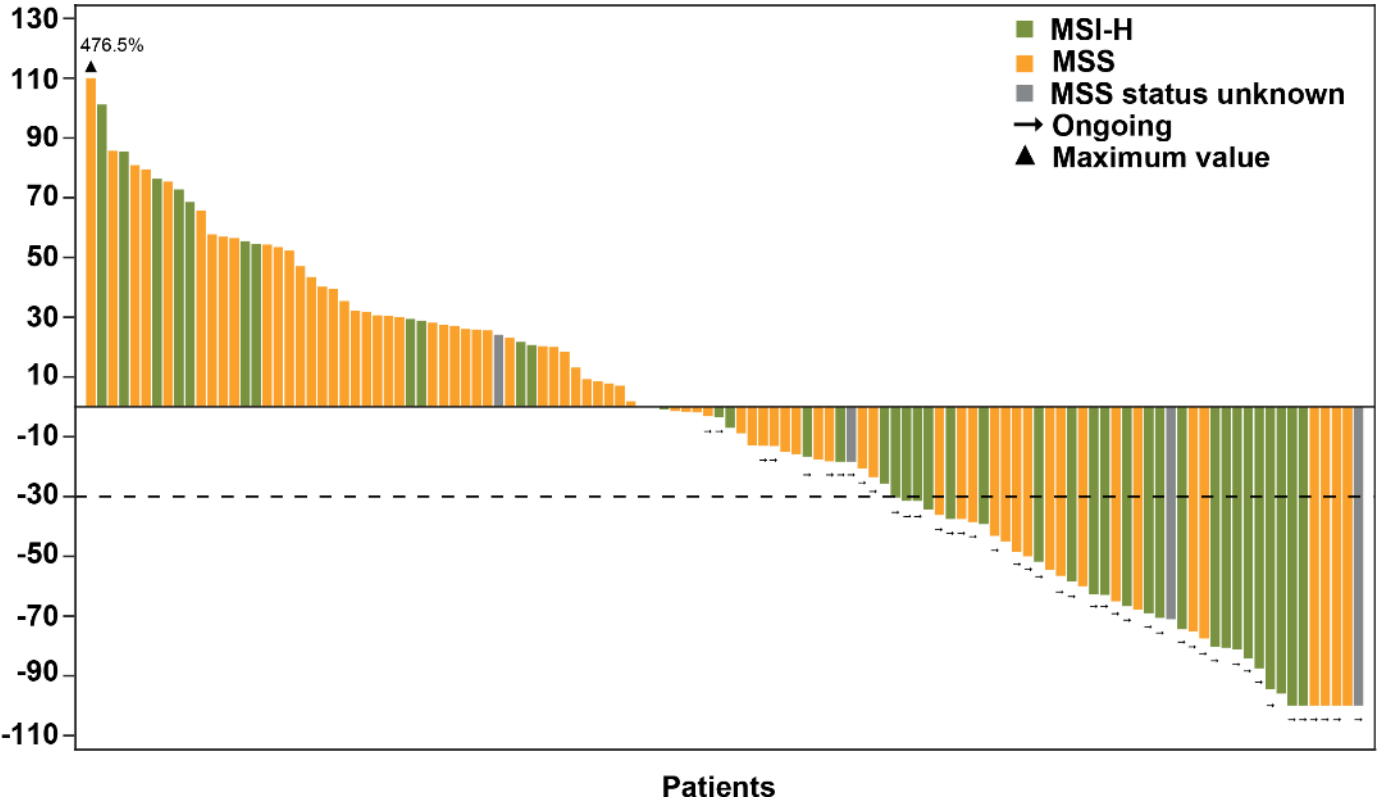
Immunotherapy

- **POLE ultramutated & MSI have**
  - high mutation load
  - Tumor-infiltrating lymphocytes (TILs)
  - counterbalanced by overexpression of PD-1 & PD-L1
  - Checkpoint (PD-1 & PD-L1) inhibitors can “re-activate” our TILs



Alexandrov, et al. Nature 2013

Dostarlimab in Endometrial Cancer: Change in Tumor Size



>50% reduction in total tumor burden in 85% of MSI-H and 69% of MSS responders

Oaknin A, et al. SGO 2019.

AVELUMAB

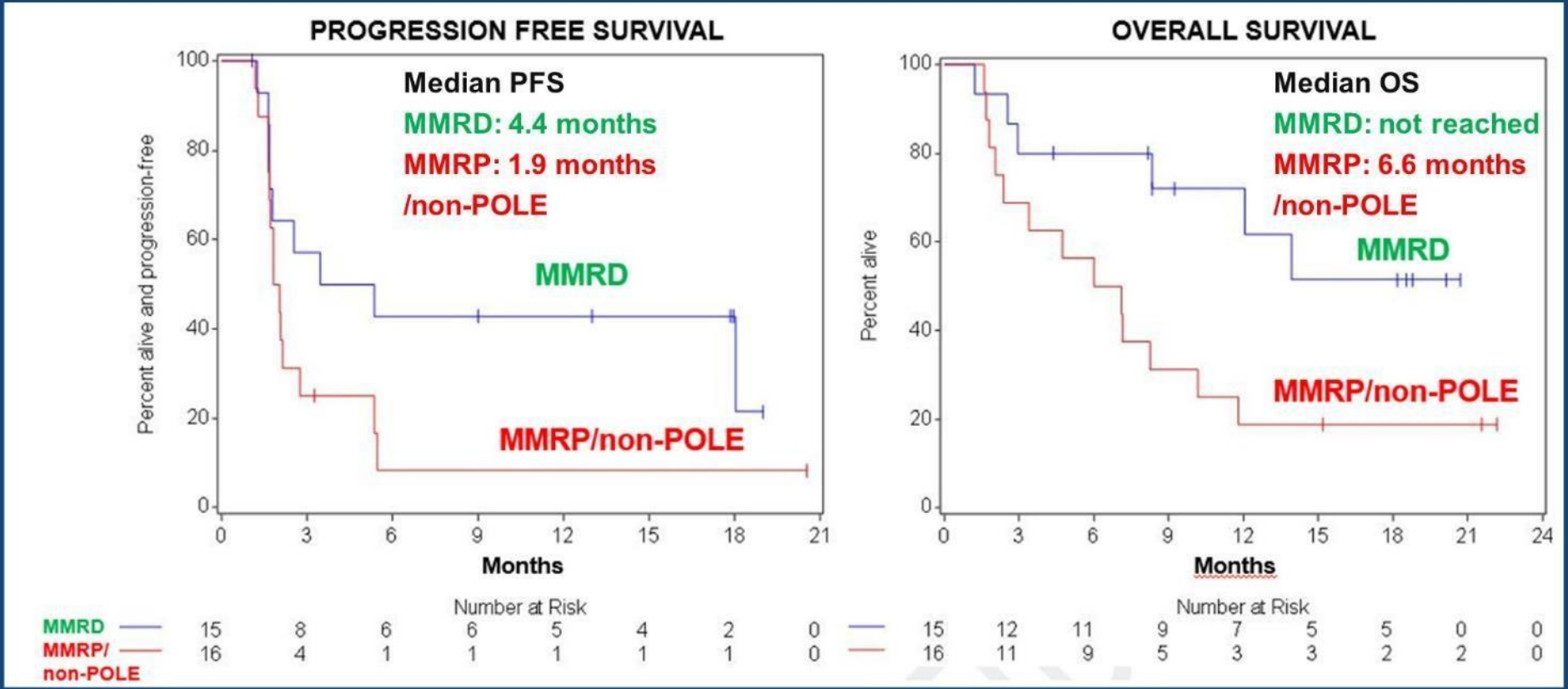
Confirmed Objective Response and PFS6

RESPONSE	Patients	
	MMRD cohort (N=15)	MMRP/non-POLE Cohort (N=16)
Best Overall Response		
CR	1	0
PR	3	1
SD	4	4
PD	4	9
Not evaluable	3	2
ORR, % (95% CI)	26.7 (7.8-55.1)	6.25 (0.16-30.2)
PFS6 Response		
Yes	6	1
No	9	15
PFS6 Response, %	40 (16.3-66.7)	6.25 (0.16-30.2)

Presented By Panagiotis Konstantinopoulos at 2019 ASCO Annual Meeting

AVELUMAB

PFS and OS in both cohorts (median follow up 18.6 months)



Presented By Panagiotis Konstantinopoulos at 2019 ASCO Annual Meeting

FDA announces international collaboration, approves pembrolizumab plus lenvatinib for endometrial cancer

September 17, 2019

The decision was based on results from the single-arm, multicenter KEYNOTE-146 trial, which enrolled 108 women with metastatic endometrial carcinoma that had progressed after at least one prior systemic therapy. Most of the women (n = 94) had tumors that were not MSI-H or dMMR, whereas 11 had tumors that were MSI-H and dMMR, and three had tumors with unknown MSI-H and dMMR status.

Results showed an ORR of 38.8% (95% CI, 29-49) among the 94 patients whose tumors were not MSI-H or dMMR. This included 10 complete responses (10.6%) and 26 partial responses (27.7%).

Median duration of response was not reached by data cutoff and 25 patients had a response of 6 months or longer.

ENGOT European Network of Gynaecological Oncological Trial groups

Model C

ENGOT-en9/A-AGO: A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Advanced or Recurrent Endometrial Carcinoma (LEAP-001)

- FIGO stage III, stage IV or recurrent endometrial carcinoma
- No prior chemotherapy (except chemoradiation)
- ECOG 0 or 1
- 612 pMMR plus appromimately
- 108 dMMR patients

1:1

R

Pembrolizumab 200 mg IV infusion Q3W15 mg/kg q3w

Up to 35 infusions

Lenvatinib 20mg orally QD

Up to 7 cycles

Carboplatin AUC 6* IV infusion Q3W

Up to 7 cycles

Paclitaxel 175 mg/m² IV infusion Q3W

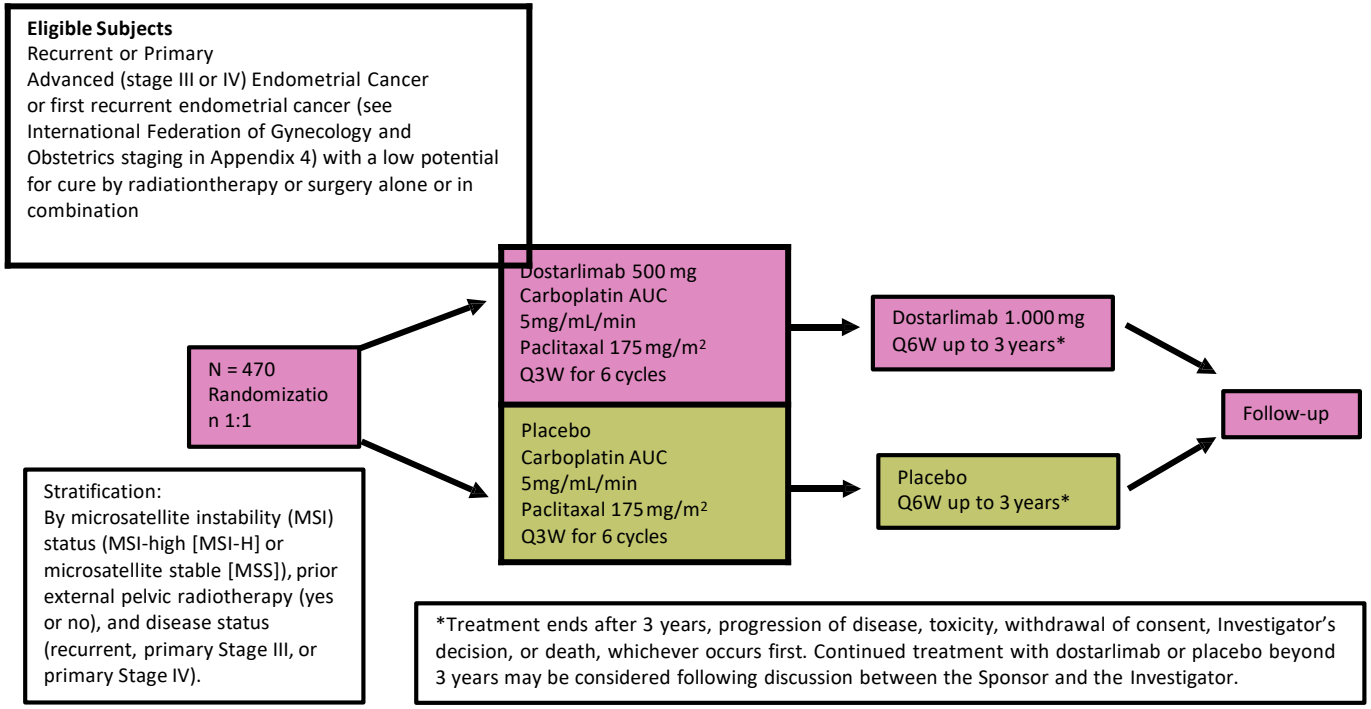
Stratify:

MMR status (pMMR vs. dMMR),

- If pMMR,
  - ECOG (0 vs. 1)
  - Measurable disease (y/n)
  - And prior chemoradiation (y/n)

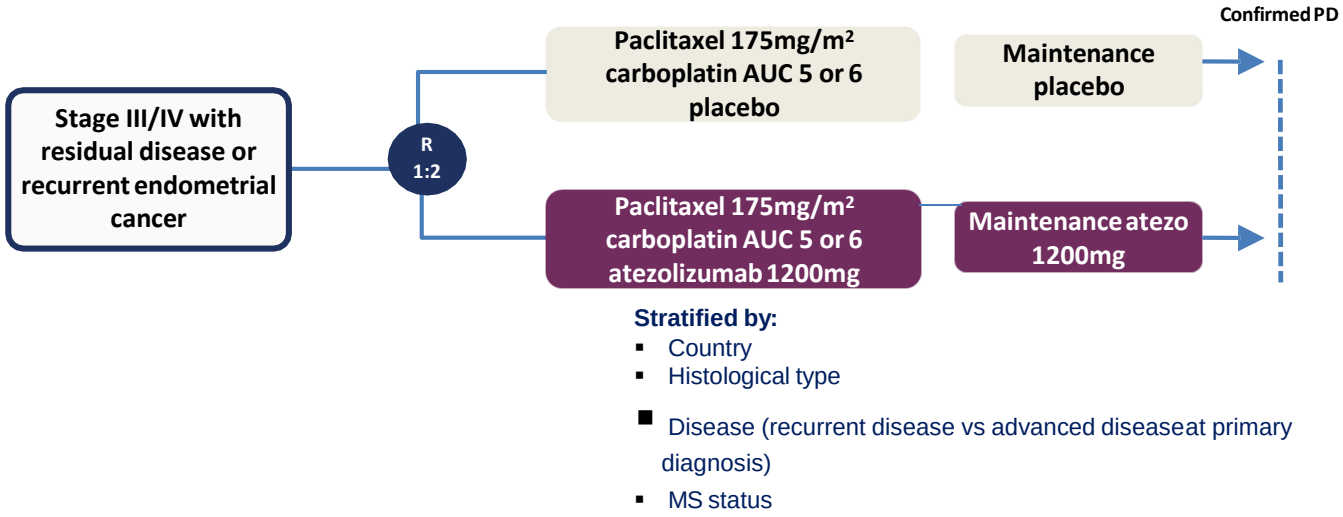
* Carboplatin AUC 5 may be administered in accordance with lobal practice

ENGOT-EN6 /NSGO - RUBY
Trial Design



AtTEnd

Atezolizumab Trial in Endometrial cancer - MaNGO

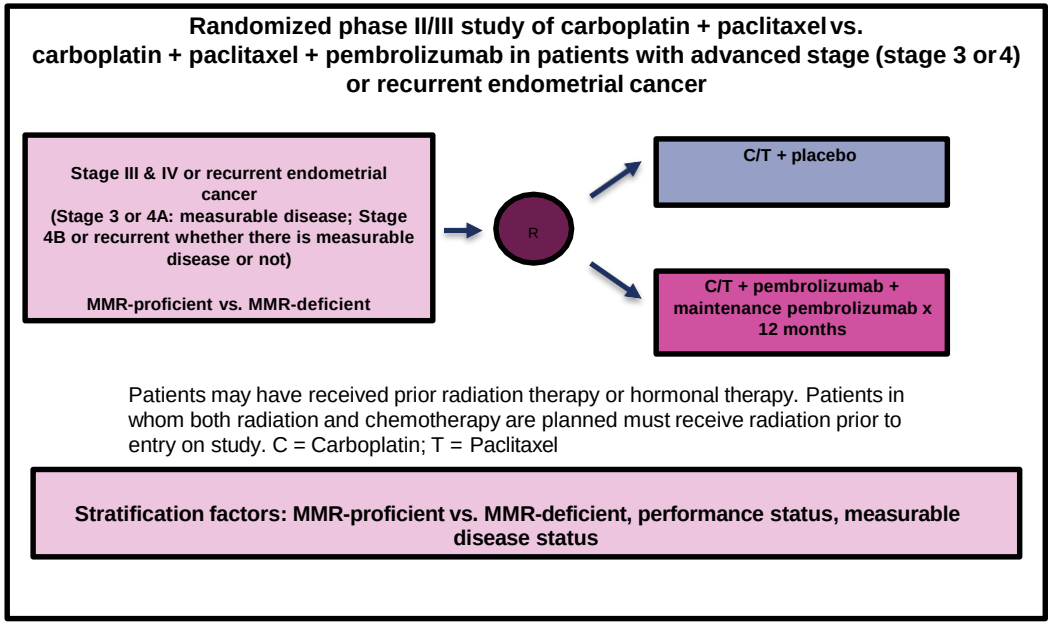


Principal Investigator**:** Nicoletta Colombo, Istituto Europeo di Oncologia - Milan

Sponsor(s): MaNGO- Istituto di Ricerche Farmacologiche Mario Negri IRCCS - Milan

Planned No. of patients: **550**

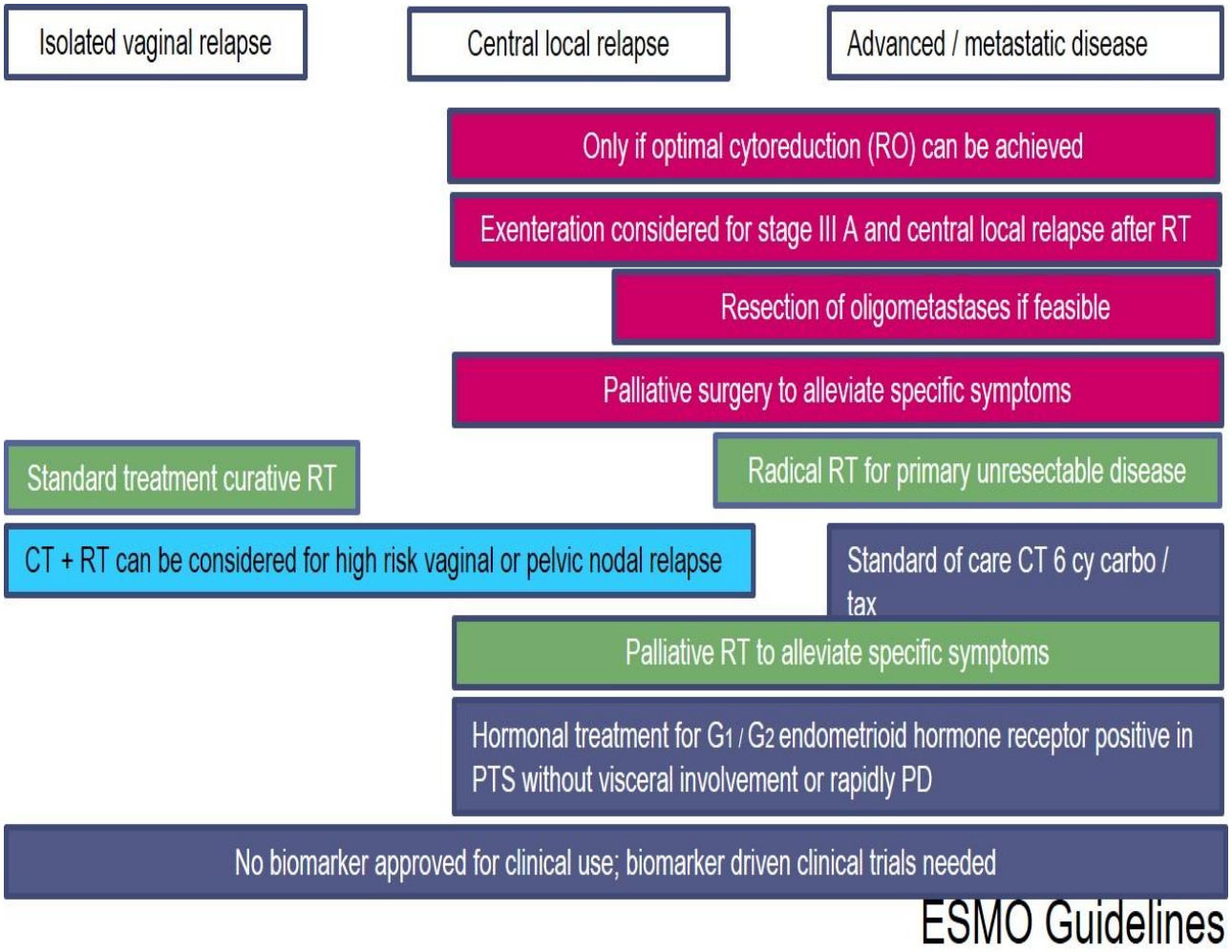
NRG-GY018



N=590 pMMR patients
N=185 deficient MMR (dMMR)

Endometrial Cancer

Advanced / recurrent disease treatment algorithms



Surgery purple; RT green; medical treatment dark blue; CT + RT light blue

Endometrial cancer Conclusion

- Complex heterogeneous disease
- Different hystological entities with different genetic aberrations and distinct dysfunctional signalling pathways (4 Groups)
- Promising targeted agents
- The clinical application of molecular classifiers can identify patients who could benefit from immunotherapy (MSI, POLE)
- Benefit of Combination of Targeted Therapy (Pembro+Len)
- Need for better combination
- Identification of biomarkers and implementation in clinical studies

Thank You

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HER2/neu-positive serous endometrial cancers

Fader *et al*. published their randomized phase II trial of paclitaxel and carboplatin with or without trastuzumab in primary stage III or IV or recurrent HER2/neu-positive uterine serous carcinomas [37]. They randomly assigned 61 patients and found a median PFS of 12.6 months in the paclitaxel, carboplatin, and trastuzumab arm versus 8.0 months in the paclitaxel and carboplatin alone arm. In the 41 patients with primary advanced-stage disease, the PFS was 17.9 months in the trastuzumab arm versus 9.3 months in the paclitaxel/carboplatin alone arm. In the 17 patients with recurrent disease, PFS was 9.2 months in the trastuzumab arm versus 6 months in the paclitaxel/carboplatin arm. There is a suggestion of an OS advantage in the trastuzumab arm, and the greatest benefit is in the up-front setting, but the data are not yet mature. These preliminary findings are of considerable interest and suggest benefit for up-front HER2/neu tumor profiling to guide adjuvant therapy of this difficult disease.

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