Targeted therapy in Gynecological Cancers

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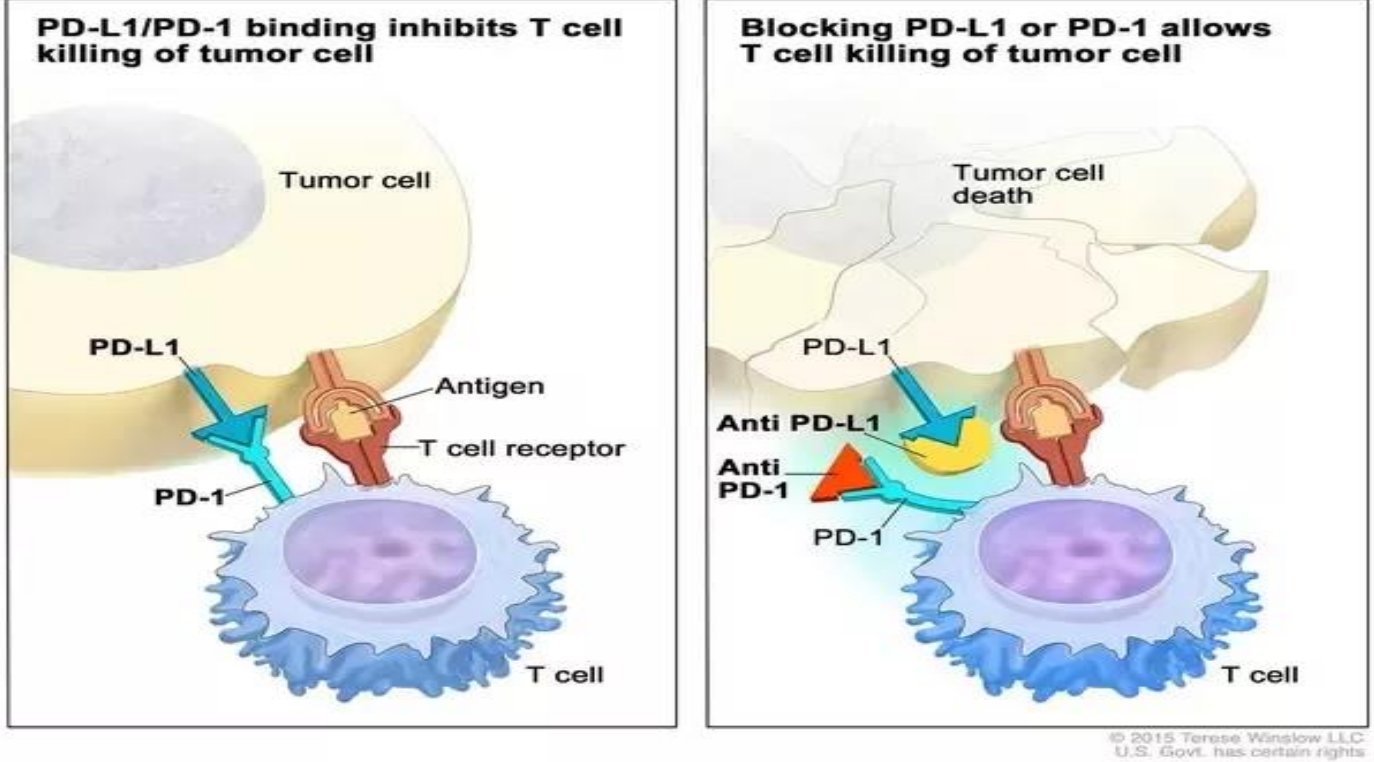
PATHOPHYSIOLOGY

- **Targeted therapy** means there is a target and a medicine that works against that target.
- The target may be receptors present on cancer cells, such as estrogen receptor and Her-2 receptor on breast cancer cells; Or a receptor present on blood vessels supplying the cancer, such as VEGF or VEGFR.
- Other targets include mutations on cancer cells, such as EGFR, ALK and ROS-1 mutations found on lung cancer cells which make the cancer cells more sensitive to EGFR and ALK inhibitors, respectively.
- But sometimes, presence of a mutation makes cells more resistant such as kras or nras mutations present on colon cancer cells make them less sensitive to EGFR inhibitors.
- Other mutations that can be targeted include PIK3CA, BRCA1 and BRCA2, and possibly ATM and PALB2 in breast and ovarian cancers.

PATHOPHYSIOLOGY

- **Immunotherapy** is mostly a group of drugs comprising immune checkpoint inhibitors (PD-L1 and PD-1 inhibitors) and CTLA4 inhibitors.
- In the human body, T-cells are activated by the cancer cell. These activated T-cells circulate, locate the cancer cells and attack the cancer cells.
- However, when PD-1 on the activated T-cell binds with the PD-L1 on the cancer cell, the T-cell becomes inactivated. Immune checkpoint inhibitors block the PD-L1 on the cancer cell, so the T-cell remains activated.
- Currently, immunotherapy is being used in kidney cancers, melanoma, bladder cancer, oesophageal cancer, lung cancer, head and neck cancer, endometrial cancer, certain types of breast cancer, and cancers that are microsatellite instable (MSI high).
- **In targeted therapies, individual patients are treated by agents targeting the changes in tumor cells that help them grow, divide, and spread.**


PD-L1/PD-1 binding inhibits T cell killing of tumor cell
Tumor cell
PD-L1
Antigen
T cell receptor
PD-1
T cell
Blocking PD-L1 or PD-1 allows T cell killing of tumor cell
Tumor cell death
PD-L1
Anti PD-L1
Anti PD-1
PD-1
T cell
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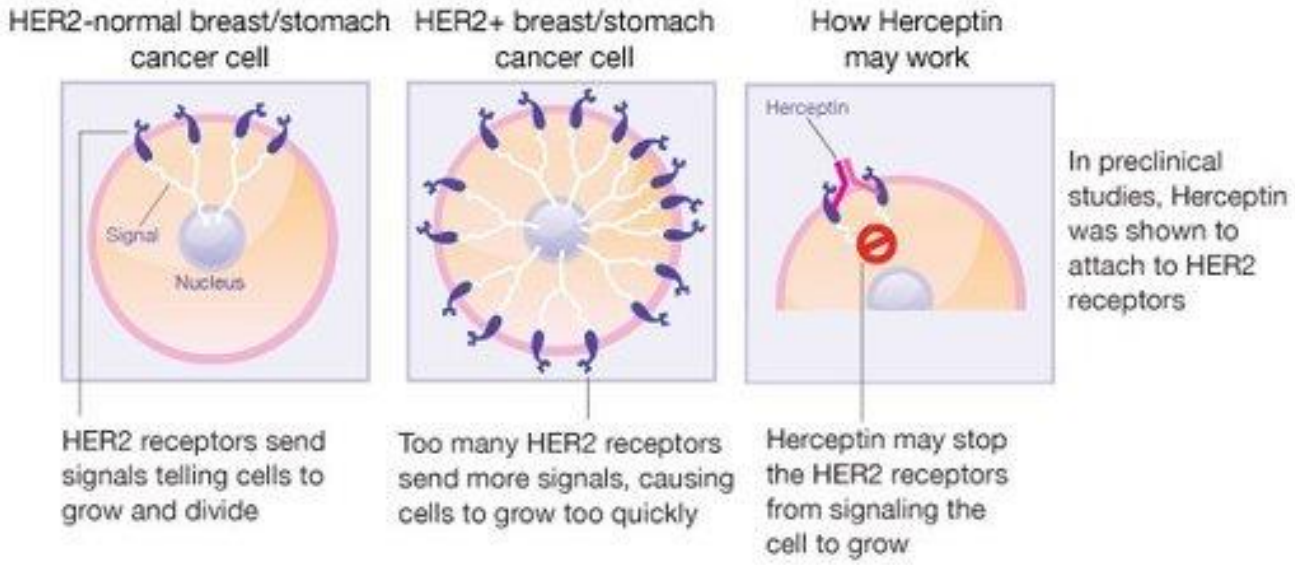
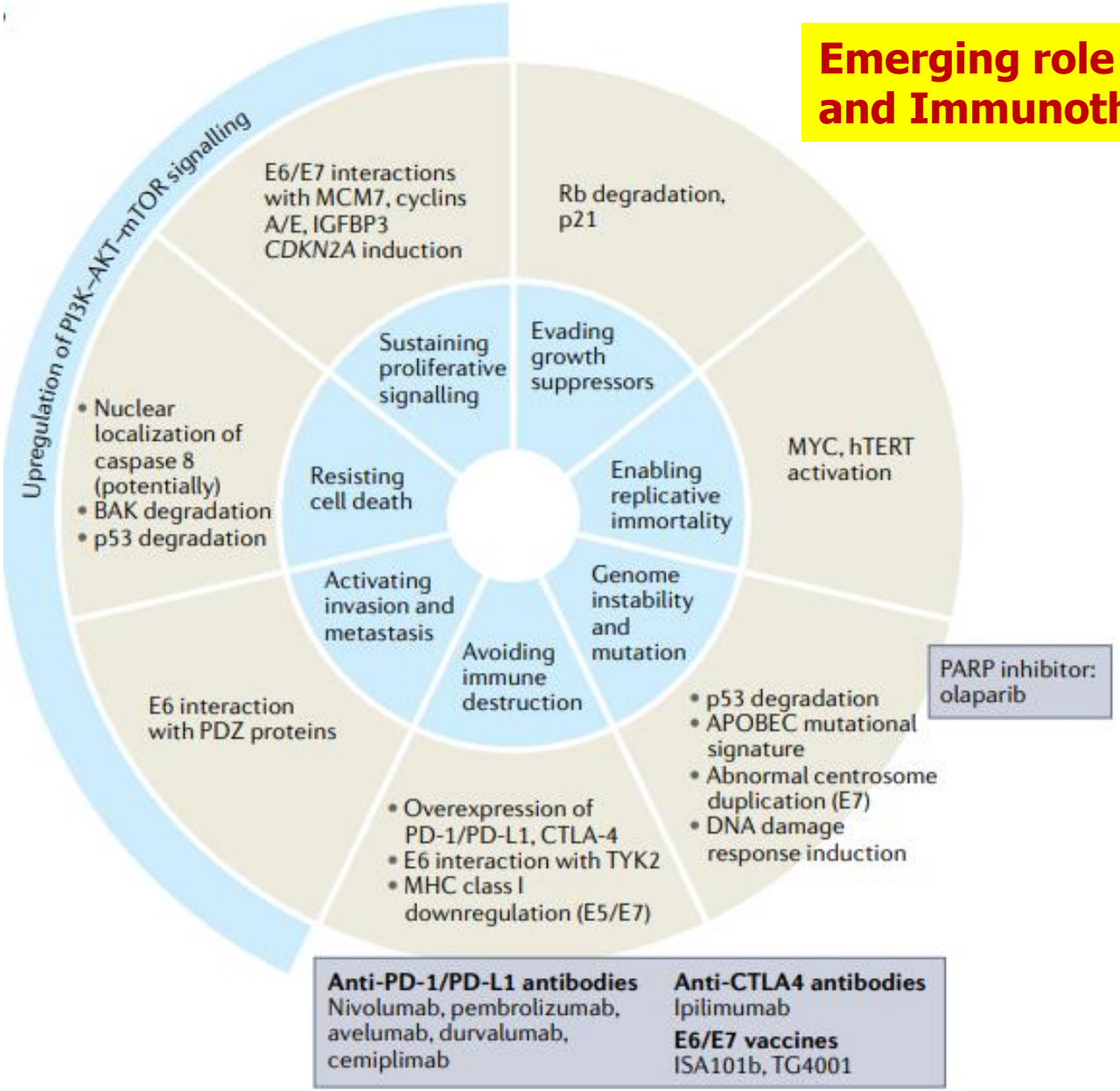
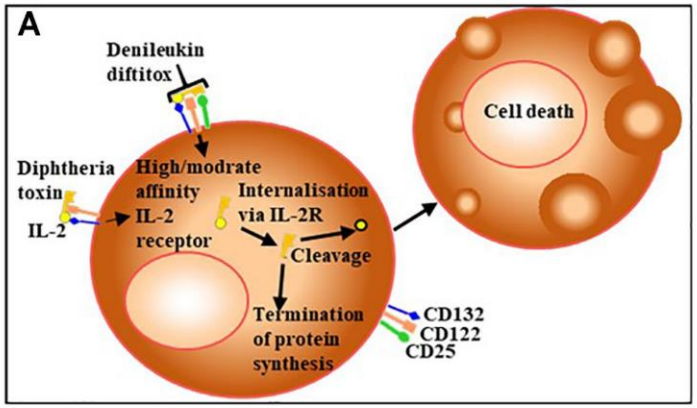
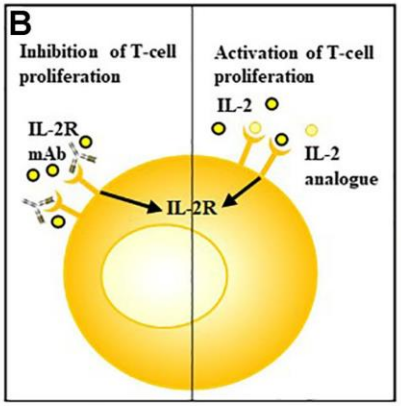

HER2-normal breast/stomach cancer cell
HER2+ breast/stomach cancer cell
How Herceptin may work
Signal
Nucleus
Herceptin
In preclinical studies, Herceptin was shown to attach to HER2 receptors
HER2 receptors send signals telling cells to grow and divide
Too many HER2 receptors send more signals, causing cells to grow too quickly
Herceptin may stop the HER2 receptors from signaling the cell to grow

Emerging role of Biomolecules and Immunotherapy

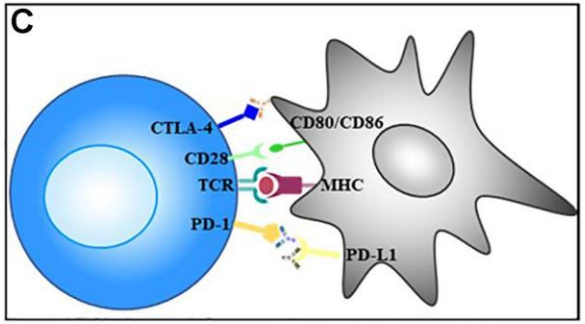




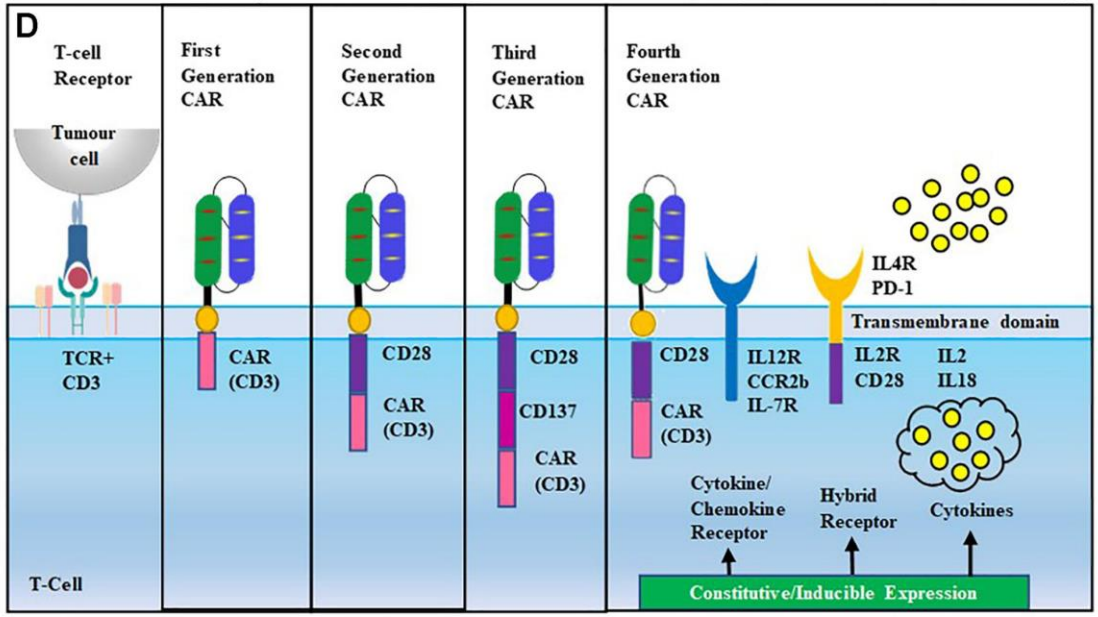
Depletion of T-reg



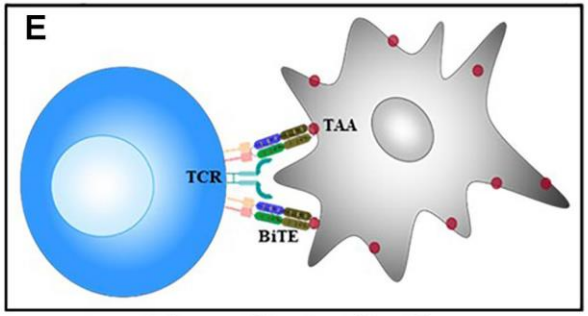
Cytokine Immunotherapy



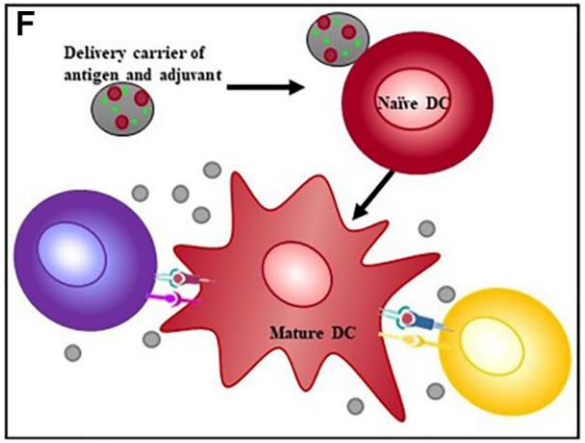
Immune Checkpoint Inhibitors



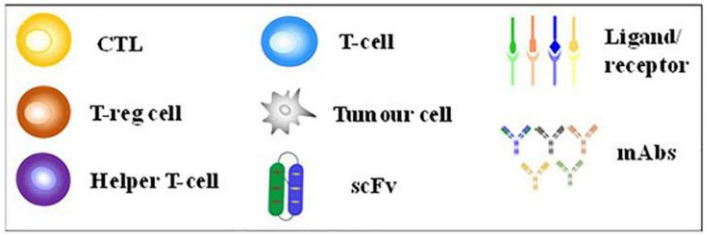
Chimeric Antigen Receptor (CAR) T-cells

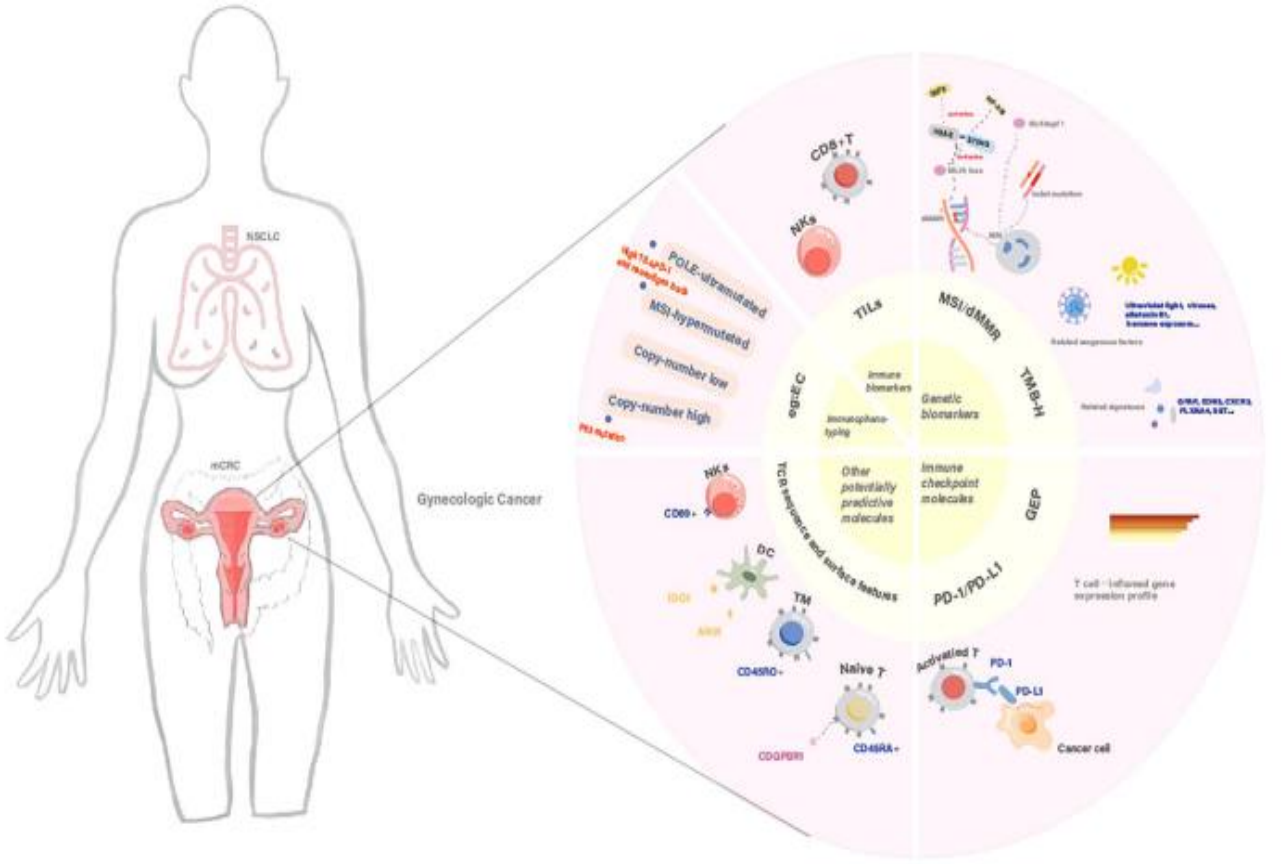


Bispecific Antibodies



Vaccines





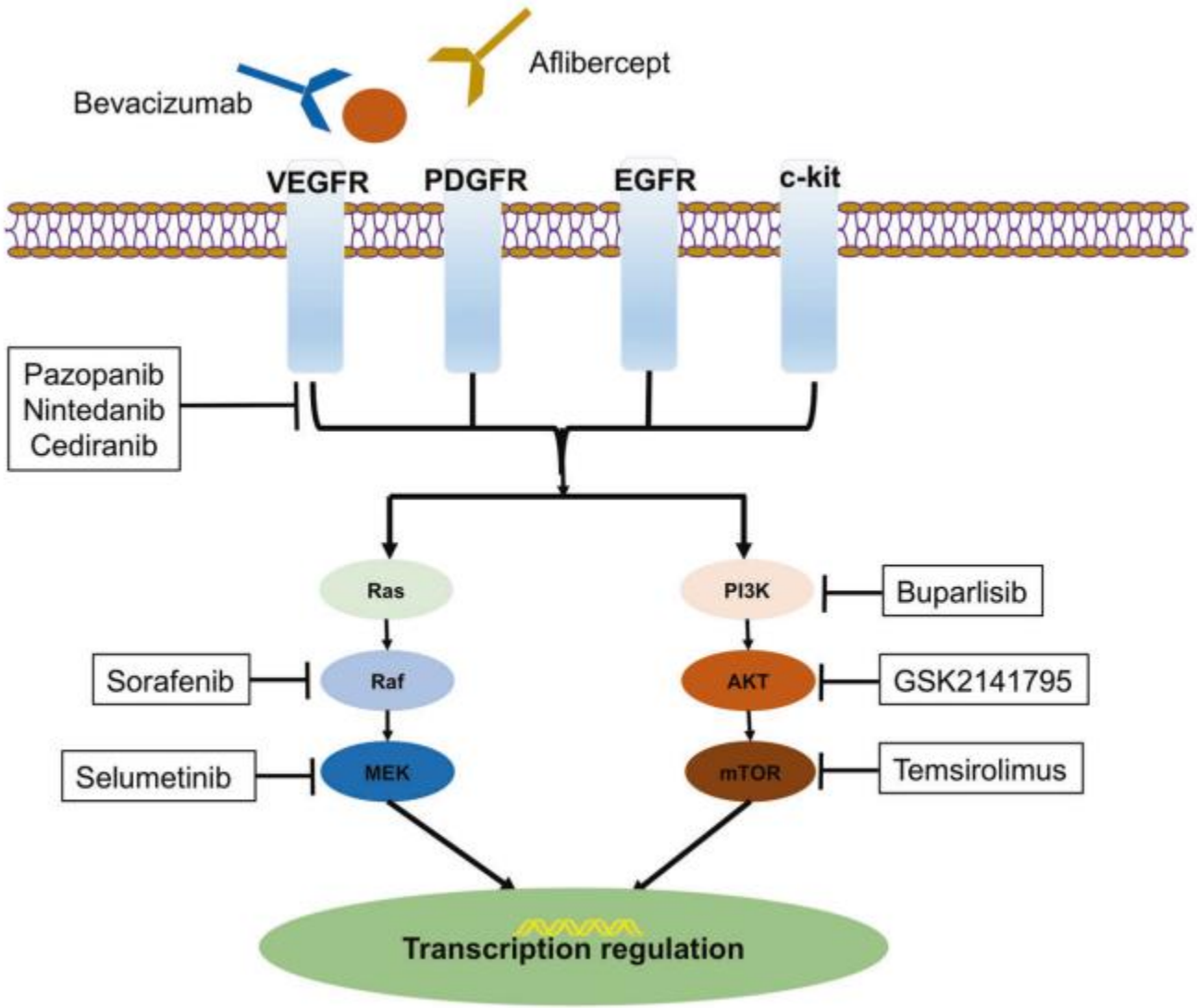
- Currently in gynecological malignancies, potential targets include tumor-intrinsic signaling pathways, angiogenesis, homologous-recombination deficiency (HDR) hormone receptors, and immunologic factors.
- The corresponding targeted agents include signaling pathway inhibitors, antiangiogenic agents, poly (ADP-ribose) polymerase (PARP) inhibitors, selective estrogen receptor down regulators, and Immune checkpoint inhibitors.

Table 1. FDA-approved targeted drugs for gynecological cancers

Target	Drug	Approval year	Indication		Administration
VEGFi	Bevacizumab (Avastin, Genentech)	2014	CC	Persistent, recurrent, or metastatic disease	15 mg/kg IV every 3 weeks with chemotherapy
		2014	OC	Platinum-resistant recurrent, and received no more than 2 prior chemotherapy regimens	10 mg/kg IV every 2 weeks with chemotherapy
		2016		Platinum-sensitive recurrent	15 mg/kg IV every 3 weeks with chemotherapy, and in maintenance
		2018		Advanced (FIGO stage III–IV)	
PARPi	Olaparib (Lynparza, AstraZeneca)	2014	OC	Advanced, with BRCAm, and have received three or more prior lines of chemotherapy	300 mg orally twice daily, until disease progression or unacceptable toxicity
		2017		Recurrent, and in complete or partial response to platinum-based chemotherapy	
		2018		Advanced, with BRCAm, and in complete or partial response to platinum-based chemotherapy	
	Rucaparib (Rubraca, Clovis)	2016	OC	Recurrent, with BRCAm, and have received two or more chemotherapies	600 mg orally twice daily, until disease progression or unacceptable toxicity
		2018		Recurrent and in a complete or partial response to platinum-based chemotherapy	
	Niraparib (Zejula, Tesaro)	2017	OC	Recurrent and in a complete or partial response to platinum-based chemotherapy	300 mg orally once daily, until disease progression or unacceptable toxicity
Anti-PD-1	Pembrolizumab (Keytruda, Merck)	2017	EC	Unresectable or metastatic, with a biomarker as MSI-H or dMMR	200 mg IV over 30 min every 3 weeks
		2018	CC	Recurrent or metastatic, with disease progression on or after chemotherapy, and expressing PD-L1	
Anti-PD-1 + VEGFi	Pembrolizumab (Keytruda, Merck) + lenvatinib (Lenvima, Eisai)	2019*	EC	Advanced disease without MSI-H/dMMR who have disease progression following prior systemic therapy, but are not candidates for surgery or radiation	Lenvatinib 20 mg orally once daily with pembrolizumab 200 mg IV over 30 min every 3 weeks

CC cervical cancer, *OC* epithelial ovarian, fallopian tube, or primary peritoneal cancer, *EC* endometrial cancer, *VEGFi* VEGF inhibitor, *PARPi* PARP inhibitor, *IV* intravenous infusion, *BRCAm* deleterious or suspected deleterious BRCA mutation, *MSI-H* microsatellite instability high, *dMMR* mismatch repair-deficient.
*Accelerated approval

ANTIANGIOGENIC PATHWAY



ANTIANGIOGENIC PATHWAY

- Vascular endothelial growth factor (VEGF), a major driver of angiogenesis in solid tumors, binds to the VEGF receptors (VEGFR, including VEGFR-1/2/3) on target cells and initiates the signaling pathway through intracellular tyrosine kinases.

- The VEGF pathway also interacts with the PI3K/AKT/mTOR pathway. Upregulation of the VEGF pathway can therefore cause tumour growth and spread and signal a poor prognosis.

- A number of antiangiogenic agents, such as bevacizumab, pazopanib, sunitinib, sorafenib, vandetanib, aflibercept, axitinib, regorafenib, ramucirumab, and lenvatinib are FDA-approved (e.g., colorectal cancer, lung cancer, renal cell carcinoma, and thyroid cancer).

- For gynecological cancers, bevacizumab was the first and only FDA-approved anti-VEGF drug. Role in Recurrent Ovarian cancers.

Table 2. Completed phase III trials of antiangiogenic agents in gynecological cancers

ID	Cancer/condition	No.	Intervention	mPFS (mon.)	mOS (mon.)	SAEs (%)	Refs
NCT00483782 ICON7	OC/high-risk stage I–IIa, IIb–IV	1528	(1) PC	17.5	58.6	–	37
			(2) PC + bevacizumab	19.9, $P = 0.25$	58.0, $P = 0.85$	–	
NCT00976911 AURELIA	OC/platinum-resistant recurrent	361	(1) Single-agent chemotherapy	3.4	13.3	27.1	42
			(2) Chemotherapy + bevacizumab	6.7, $P < 0.001$	16.6, $P = 0.174$	31.28	
NCT00434642 OCEANS	OC/platinum-sensitive recurrent	484	(1) GC + placebo	8.4	32.9	25.32	40
			(2) GC + bevacizumab	12.4, $P < 0.0001$	33.6, $P = 0.65$	36.44	
NCT00262847 GOG-0218	OC/stage III–IV	1873	(1) PC + placebo	10.3	41.1	38.49	35
			(2) PC + bevacizumab throughout	14.1, $P < 0.001$	40.8, $P = 0.34$	41.19	
			(3) PC + bevacizumab combination only	11.2, $P = 0.16$	43.4, $P = 0.53$	46.37	
NCT00565851 GOG-0213	OC/platinum-sensitive recurrent	674	(1) PC	10.4	37.3	86	41
			(2) PC + bevacizumab	13.8, $P < 0{\cdot}0001$	42.2, $P = 0.045$	96	
NCT00803062 GOG-0240	CC/metastatic, persistent, or recurrent	452	(1) PC	6	13.3	37.5	42,43
			(2) PT			34.58	
			(3) PC + bevacizumab			47.75	
			(4) PT + bevacizumab	8.2, $P = 0.002$	16.8, $P = 0.007$	55.96	
NCT00532194 ICON6	OC/platinum-sensitive recurrent	486	(1) Chemotherapy + placebo	8.7	–	–	73
			(2) Chemotherapy + cediranib throughout	9.9		–	
			(3) Chemotherapy + cediranib combination only	11, $P < 0.0001$		–	
NCT01015118 AGO-OVAR12	OC/stage IIb–IV	1503	(1) PC + placebo	16.6	62.8	34.89	67
			(2) PC + nintedanib	17.2, $P = 0.24$	62, $P = 0.087$	42.02	
NCT00866697 AGO-OVR16	OC/stage II–IV, after first-line chemotherapy	940	(1) Placebo	12.3	64.0	11.06	63
			(2) Pazopanib	17.9, $P = 0.0021$	59.1, $P = 0.64$	25.37	
NCT01204749 TRINOVA-1	OC/recurrent	919	(1) Paclitaxel + placebo	5.4	17.3	52	78
			(2) Paclitaxel + trebananib	7.2, $P < 0.0001$	19.0, $P = 0.19$	53	
NCT01281254 TRINOVA-2	OC/recurrent	223	(1) PLD + placebo	7.2	17.0	72	81
			(2) PLD + trebananib	7.6, $P = 0.57$	19.4, $P = 0.76$	73	
NCT01493505 TRINOVA-3	OC/stage III–IV	1164	(1) PC + placebo	15.0	–	66	80
			(2) PC + trebananib	15.9, $P = 0.36$		73	

ID identifier, *No.* enrollment number, *mPFS* median progression-free survival, *mOS* median overall survival, *Mon.* months, *SAEs* serious adverse events, *Refs* references, *Stage* FIGO stage, *PC* paclitaxel + carboplatin, *GC* gemcitabine + carboplatin, *PT* topotecan + paclitaxel, *PLD* pegylated liposomal doxorubicin

Table 3. Completed phase II trials of antiangiogenic agents in gynecological cancers

ID	Cancer/condition	No.	Intervention	ORR (%)	mPFS (mon.)	mOS (mon.)	SAEs (%)	Refs
NCT00025233	CC/persistent or recurrent	46	Bevacizumab	10.9	3.4	7.29	58.7	45
NCT00548418 GSK1072 8	CC/persistent or recurrent	27	Bevacizumab + topotecan + cisplatin	59	7.1	13.2	44.44	46
NCT00369122 RTOG041 7	CC/stage Ib–IIIb	60	Bevacizumab + cisplatin + radiotherapy	68.7	–	–	22.03	49
–	CC/advanced or recurrent	34	Bevacizumab + PC	88	9	26	–	47
NCT00937560 OCTAVIA	OC/stage IIb–IV	189	Bevacizumab + PC	84.6	23.7	–	22.8	396
NCT01010126	EC/stage III–IV	26	Bevacizumab + temsirolimus	25.1	6.0	11.5	61.5	60,339
	OC/stage III–IV	58		6.4	5.6	16.3	58.6	
NCT01305213 GOG-0186I	OC/recurrent	107	(1) Bevacizumab	28.2	4.8	–	16.98	397
			(2) Bevacizumab + fosbretabulin	35.7	7.3, $P = 0.05$		29.6	
NCT00696670	OC/resistant	39	Bevacizumab + erlotinib	23.1	4	–	30	398
NCT00945139	OC/platinum-resistant recurrent	46	Bevacizumab + PLD	30.2	6.6	33.2	6.52	399
NCT01091259	OC/recurrent	29	Bevacizumab + irinotecan	27.6	6.8	15.4	31	400
NCT00886691 GOG-0186G	OC/recurrent	150	(1) Bevacizumab	12.1	4.5	17.3	32	401
			(2) Bevacizumab + temsirolimus	22.2	5.9, $P = 0.39$	16.6, $P = 0.55$	46.7	
NCT00407563 ACORN	OC/platinum-resistant recurrent	48	Bevacizumab + abraxane	50	8.08	17.15	27.1	
NCT00267696 OSU-05070	OC/platinum-resistant recurrent	45	Bevacizumab + GC	69	13.3	36.1	8.9	
NCT00977574 GOG-0086P	EC/stage III–IV	339	(1) Bevacizumab + PC	60	–	34	42.9	
			(2) Temsirolimus + PC	55		25	50.4	
			(3) Bevacizumab + carboplatin	53		25.2	46.5	
NCT01770171 MITO END-2	EC/advanced or recurrent	108	(1) PC	53.1	10.5	29.7	–	
			(2) PC + bevacizumab	74.4	13.7, $P = 0.43$	40.0, $P = 0.24$		
NCT01005329 RTOG 0921	EC/high risk	34	Bevacizumab + cisplatin + radiotherapy	The 2-year estimate of OS was 96.7%			26.7	
NCT00879359	EC/advanced or recurrent	15	Bevacizumab + PC	73	18	58	73.3	52
NCT00723255 GOG-0229G	EC/recurrent	43	Bevacizumab + temsirolimus	24.5	5.6	16.9	63.3	405
NCT00301964 GOG-0229E	EC/persistent or recurrent	56	Bevacizumab	13.5	4.2	10.5	34.6	51
-	EC/persistent or recurrent	46	Bevacizumab + pemetrexed	41	7.9	25.7	52	406
NCT01468909	OC/recurrent	106	(1) Paclitaxel	1.8	7.5	23.3	30.00	407
			(2) Pazopanib + paclitaxel	22.7	6.2, $P = 0.20$	20.7, $P = 0.90$	42.31	
NCT01644825 MITO-11	OC/stage Ic–IV	74	(1) Paclitaxel	25	6.5	–	34	408
			(2) Pazopanib + paclitaxel	56	16.1, $P < 0.01$		46	
NCT00430781	CC/stage IVb, persistent, or recurrent	230	(1) Pazopanib	9	4.22	–	37.84	257
			(2) Lapatinib	5	3.99, $P = 0.03$		29	
NCT02055690	OC/recurrent	21	(1) Pazopanib	22	3.7	–	–	45
			(2) Pazopanib + fosbretabulin	18	7.6, $P = 0.08$			
NCT01669798	OC/recurrent, bevacizumab-resistant	27	Nintedanib	7.4	1.8	16	22.2	68
NCT01225887 GOG-0229K	EC/recurrent	37	Nintedanib	9.4	3.3	10.1	43.8	69
NCT01210222 GOG-0229L	EC/recurrent	35	Trebananib	3.1	1.7	6.6	43	82
NCT01253681	OC/recurrent	61	(1) Placebo	27	4.6	–	64	409
			(2) Trebananib	19	5.7		55	
			(3) Trebananib + paclitaxel	37	7.2		65	
NCT01111461	EC/recurrent	133	Lenvatinib	14.3	5.4	10.6	46.62	410
NCT00278343	OC/recurrent	74	Cediranib	26	4.9	18.9	6.8	72
NCT01132820 GOG-0229J	EC/recurrent	48	Cediranib	12.5	3.65	12.5	41.7	74

Most trials are OC or EC

Table 3. continued

ID	Cancer/condition	No.	Intervention	ORR (%)	mPFS (mon.)	mOS (mon.)	SAEs (%)	Refs
NCT00888173 GOG-0229I	EC/recurrent	43	Brivanib	7	3.3	10.7	41.86	95
NCT01267253 GOG-0227G	CC/recurrent	28	Brivanib	8	3.2	7.9	50	94
NCT02867956	OC/platinum-refractory	35	Apatinib + etoposide	54	–	–	5.7	87
NCT02867956	OC/recurrent	29	Apatinib	41.4	5.1	14.5	31	86
NCT00979992 GOG-0254	OC/clear cell, recurrent or persistent	30	Sunitinib	6.7	2.7	12.8	–	91
NCT00388037	OC/recurrent	30	Sunitinib	3.3	4.1	–	50.00	90
NCT00543049 AGO 2.11	OC/platinum-resistant recurrent	76	Sunitinib (noncontinuous/ continuous)	16.7/5.4	4.8/4.9	13.6/13.7	–	89
NCT00768144	OC/recurrent, platinum-refractory	35	Sunitinib	8.3	9.9	–	19.44	88
NCT00478426	EC/metastatic or recurrent	33	Sunitinib	18.1	3	19.4	52	92
NCT00389974	CC/advance or metastatic	19	Sunitinib	0	3.5	–	73.68	93

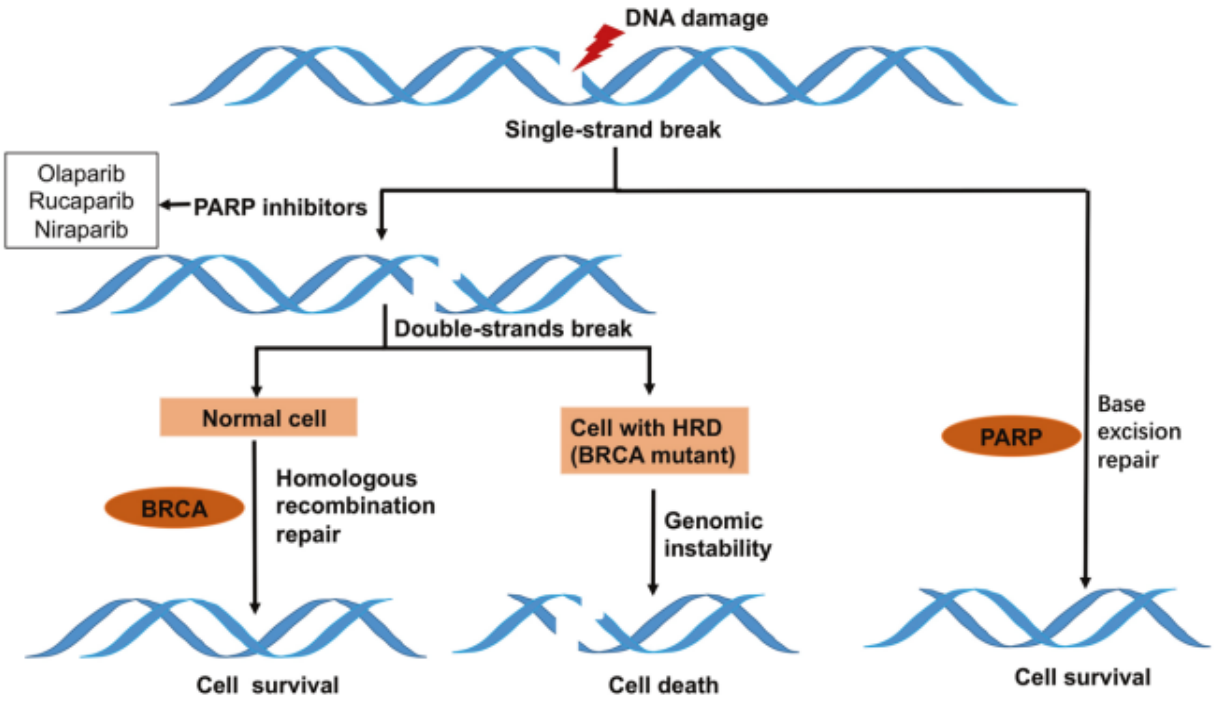
ORR objective response rate

Pazopanib: limited data of clinical trials for patients with CC or EC.
Nintedanib: limited clinical data of phase II/III trials in EC and CC. One phase II trial, GOG0229K (NCT01225887), showed modest activity with ORR 9.4% in advanced, recurrent, or metastatic EC.
Sunitinib: In metastatic or recurrent EC, promising activity in a phase II trial (NCT00478426) with ORR 18.1%

Most studies reported so far showed that antiangiogenic agents led to no significant improvement in OS for patients with gynecological cancers.

Thus, identification of predictive biomarkers for antiangiogenic agents and development of other targeted drugs is anticipated.

BASE-EXCISION REPAIR / SINGLE-STRAND BREAK PATHWAY



Inhibition of PARP-1 causes the accumulation of DNA SSBs and ultimately results in DSBs during DNA replication. In cells with HRD, DSBs are left unrepaired or repaired by the error-prone Nonhomologous end joining (NHEJ) pathway, which result in genomic instability and ultimately cell death

- In gynecological cancers, germline and somatic BRCA1/2 mutations (gBRCAm and sBRCAm) occur in ~10 even more frequently in patients with high-grade serous OC (HGSOC), which is the most common type – 15% of OC.

- Comprehensive genomic analysis has identified that ~50% of high-grade serous tumors (including OC and EC) exhibit HRD.

- Presence of HRD predicts a favorable response to platinum therapies and to PARP inhibitors. PARP inhibitors are also known to sensitize DNA-damaging agents, including carboplatin. **Are an exciting new option for patients with OC by significantly increasing both PFS and OS, especially for those with HRDs.**

- Olaparib is the first PARP inhibitor applied in clinic and approved by FDA for cancer treatment, followed by rucaparib and niraparib. In other gynecological cancers, only clinical case reports of benefit found in literature.

Table 4. Phase III trials (with results) of PARP inhibitors in gynecological cancers

ID	Cancer/condition	No.	Intervention	mPFS (Mos.)	SAEs (%)	Refs
NCT01844986 SOLO-1	OC/BRCAm	319	(1) Placebo	13.8	12.3	121
			(2) Olaparib	Not reached, $P < 0.0001$	20.8	
NCT01874353 SOLO-2	OC/recurrent, BRCAm	295	(1) Placebo	5.5	8.08	120
			(2) Olaparib	19.1, $P < 0.0001$	17.95	
NCT02477644 PAOLA-1	OC/stage III–IV	806	(1) Bevacizumab+ placebo	16.6	31	122
			(2) Bevacizumab+ olaparib	22.1, $P < 0{\cdot}0001$	31	
NCT01847274 NOVA	OC/platinum-sensitive recurrent	553	(1) Placebo	HRD:10.4; All:8.2	15.08	138
			(2) Niraparib	HRD: 21.9; All:13.8, $^{*}P < 0.0001$	29.97	
NCT02655016 PRIMA	OC/stage III–IV	733	(1) Placebo	8.2	18.9	140
			(2) PC + Niraparib	13.8, $P < 0{\cdot}0001$	70.5	
NCT01968213 ARIEL3	OC/platinum-sensitive recurrent	564	(1) Placebo	BRCAm: 5.4; HRD: 5.4	10.58	136
			(2) Rucaparib	BRCAm: 16.6; HRD: 13.6, $^{**}P < 0.0001$	21	
NCT02470585 GOG-3005	OC/stage III–IV, HGSOC	1140	(1) Placebo	BRCAm: 22.0; HRD: 20.5	32	150
			(2) Veliparib combination only	-	27	
			(3) Veliparib throughout	BRCAm: 34.7; HRD: 31.9, $^{***}P < 0.0001$	45	

HRD homologous-recombination deficiency, *HGSOC* high-grade serous ovarian cancer. *P-value of both HRD cohort and all population are <0.0001. ** and *** P-value of both BRCAm and HRD cohorts are <0.0001

Olaparib: newly diagnosed OC had significantly improved median PFS with olaparib plus bevacizumab maintenance treatment, following first-line chemotherapy (5.5 months longer, P < 0.0001). Also PFS benefit in subgroups of patients with BRCAm and patients with other HRD was even more obvious.

Rucaparib: FDA approved for maintenance treatment of recurrent OC patients who are in a complete or partial response to platinum-based chemotherapy.

Table 5. Phase II trials (with results) of PARP inhibitors in gynecological cancers

ID	Cancer/condition	No.	Intervention	ORR (%)	mPFS (mon.)	mOS (mon.)	SAEs (%)	Refs
NCT00494442 STUDY9	OC/advanced, BRCAm	58	Olaparib	33.3	–	–	36.4	[411]
NCT00753545 STUDY19	OC/serous, recurrent	265	(1) Placebo: BRCAm/ BRCAwt	4.2	4.3/5.5, $P <$ 0.0001	34.9/30.2, $P = 0.025$	8.6	[115,412]
			(2) Olaparib: BRCAm/ BRCAwt	12.3	11.2/7.4, $P = 0.0075$	26.6/24.5, $P = 0.37$	22.8	
NCT00679783 STUDY 20	OC/recurrent, HGSOC	91	Olaparib: BRCAm/ BRCAwt	41/24	7.4/6.4	–	16	[111]
NCT00628251 STUDY12	OC/advanced, BRCAm	98	(1) Olaparib (200 mg twice daily)	25	5	9	15.6	[413]
			(2) Olaparib (400 mg twice daily)	31.3	5	11	18.8	
			(3) PLD	18.2	4.8	13, All $P > 0.5$	15.6	
NCT01078662 STUDY42	OC/BRCAm	193	Olaparib	31.1	7.03	16.62	30.2	[118]
NCT01081951	OC/advanced or platinum-sensitive recurrent	173	(1) PC	–	9.6	–	20.99	[414]
			(2) Olaparib + PC		12.2, $P = 0.0012$		25.33	
NCT01116648	OC/platinum-sensitive recurrent	90	(1) Olaparib	48.7	8.2	33.3	–	[124,128]
			(2) Cediranib + olaparib	79.6	16.5, $P = 0.007$	44.2, $P = 0.11$	70	
NCT02354586 QUADRA	OC/HGSOC, recurrent, HRD	47	Niraparib	28	5.5	19	56	[141]
NCT02657889 KEYNOTE-162	OC/platinum-resistant recurrent	62	Niraparib + pembrolizumab	18	3.4	Not mature	–	[143]
NCT02354131 ENGOT-ov24	OC/platinum-sensitive recurrent	97	(1) Niraparib	30	5.5	Not mature	–	[142]
			(2) Niraparib + bevacizumab	62	11.9, $P < 0.0001$		65	
NCT01891344 ARIEL2	OC/platinum-sensitive recurrent, HRD	204	Rucaparib: BRCAm	80	12.8	–	24.5	[133]
			BRCAwt, LOH-high	29.3	5.7			
			BRCAwt, LOH-low	10	5.2			
NCT01482715 STUDY10	OC/BRCAm	42	Rucaparib	59.5			76.2	[134]
NCT01306032	OC/HGSOC, BRCAm	75	(1) Cyclophosphamide	19.4	3	–	0	*
			(2) Cyclophosphamide+ veliparib	11.8	3, $P = 0.68$		8.11	
NCT01540565	OC/BRCAm	52	Veliparib	26	8.18	–	20	[146]
NCT01266447	CC/persistent or recurrent	27	Veliparib + topotecan + filgrastim	7	2	8	59.3	[151]

BRCAwt BRCA wild-type. *LOH* genomic loss of heterozygosity. *Unpolished data found in ClinicalTrials.gov

Table 6. Ongoing phase II–III trials of PARP inhibitors in gynecological cancers (not including novel combination therapy)

ID	Cancer/condition	Setting	No.	Start date	Intervention	Phase/assignment	Status
NCT02282020 SOLO-3	OC/platinum-sensitive recurrent, BRCAm	Maintenance	266	2015.2	Olaparib vs. single-agent chemotherapy	III/randomized, parallel	Active, not recruiting
NCT03402841 OPINION	OC/platinum-sensitive recurrent, without BRCAm	Maintenance	279	2018.1	Olaparib	III/single group	Active, not recruiting
NCT03534453 L-MOCA	OC/platinum-sensitive recurrent	Maintenance	300	2018.5	Olaparib	III/single group	Active, not recruiting
NCT02855944 ARIEL4	OC/recurrent	Monotherapy	345	2016.9	Rucaparib vs. chemotherapy	III/randomized, crossover	Recruiting
NCT04227522 MAMOC	OC/advanced	Maintenance	190	2020.1	Rucaparib vs. placebo	III/randomized, parallel	Not yet recruiting
NCT03519230	OC/platinum-sensitive recurrent	Maintenance	216	2018.5	Pamiparib vs. placebo	III/randomized, parallel	Recruiting
NCT03709316	OC/advanced	Maintenance	381	2018.6	Nirapairb vs. placebo	III/randomized, parallel	Recruiting
NCT03863860	OC/platinum-sensitive recurrent	Maintenance	216	2019.1	Fluzoparib vs. placebo	III/randomized, parallel	Not yet recruiting
NCT04169997	OC/advanced	Maintenance	393	2020.2	IMP4297 vs. placebo	III/randomized, parallel	Recruiting
NCT02489006	OC/recurrent	Neoadjuvant	24	2016.7	Olaparib vs. platinum-based chemotherapy	II/ randomized, parallel	Recruiting
NCT03470805	OC/recurrent, after PLD	Maintenance	9	2018.6	Olaparib	II/ single group	Active, not recruiting
NCT04377087	OC/recurrent	Delayed maintenance	75	2020.5	Olaparib	II/ single group	Not recruiting
NCT03016338	EC/recurrent	–	44	2017.11	Niraparib	II/ single group	Recruiting
NCT03644342	CC/metastatic invasive	Concurrently	20	2019.7	Niraparib + radiotherapy	II/ single group	Recruiting
NCT03891576	OC/platinum-sensitive recurrent	Maintenance	105	2019.10	Niraparib	II/ single group	Not yet recruiting
NCT04217798	OC/platinum-resistant or -refractory	Maintenance	32	2020.1	Niraparib + etoposide	II/ single group	Not yet recruiting
NCT03617679	EC/metastatic and recurrent	Maintenance	138	2019.3	Rucaparib vs. placebo	II/randomized, parallel	Recruiting
NCT03795272	CC/locally advanced	Maintenance	162	2019.11	Rucaparib vs. placebo	II/randomized, parallel	Withdrawn
NCT04171700 LODESTAR	Solid tumor/HRD	–	220	2019.11	Rucaparib	II/ single group	Recruiting
NCT03509636	OC/recurrent, BRCAm	–	113	2018.4	Fluzoparib	II/ single group	Active, not recruiting

PI3K/AKT/mTOR PATHWAY

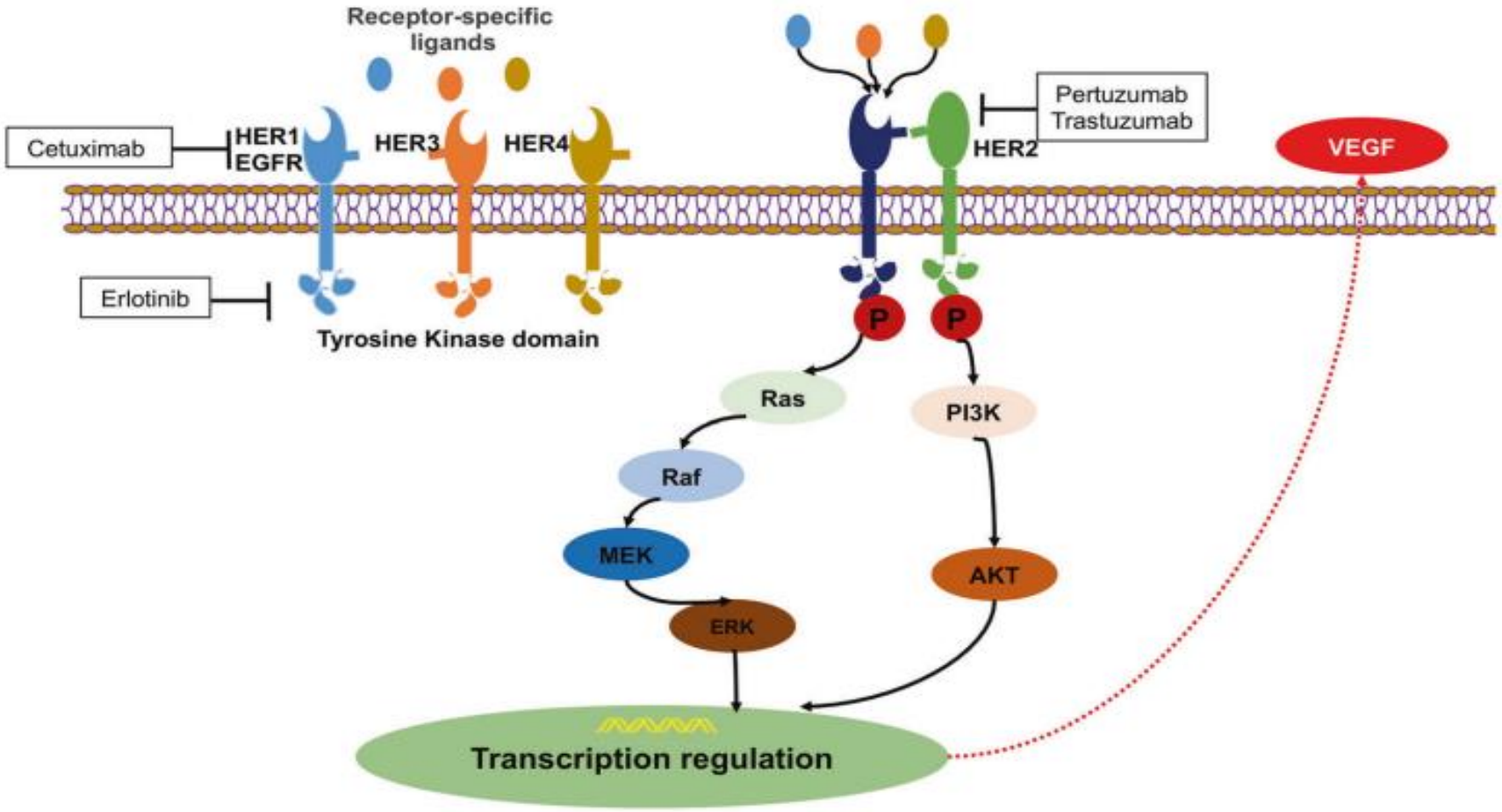
- The phosphatidylinositol 3-kinase / protein kinase B / mammalian target of rapamycin (PI3K/AKT/mTOR) signaling is one of the critical intracellular pathways that regulates important cell activities, such as cell growth, survival, proliferation, differentiation, metabolism, apoptosis, and angiogenesis.
- mTOR is a serine/threonine protein kinase and the best-described downstream target of AKT, composed of mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2).
- The most tested drugs in the PI3K/AKT/mTOR pathway are those blocking mTOR activity. **Temsirolimus, everolimus, and ridaforolimus are the most-studied mTOR inhibitors in gynecological cancers**. But there is modest effect of mTOR inhibitors as monotherapy in OC and CC based on current clinical evidence.
- Currently, no specific predictive biomarker has been recognized. Tumors with PI3K or PTEN mutations don't necessarily respond to mTOR inhibitors.
- The role of the PI3K/AKT/mTOR pathway inhibitors in gynecological cancers is not yet clear. The reasons for the unsatisfactory results may be related to the feedback loops and compensatory activation of Ras pathway.

Table 7. Completed phase II trials of PI3K/AKT/mTOR pathway inhibitors in gynecological cancers

ID	Cancer/condition	No.	Intervention	ORR (%)	CBR (%)	mPFS (mon.)	mOS (mon.)	SAEs (%)	Refs
NCT001460979	EC/advanced	22	Temsirolimus	10	35	3.0	21.3	–	415
AGO-GYN8	OC/advanced	22		4.8	38.1	3.4	21.9		
NCT00429793	OC/recurrent	54	Temsirolimus	9.3	–	3.1	11.6	9.26	416
NCIC IND 160	EC/recurrent or metastatic	23	Temsirolimus	26	89	–	–	–	188
NCT00723255	EC/recurrent	53	Temsirolimus + bevacizumab	24.5	40	5.6	16.9	63.27	417
NCT00729686	EC/advanced or recurrent	71	(1) Temsirolimus	22	52.4	4.9	10.8	36	187
			(2) Temsirolimus + hormone therapy	14.3	–			61.9	
NCT00072176 NCIC CTG	EC/locally advanced, recurrent, or metastatic	60	(1) Temsirolimus + hormone therapy	14	89	7.33	–	33.33	418
			2) Temsirolimus + chemotherapy	4	50	3.25		33.33	
NCT00977574 GOG-86P	EC/stage III–IV or recurrent	349	(1) Bevacizumab + PC	59.5	–	–	34	42.8	197
			(2) Temsirolimus + PC	55.3			25	50.4	
			(3) Bevacizumab + IC	52.9			25.2	46.5	
NCT01026792 NCIC IND199	CC/advanced or metastatic	38	Temsirolimus	3	60.6	3.52	–	40.5	419
NCT00087685	EC/progressive or recurrent	35	Everolimus	21	45.1	–	–	–	192
NCT01068249	EC/recurrent	38	Everolimus + letrozole	32	40	3	14	31.6	194
NCT01797523	EC/recurrent	58	Everolimus + letrozole + metformin	29	66.7	–	–	–	193
NCT02283658	OC/ER +, recurrent	20	Everolimus + letrozole	16	37	3.9	13	63	420
NCT00739830	EC/stage III–IV	130	(1) Hormone or chemotherapy	4	17	1.9	–	34	421
			(2) Ridaforolimus	0	35	3.6		57	
NCT00122343	EC/recurrent	45	Ridaforolimus	11	19	–	–	33	422
NCT00770185	EC/recurrent	35	Ridaforolimus	8.8	62	–	–	37.1	423
–	EC/progressive	45	Ridaforolimus	7.4	33	–	–	35.6	424
NCT01935973	EC/recurrent or persistent	26	GSK2141795 + trametinib	8.3	–	–	–	61	203
NCT02538627	CC/persistent or recurrent	35	GSK2141795 + trametinib	7.1	44	3.6	14.8	57	202
NCT01307631	EC/recurrent	37	MK2206	5.5	33	–	8	37.84	205
NCT01397877 ENDOPIK	EC/advanced or recurrent	40	BKM120	0	60	4.5		21	209
NCT02193633	OC/HGSOC	27	Vistusertib + chemotherapy	52	78	5.8	–	–	198
NCT01587040	EC/advanced or recurrent	67	Pilaralisib	6	13.4	–	–	52.9	210
NCT01420081	EC/recurrent	40	Gedatolisib	16	5	3.6	–		212

CBR clinical benefit rate = complete response + partial response + stable disease, *ER* + estrogen receptor positive

HER SIGNAL TRANSDUCTION PATHWAY



HER SIGNAL TRANSDUCTION PATHWAY

- Structural features of HER proteins include extracellular ligand binding domain, transmembrane domain, and intracellular protein tyrosine kinase domain.
- HER-targeted drugs include monoclonal antibodies and small molecule inhibitors. Monoclonal antibodies against the extracellular domain of the HER receptor include cetuximab, nimotuzumab, trastuzumab, pertuzumab, and ado-trastuzumab emtansi.
- **HER2 is an important oncogene in high grade and stage EC, especially in uterine serous carcinoma.**
- **In OC, the rate of HER2 overexpression is highly variable (ranging from 2% to 66%), and the rate of EGFR overexpression is 30–70%.**
- **In CC, the rate of EGFR overexpression ranges from 6% to 90%.**
- However, clinical significance of EGFR/HER2 gene amplification or protein overexpression and the efficacy of HER-targeted therapy are still controversial in gynecological cancers

Table 8. Completed phase II–III trials of HER-targeted therapy in gynecological cancers

ID	Cancer/condition	Phase	No.	Intervention	ORR (%)	mPFS (mon.)	mOS (mon.)	SAEs (%)	Refs
NCT02095119	CC/recurrent or metastatic	I/II	17	Nimotuzumab	0	5.43	9.9	–	[425]
NCT00997009 MITO CERV-2	CC/recurrent	II	108	(1) PC	84.6	5.2	17.7	–	[244]
				(2) PC + cetuximab	76.4	7.6, $P = 0.20$	17, $P = 0.27$		
NCT10101192	CC/advanced, persistent, or recurrent	II	27	Cetuximab + cisplatin	29.6	3.91	8.77	–	[245]
NCT00499031	CC/persistent or recurrent	II	38	Cetuximab	0	1.97	6.7	42.86	[426]
NCT00086892	OC/platinum-sensitive recurrent	II	29	Cetuximab	32.1	9.4	–	–	[248]
NCT01684878	OC/platinum-resistant, with low tumor	III	156	(1) Placebo + chemotherapy	8.7	2.6	8.4	37.66	[253,254]
PENELOPE	HER3 mRNA expression			(2) Pertuzumab + chemotherapy	13.1	4.3, $P = 0.14$	10.2, $P = 0.60$	43.42	
NCT02004093	OC/recurrent	II	149	(1) Chemotherapy	-	9.3	Not reached	16.2	*
				(2) Pertuzumab + chemotherapy		8.0, $P = 0.3967$	28.2	26.7	
NCT00096993	OC/platinum-resistant recurrent	II	103	(1) Placebo + chemotherapy	4.6	2.6	13.1	61.54	[252]
				(2) Pertuzumab + chemotherapy	13.8	2.9, $P = 0.07$	13.0, $P = 0.65$	35.38	
NCT02004093	OC/platinum-sensitive recurrent	II	149	(1) PC	–	9.3	Not yet estimable	16.22	[255]
				(2) PC + pertuzumab	–	8.5	28.2	26.67	
NCT00189579	OC/recurrent or refractory, HER2 +	II	41	Trastuzumab	7.3	2.0	–	–	[239]
NCT00006089	EC/recurrent or stage III–IV, HER2 +	II	34	Trastuzumab	0	1.8	6.8	–	[249]
NCT01367002	EC/advanced or recurrent, serous	II	61	(1) Chemotherapy	75	8.0	–	51	[250]
				(2) Trastuzumab + chemotherapy	44	12.6, $P = 0.005$			
NCT00023699	OC/persistent or recurrent	II	30	Gefitinib	0	1.23	3.7	–	[427]
NCT00189358	OC/platinum-resistant recurrent	II	56	Gefitinib + tamoxifen	0	1.9	8.4	3.6	[428]
-	CC/advanced or metastatic	II	28	Gefitinib	0	1.2	3.6	–	[266]
NCT00113373	OC/recurrent	II	28	Lapatinib	0	8.0	–	40	[258]
NCT00436644	OC/platinum-resistant recurrent	II	18	Lapatinib + topotecan	5.6	3.5	15.5	22.2	[260]
NCT00888810	OC/recurrent	II	39	Lapatinib + topotecan	14	–	–	–	[259]
NCT00096447	EC/persistent or recurrent	II	30	Lapatinib	3.3	1.82	7.33	33.3	[256]
NCT00430781	CC/metastatic	II	230	(1) Lapatinib	5	4.0	9.1	28.95	[257]
				(2) Pazopanib	9	4.2, $P < 0.013$	11.8, $P = 0.045$	37.84	
NCT00263822	OC/no progression after first-line PC	III	835	(1) Erlotinib	–	12.7	50.8	67	[262]
				(2) Observation		12.4, $P = 0.525$	59.1, $P = 0.903$		
NCT00030446	OC/recurrent	II	50	Erlotinib + carboplatin	57	–	–	38	[429]
NCT00126542	OC/recurrent	II	13	Erlotinib + bevacizumab	15	4.1	11	–	[261]
NCT00130520	OC/advanced	II	40	Erlotinib + bevacizumab	23.1	4	–	30	[398]
NCT00059787	OC/advanced	II	56	Erlotinib + chemotherapy	29	34.3	–	35.71	[430]
NCT00217529	OC/advanced	I/II	159	Erlotinib + chemotherapy	Terminated because of gastrointestinal toxicity.				[431]
NCT00031993	CC/recurrent or persistent	II	28	Erlotinib	0	Only 1 patient PFS > 6 mths			[432]

*Unpublished data found in ClinicalTrials.gov

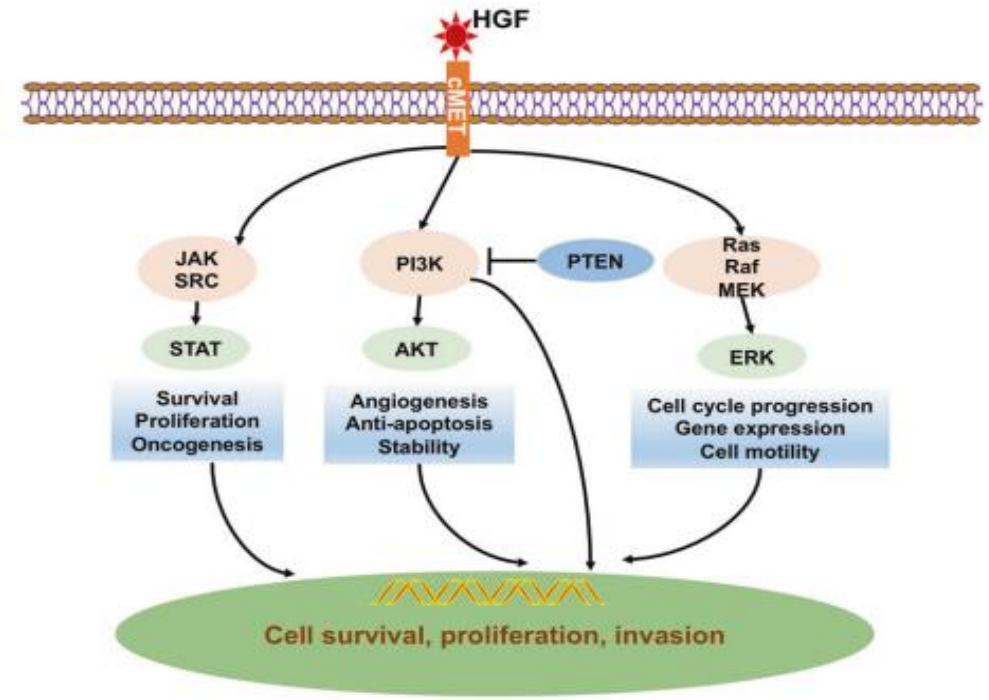
- Lapatinib had limited activity in unselected cases in EC, as well as in OC and CC.
- For CC, a phase II trial evaluated the efficacy of erlotinib combined with chemoradiation in treating patients with locally advanced CC, showing a promising activity with a complete response of 94.4%.
- Other HER-targeted TKIs (e.g., gefitinib, canertinib, and vandetanib) showed minimal clinical activities in gynecological cancers in current clinical trials.

Other Molecular Pathways

- In the **Ras/Raf/MEK signaling pathway**, Ras activation is the first process in activation of the mitogen-activated protein kinases (MAPKs) cascade.
- Then, Raf is recruited to the cell membrane where subsequent changes in Raf phosphorylation status result in activating MEK kinases (MEK1 and MEK2). MEK1 and MEK2 furtherly trigger Erk1 and Erk2.
- Inhibition of Ras/Raf/MEK signaling has promising potent as an antitumor targeted therapy, the clinical efficacy of this strategy in gynecological cancers is currently limited.
- The **Janus Kinase/signal transducer and activator of the tran-ions (JAK/STAT)** pathway has been proved to mediate the action of cytokines, interferons and growth factors, and their control of gene expression and activation of this is seen in many cancers.

THE HGF/C-MET SIGNAL TRANSDUCTION PATHWAY

hepatocyte growth factor (HGF) can trigger important cellular processes



Aberrant MET signaling derives from the upregulation of HGF transcription, leading to receptor and ligand overexpression

In OC, MET overexpression was detected in more than 20% (range from 22% to 41%) ovarian clear cell adenocarcinomas. **And increased expression of HGF and -Met signaling is associated with a poor prognosis of EC patients.** Therefore, targeting the interaction of c-MET and HGF would be beneficial in treating gynecological cancers. But currently there is no FDA-approved indication of this targeted therapy in cancers.

Table 9. Phase II trials (with results) of molecular targets in gynecological cancers

ID	Cancer/condition	No.	Target	Intervention	ORR (%)	mPFS (mon.)	mOS (mon.)	SAEs (%
NCT01936363	OC	63	MEK	(1) Pimasertib + XL765	12.5	9.99	–	50
				(2) Pimasertib + placebo	12.1	12.71		56.25
NCT00551070	OC/recurrent, low-grade serous	52		Selumetinib	15	–	–	63.46
NCT01011933	EC/recurrent or persistent	54		Selumetinib	6	2.3	8.5	64
NCT02538627	CC/recurrent or persistent	35		Trametinib + Uprosertib	7.1	3.6	14.8	57
NCT01935973	EC/ recurrent or persistent	26		Trametinib + Uprosertib	8.3	PFS at 6 months = 14%		61
NCT01047891 TRIAS	OC/platinum-resistant recurrent	185	Raf	(1) Sorafenib + topotecan	31	6.7	17.1	59
				(2) Placebo + topotecan	12	4.4, $P = 0.0018$	10.1, $P = 0.017$	51
NCT00390611	OC/first-line treatment	85		(1) Sorafenib + PC	69	15.4	36.5	27.91
				(2) PC	74	16.3, $P = 0.38$	Not reached	23.81
NCT00096200	OC/platinum-sensitive recurrent	36		(1) Sorafenib + PC	61	16.8	25.9	21.43
				(2) Sorafenib	15	5.6, $P = 0.012$	25.6, $P = 0.974$	16.67
NCT00791778	OC/maintenance	246		(1) Sorafenib	–	12.7	–	21.14
				(2) Placebo		15.7		20.33
NCT00093626	OC/third-line therapy	11		Sorafenib	–	2.00	11.78	low
NCT00436215	OC/recurrent	55		Sorafenib + bevacizumab	19	6.1		45.45
NCT00281515	OC/stage IIb–IV	105	Ras	(1) Lonafarnib + PC	–	11.5	20.6	–
				(2) PC		16.4, $P = 0.0141$	43.4, $P = 0.012$	
NCT01164995 M10MKO	OC/p53 mutated refractory	21	Wee1	Adavosertibc (AZD1775)	43	5.3	12.6	–
NCT01039207	OC/recurrent or persistent	31	c-MET	Rilotumumab	3.2	PFS at 6 months = 6.5%		45.16
NCT01716715	OC/recurrent	111		(1) Cabozantinib	7	5.3	19.4	–
				(2) Paclitaxel	24.1	5.5	Not reached	
NCT02315430 NRG-GY001	OC/recurrent	13		Cabozantinib	0	3.6	8.1	–
NCT00940225	OC	70		Cabozantinib	15	4.9	–	74.5
NCT02059265	OC/ recurrent or persistent	35	Src	Dasatinib	3.6	2.1	17.7	57.14
NCT01196741	OC/platinum-resistant recurrent	107		(1) Saracatinib + placitaxel	29	4.7	–	57.97
				(2) Placebo + placitaxel	43	5.3, $P = 0.99$		51.43
NCT01175343	OC/platinum-resistant recurrent	45	Notch	RO4929097	0	1.3	–	22.73

*Unpublished data found in ClinicalTrials.gov

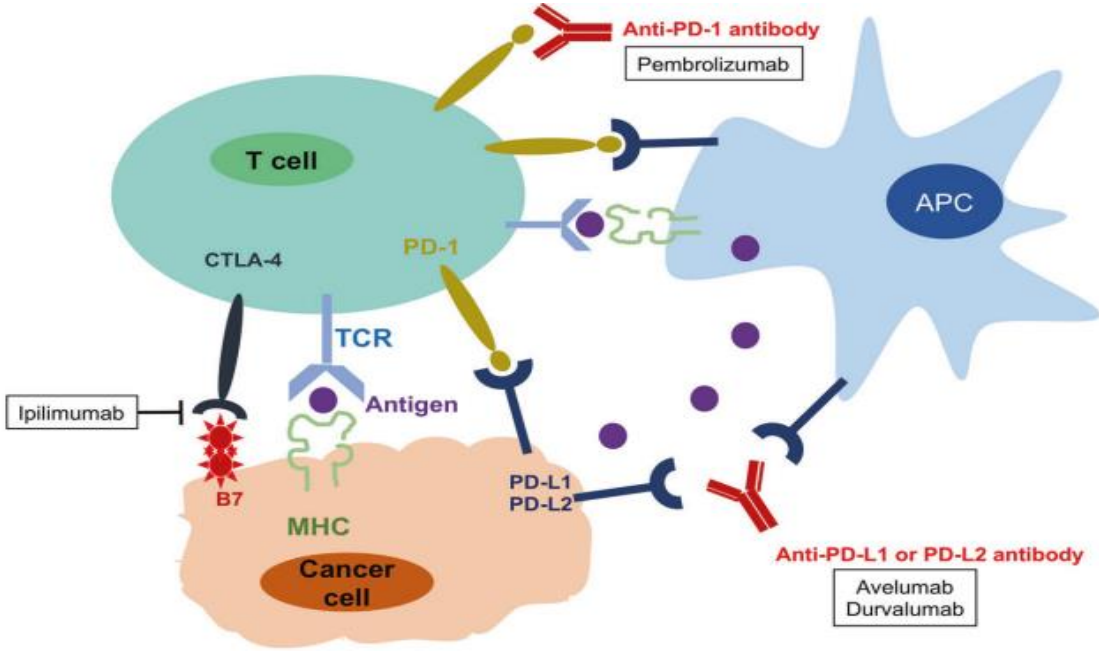
- Sarcoma proto-oncogene tyrosine kinase (Src) is a downstream component of many growth factor receptors, such as VEGFR, EGFR, and c-MET.
- Src is thought to increase chemotherapy resistance through activating Ras and AKT.

The activities of ATR inhibitors (e.g., AZD6738) and Wee1 inhibitors (e.g., AZD1775) investigated in early-phase trials in gynecological cancers

Notch pathway is associated with the epithelial–mesenchymal transition (EMT) processes in OC and CC

ANTIBODIES AND PD/L - 1 INHIBITORS

By binding to the antigens on the tumor cell surface, the ADCs release the drug components intracellularly and lead to the death of tumor cell.



- Programmed death protein-1 (PD-1) is an immune checkpoint molecule which is more commonly studied in immunotherapy researches of gynecological cancers. It plays an important role in T-cell co-inhibition and exhaustion, and subsequently helps tumor cells evade immune surveillance.
- Expression of immunosuppressive PD-1 ligands (PD-L1 or PD-L2) on the surface of tumor cells is an important predictive biomarker of response to PD-1 blockade.
- Mismatch repair-deficient (dMMR) tumors, including dMMR EC, are sensitive to PD-1 blockade.

Table 10. Completed phase I/II trials of anti-PD-1/PD-L1 in gynecological cancers

ID	Cancer/condition	Phase	No.	Intervention	ORR (%)	mPFS (mon.)	mOS (mon.)	SAEs (%)	Refs
–	OC/platinum-resistant recurrent	II	20	Nivolumab	15	3.5	20	40	378
NCT02873962	OC/recurrent	II	38	Nivolumab + bevacizumab	21	9.4	–	–	377
NCT00729664	OC/advanced	I	17	Nivolumab	5.9	–	–	5	435
NCT02488759 CheckMate 358 trial	CC/recurrent or metastatic	I/II	19	Nivolumab	26	–	21.9	–	375
NCT02257528	CC/persistent or recurrent	II	26	Nivolumab	4	–	–	24	376
NCT02674062 KEYNOTE100	OC/advanced or recurrent	II	376	Pembrolizumab	7.4–9.9	2.1	17.6	19.7	373
NCT02657889 KEYNOTE-162	OC/recurrent	I/II	62	Pembrolizumab+ niraparib	18	Not reached	–	–	143
NCT02537444	OC/recurrent	II	78	(1) ACP-196	2.9	–	–	21	*
KEYNOTE191				(2) ACP-196+ pembrolizumab	9.1			41	
NCT02628067 KEYNOTE 158	CC/advanced	II	98	Pembrolizumab	12.2	2.1	9	12.2	365
-	EC/dMMR recurrent or persistent	II	9	pembrolizumab	56	–	Not reached	0	370
NCT02501096 KEYNOTE 146	EC/advanced	II	54	Pembrolizumab+ lenvatinib	39.6	7.4	–	30	366
NCT02054806 KEYNOTE 028	EC/advanced, PD-L1(+)	Ib	24	Pembrolizumab	13	–	–	16.7	367
NCT02054806 KEYNOTE028	OC/advanced, PD-L1(+)	Ib	26	Pembrolizumab	11.5	1.9	13.8	3.8	368
	CC/advanced, PD-L1(+)		24		17	–	–	21	369
NCT02431559	OC/platinum-resistant recurrent	I/II	40	Durvalumab+ PLD	15	5.5	–	57.5	*
NCT01772004 JAVELIN Solid Tumor	OC/recurrent or refractory	Ib	124	Avelumab	9.7	2.7	10.8	6.5	381
NCT02912572	EC/MSS	II	33	Avelumab	27.6	–	–	19	380
	EC/POLE or MSI				6.25				
NCT01375842	EC/advanced or recurrent	Ia	15	Atezolizumab	13.3	1.7	9.6	13.3	379
NCT01375842	OC/recurrent	I	12	Atezolizumab	22.2	2.9	11.3	25.0	436
	EC/recurrent		15		13.3	1.4	9.6	43.3	

dMMR mismatch repair-deficient, *MSS* microsatellite stable, *MSI* microsatellite instable, *POLE* polymerase-ε. *Unpublished date found in clinicaltrials.gov

Table 11. Ongoing phase II trials of anti-PD-1/PD-L1 in gynecological cancers (not including novel combination therapy)

ID	Cancer/condition	No.	Start date	Intervention	Design	Status
NCT02725489	Women's cancers	13	2016.6	Durvalumab	Non-randomized parallel	Not yet recruiting
NCT02811497 METADUR	OC/platinum-resistant recurrent	60	2016.9	Durvalumab + azacitidine	Single group	Recruiting
NCT03899610	OC/advanced	24	2019.7	Durvalumab + tremelimumab + chemotherapy	Single group	Recruiting
NCT03357757 LATENT	Virus associated cancer	39	2018.2	Avelumab + valproic acid	Single group	Recruiting
NCT03503786 MITO END-3	EC/advanced or recurrent	120	2018.4	Avelumab + PC vs. avelumab	Randomized parallel	Not yet recruiting
NCT02440425	OC/platinum-resistant recurrent	43	2015.8	Pembrolizumab + paclitaxel	Single group	Active, not recruiting
NCT02635360	CC/advanced	88	2016.1	Pembrolizumab maintenance/throughout, plus chemoradiation	Randomized parallel	Recruiting
NCT02608684 PemCiGem	OC/platinum-resistant recurrent	21	2016.2	Pembrolizumab + standard treatment	Single group	Active, not recruiting
NCT02530154	OC/stage III–IV	30	2016.7	Pembrolizumab + PC	Single group	Recruiting
NCT02899793	EC/recurrent or metastatic	25	2016.9	Pembrolizumab	Single group	Recruiting
NCT02865811	OC/platinum-resistant recurrent	26	2016.9	Pembrolizumab + doxorubicin	Single group	Active, not recruiting
NCT02901899	OC/recurrent	38	2016.11	Pembrolizumab + gemcitabine	Single group	Recruiting
NCT02900560	OC/platinum-resistant recurrent	34	2016.12	Pembrolizumab + azacytidine vs. pembrolizumab	Non-randomized parallel	Active, not recruiting
NCT02834975	OC/advanced	40	2016.12	Pembrolizumab + PC	Single group	Recruiting
NCT03192059 PRIMMO	CC or EC	43	2017.7	Pembrolizumab	Single group	Recruiting
NCT02549209	EC/recurrent	46	2017.8	Pembrolizumab + PC	Single group	Recruiting
NCT03126812	OC/stage IV	15	2017.11	Pembrolizumab as neoadjuvant	Single group	Recruiting
NCT03275506 NEOPEMBROV	OC/stage IV	45	2018.2	Pembrolizumab + chemotherapy vs. ch	Non-randomized parallel	Recruiting
NCT03029403	OC/advanced	42	2018.2	Pembrolizumab + DPX-Survivac (vaccine) + cyclophosphamide	Non-randomized parallel	Recruiting
NCT03410784 MITO28	OC/advanced	72	2018.4	Pembrolizumab + PC	up	Not yet recruiting
NCT03276013 TOPIC	EC/advanced, recurrent or metastatic	51	2018.5	Pembrolizumab + doxorubicin		Recruiting
NCT03539328 MITO27	OC/platinum-resistant recurrent	138	2018.6	Pembrolizumab + chemotherapy vs. chemotherapy	Ran	Not yet recruiting
NCT03732950	OC/recurrent	30	2019.3	Pembrolizumab	Single gr	Recruiting
NCT03430700 PROMPT	OC/platinum-resistant recurrent	28	2019.5	Pembrolizumab + paclitaxel	Single group	cruiting
NCT04375956	OC/platinum-resistant recurrent	100	2020.5	Pembrolizumab	Single group	Not yet recruiting
NCT04238988	CC/locally advanced	45	2020.3	Pembrolizuma + PC	Single group	Not yet recruiting
NCT03340376	CC/recurrent	48	2017.8	Atezolizumab vs. atezolizumab + doxorubicin vs. doxorubicin	Randomized parallel	Recruiting
NCT03612791	CC/advanced	190	2018.6	Atezolizumab + radiotherapy vs. radiotherapy	Randomized parallel	Recruiting
NCT03614949	CC/recurrent, persistent, or metastatic	26	2019.1	Atezolizumab	Single group	Recruiting
NCT02498600	OC/recurrent	96	2015.6	Nivolumab vs. nivolumab + ipilimumab	Randomized parallel	Active, not recruiting
NCT03241745	EC/metastatic or recurrent	40	2017.8	Nivolumab	Single group	Recruiting
NCT03808857	CC/recurrent or metastatic	80	2019.2	GB226	Single group	Recruiting
NCT03972722	CC/recurrent or metastatic	89	2019.5	GLS-010	Single group	Recruiting
NCT04188860	CC/recurrent	34	2019.12	Camrelizumab + paclitaxel	Single group	Recruiting
NCT04368273	CC/advanced	30	2020.5	Toripalimab	Single group	Not yet recruiting
NCT03104699	CC/advanced	211	2017.4	Balstilimab	Single group	Active, not recruiting

Table 12. Ongoing phase III trials of anti-PD-1/PD-L1 in gynecological cancers (not including novel combination therapy)

ID	Cancer/condition	No.	Start date	Intervention	Status
NCT02580058 JAVELIN Ovarian 200	OC/platinum-resistant, or- refractory recurrent	566	2015.12	Avelumab + PLD vs. avelumab vs. PLD	Active, not recruiting
NCT02891824 ATALANTE	OC/platinum-sensitive recurrent	405	2016.9	Atezolizumab vs. placebo, plus PC + bevacizumab	Recruiting
NCT03038100 IMagyn050	OC/stage III–IV	1300	2017.3	Atezolizumab vs. placebo, plus PC + bevacizumab	Active, not recruiting
NCT03353831	OC/platinum-resistant recurrent	664	2018.9	Atezolizumab vs. placebo, plus paclitaxel or PLD	Recruiting
NCT03556839	CC/stage IVb	404	2018.9	Atezolizumab vs. placebo, plus PC + bevacizumab	Recruiting
NCT03603184 AtTEnd	EC/advanced	550	2018.10	Atezolizumab vs. placebo, plus PC	Recruiting
NCT03635567 KEYNOTE-826	CC/persistent, recurrent, or metastatic	600	2018.10	Pembrolizumab vs. placebo, plus PC + bevacizumab	Recruiting
NCT03914612	EC/advanced or recurrent	810	2019.7	Pembrolizumab vs. placebo, plus PC	Recruiting
NCT04221945	CC/locally advanced	980	2020.4	Pem[illegible]umab vs. placebo, plus ch[illegible]on	Recruiting
NCT03830866 CALLA	CC/locally advanced	714	2019.2	Du[illegible]cebo, plus chemo[illegible]	Recruiting
NCT03981796 RUBY	EC/recurrent or stage III–IV	470	2019.7	Dostarlimab [illegible] PC	Recruiting
NCT03912415 FERMATA	CC/advanced	316	2019.9	Prolgolimab vs. pla[illegible] bevacizumab	Not yet recruiting

ONGOING STUDIES

Table 13. Ongoing phase III trials of novel combination targeted therapy in gynecological cancers

ID	Cancer/condition	No.	Start date	Target	Intervention	
NCT02502266 COCOS	OC/platinum-resistant or -refractory recurrent, BRCAm	680	2016.2	VEGF, PARP	Cediranib + olaparib vs. cediranib vs. chemotherapy	Recruiting
NCT02446600	OC/platinum-sensitive recurrent	549	2016.2	VEGF, PARP	Cediranib + olaparib vs. olaparib vs. chemotherapy	Active, not recruiting
NCT03522246 ATHENA	OC/stage III–IV	1012	2018.5	PARP, PD-1	Rucaparib + nivolumab vs. rucaparib + placebo vs. nivolumab + placebo vs. placebo	Recruiting
NCT03602859 ENGOT-0V44 /FIRST	OC/stage III–IV	912	2018.10	PARP, PD-1	Dostarlimab + niraparib vs. niraparib + placebo vs. placebo	Recruiting
NCT03884101 ENGOT-en9	EC/recurrent or stage III–IV	720	2019.4	VEGF, PD-1	Lenvatinib + pembrolizumab vs. chemotherapy	Recruiting
NCT03740165 KEYLYNK-001/ENGOT-ov43	OC/fist-line treatment	1086	2018.12	VEGF, PARP, PD-1	Pembrolizumab + olaparib vs. pembrolizumab + placebo vs. placebo, plus PC + bevacizumab	Recruiting
NCT03737643 DUO-O	OC/stage III–IV	1056	2019.1	VEGF, PARP, PD-1	Durvalumab + olaparib vs. durvalumab + placebo vs. placebo, plus PC + bevacizumab	Recruiting
NCT03806049 NSGO/AVANOVA-Triplet	OC/platinum-sensitive recurrent	337	2019.6	VEGF, PARP, PD-1	Niraparib + bevacizumab + dostarlimab vs. niraparib + bevacizumab vs. chemotherapy	Not yet recruiting

Table 14. Ongoing phase II trials of novel combination therapy in gynecological cancers

ID	Cancer/condition	No.	Started date	Targets	Drugs	Design	Status
NCT02345265	OC/recurrent	70	2015.12	VEGF, PARP	Cediranib + olaparib	Single group	Active, not recruiting
NCT02502266	OC/ platinum-resistant recurrent	680	2016.2	VEGF, PARP	Cediranib + olaparib vs. cediranib vs. olaparib	Randomized parallel	Recruiting
NCT02889900 CONCERTO	OC/platinum-resistant recurrent	62	2017.1	VEGF, PARP	Cediranib + olaparib	Single group	Active, not recruiting
NCT03117933 OCTOVA	OC/platinum-resistant recurrent	138	2017.3	VEGF, PARP	Paclitaxel vs. cediranib + paclitaxel vs. cediranib + olaparib	Randomized parallel	Active, not recruiting
NCT0331574 BARCCO	OC/recurrent	100	2017.6	VEGF, PARP	Paclitaxel vs. cediranib + olaparib	Randomized parallel	Recruiting
NCT03326193	OC/advanced	105	2018.1	VEGF, PARP	Niraparib + bevacizumab	Single group	Active, not recruiting
NCT03462212 MITO25	OC/advanced, high grade	234	2018.2	VEGF, PARP	Rucaparib + bevacizumab + chemotherapy vs. rucaparib + chemotherapy vs. bevacizumab + chemotherapy	Randomized parallel	Recruiting
NCT03570437 COPELIA	EC/advanced	129	2018.5	VEGF, PARP	Paclitaxel vs. cediranib + paclitaxel vs. cediranib + olaparib	Randomized parallel	Recruiting
NCT03476798	CC or EC/recurrent	70	2018.6	VEGF, PARP	Rucapa vacizumab	Single group	Recruiting
NCT03660826	EC/recurrent, refractory, or metastatic	120	2018.9	VEGF, PARP	Cedir vs. cediranib + olaparib	Randomized parallel	Active, not recruiting
NCT03895788	OC/recurrent	24	2019.1	VEGF, PARP	Niraparib + br	Single group	Recruiting
NCT02476798 Clovis-001	CC or EC/recurrent	70	2019.6	VEGF, PARP	Rucaparib + bevaciz	Single group	Active, not recruiting
NCT04376073 ANNIE	OC/platinum-sensitive recurrent	40	2020.5	VEGF, PARP	Niraparib + anlotinib	Single group	Recruiting
NCT02921269	CC/recurrent	22	2017.3	VEGF, PD-1	Atezolizumab + bevacizumab	le group	Not yet recruiting
NCT03572478	EC/metastatic or recurrent	60	2018.8	VEGF, PD-1	Rucaparib vs. nivolumab vs. rucaparib + nivolumab	ized parallel	Recruiting
NCT03526432	EC/advanced, recurrent or persistent	55	2018.8	VEGF, PD-1	Atezolizumab + bevacizumab	Sing group	Recruiting
NCT03367871	CC/recurrent, persistent, or metastatic	39	2018.12	VEGF, PD-1	Pembrolizumab + bevacizumab	Single group	Recruiting
NCT03816553	CC/recurrent, persistent, or metastatic	49	2019.1	VEGF, PD-1	Camrelizumab + apatinib	Single group	Recruiting
NCT04068974	OC/platinum-resistant recurrent	28	2019.8	VEGF, PD-1	Camrelizumab + apatinib	Single group	Not yet recruiting
NCT04197219	EC/recurrent	26	2020.1	VEGF, PD-1	Pembrolizumab + axitinib	Single group	Not yet recruiting
NCT03797326	Advanced solid tumors	180	2019.2	VEGF, PD-1	Pembrolizumab + lenvatinib	Single group	Recruiting
NCT04236362	OC	30	2020.1	EGFR, PD-1	TQB2450 + anlotinib	Single group	Not yet recruiting
NCT02571725	OC/recurrent, BRCAm	50	2016.2	PARP, PD-1	Olaparib + tremelimumab	Single group	Recruiting
NCT02912572	EC/recurrent	70	2016.12	PARP, PD-1	Talazoparib + avelumab	Non-randomized parallel	Recruiting
		242	2017.10	PARP, PD-1	Talazoparib + avelumab		Recruiting

Table 14. continued

ID	Cancer/condition	No.	Started date	Targets	Drugs	Design	Status
NCT03330405 Javelin Parp Medley	OC/platinum-sensitive recurrent					Non-randomized parallel	
NCT03572478	EC/ metastatic or recurrent	60	2018.8	PARP, PD-1	Rucaparib + nivolumab vs. nivolumab vs. rucaparib	Randomized parallel	Recruiting
NCT03651206 ROCSAN	OC/recurrent	196	2019.1	PARP, PD-1	Niraparib/dostarlimab + niraparib vs. chemotherapy	Randomized parallel	Active, not recruiting
NCT03824704	OC/HGSOC or endometroid	139	2019.5	PARP, PD-1	Rucaparib + nivolumab	Single group	Recruiting
NCT04068753 STAR	CC/platinum-resistant recurrent	150	2019.6	PARP, PD-1	Dostarlimab + niraparib	Single group	Active, not recruiting
NCT03951415 DOMEC	EC/recurrent	55	2019.7	PARP, PD-1	Durvalumab + olaparib	Single group	Recruiting
NCT03955471 MOONSTONE	OC/progressive or recurrent	68	2019.9	PARP, PD-1	Dostarlimab + niraparib	Single group	Recruiting
NCT04034927	OC/recurrent	170	2019.10	PARP, PD-1	Olaparib vs. olaparib + tremelimumab	Randomized parallel	Recruiting
NCT02953457	OC/recurrent or refractory, BRCAm	39	2017.6	PARP, PD-1, CTLA-4	Olaparib + durvalumab + tremelimumab	Single group	Recruiting
NCT02484404	Advanced solid tumors	384	2015.6	VEGF, PARP, PD-1	Olaparib + cediranib + durvalumab	Non-randomized parallel	Recruiting
NCT02873962	OC/recurrent	76	2016.11	VEGF, PARP, PD-1	Nivolumab + bevacizumab vs. nivolumab + bevaci[illegible]b + rucaparib	Non-randomized sequential	Recruiting
NCT03574779 OPAL	OC/recurrent	41	2019.1	VEGF, PARP, PD-1,	Dost[illegible]parib + bevacizumab	Single group	Active, not recruiting
NCT04015739 BOLD	OC/recurrent	63	2019.2	VEGF, PARP, PD-1	MEDI4736 + [illegible]izumab	Single group	Recruiting
NCT03694262 EndoBARR	EC/persistent or progressive	30	2019.7	VEGF, PARP, PD-1	Atezolizumab + r[illegible]zumab	Single group	Recruiting
NCT04361370 OPEB-01	OC/platinum-resistant recurrent	44	2020.4	VEGF, PARP, PD-1	Olaparib + pembrolizu[illegible]b	Single group	Active, not recruiting
NCT03699449 AMBITON	OC/platinum-resistant recurrent	68	2018.11	VEGF, PARP, PD-1, CTLA-4	Olaparib + cediranib vs. durvalum[illegible] durvalumab + chemotherapy vs. durva[illegible] tremelimumab + chemotherapy	Randomized parallel	Recruiting
NCT02208375	EC or OC/recurrent	150	2014.11	PARP, mTOR, AKT	Olaparib + vistusertib vs. olaparib + capivasertib	[illegible]rallel	Active, not recruiting
NCT03462342 CAPRI	OC/recurrent	86	2018.3	PARP, ATR	Olaparib + AZD6738	Single g[illegible]	[illegible]cruiting
NCT04065269 ATARI	Gynecological cancers, AR1A loss	40	2019.11	PARP, ATR	AZD6738 vs. AZD6738 + olaparib	Randomized p[illegible]	[illegible]ecruiting
NCT04239014 DUETTE	OC/platinum-sensitive recurrent	192	2020.3	PARP, ATR	AZD6738 vs. AZD6738 + olaparib vs. placebo + olaparib	Randomized parallel	Not yet Recruiting
NCT03579316	OC/recurrent	70	2018.12	PARP, Wee	Adavosertib vs. adavosertib + olaparib	Randomized parallel	Recruiting
NCT03924245	OC/platinum-resistant recurrent	73	2019.12	PARP, HDAC	Olaparib + entinostat	Single group	Active, not recruiting
NCT02764333	OC/platinum-resistant recurrent	29	2016.5	PD-1, cancer vaccine	Durvalumab + TPIV200	Single group	Active, not recruiting
NCT03946358	CC/HPV +	47	2019.9	PD-1, cancer vaccine	Atezolizumab + UCPVax (vaccine)	Single group	Not yet Recruiting
NCT03015129	EC	80	2017.1	PD-1, CTLA-4	Durvalumab + tremelimumab vs. durvalumab	Randomized parallel	Recruiting
NCT03026062	OC/platinum-resistant recurrent	100	2017.5	PD-1, CTLA-4	Durvalumab vs. durvalumab + tremelimumab	Randomized parallel	Recruiting
NCT03277482	Gynecological cancer	32	2018.2	PD-1, CTLA-4	Durvalumab + tremelimumab + radiotherapy	Single group	Recruiting

Molecular markers in Risk identification and Prognosis

Table I. Expression of biomarkers in type 1 and type 2 endometrial cancer.

Target	Function	Change	Type 1 (%)	Type 2 (%)
K-ras	Oncogene	Mutation	13-26	0-10
HER-2/neu	Oncogene	Enhanced expression	Rare	18-80
PIK3CA	Oncogene	Mutation	26-36	26-36
FGFR2	Oncogene	Mutation	12	12
PTEN	Tumor suppressor	Mutation, deletion, methylation	35-55	0-11
p53	Tumor suppressor	Mutation	5-10	80-90
p16	Cancer suppressor	Mutation, methylation, enhanced expression	10	10-40
MLH1	DNA repair	Methylation	20-35	0-10
Bcl-2	Tumor suppressor	Mutation	65	67
Bax	Oncogene	Mutation	48	43
ER, PR	Transcription factor	Enhanced expression	70-73	19-24
β-catenin	Oncogene	Mutation	25-38	0-5
E-cadherin	Tumor suppressor	Mutation, methylation	22-43	57-75
EZH2	Transcription factor	Enhanced expression	16	36
BMI-1	Transcription factor	Enhanced expression	53	62

Table II. Biomarkers as prognostic predictors in endometrial cancer.

Evidence level	Biomarker
Consistent results obtained in retrospective studies	DNA ploidy *ER/PR* *p53* *Ki-67* *Bcl-2*
Inconsistent results obtained in several studies	*HER-2/neu* *PTEN* *p16* MSI β-catenin *K-ras*
An association with prognosis suggested in a few studies	Angiogenesis markers (MVD, *VEGF-A*, *VPI*, *VMI*, *GMP*) E-cadherin *PI3K* signal activation

Table from ref. 3. *PTEN*, phosphatase and tensin homolog; ER, estrogen receptor; PR, progesterone receptor; *VEGF-A*, vascular endothelial growth factor A.

Tumor types	POLE-ultramutated	mismatch repair deficient (MMRd)	TP53 mutant	No specific molecular profile (NSMP)
Previous naming	Polymerase Epsilon exonuclease domain mutated、	Microsatellite instability (MSI)	p53-mutated/Copy-number high	p53 wild-type/microsatellite stable (MSS)/Copy-number low
Somatic copy-number alterations (SCNA)	Very low	Low	High	Low
Mutational frequency	>100 mutations/Mb	100–10 mutations/Mb	<10 mutations/Mb	<10 mutations/Mb
Prognosis in early stage (I–II)	Favorable	Intermediate	Poor	Good/intermediate
Confirmatory test	Sanger/NGS Tumor mutation burden	MMR-IHC (MLH1, MSH2, MSH6, PMS2) MSI assay Tumor mutation burden	p53-IHC NGS Somatic copy-number aberrations	
Histological features	Endometrioid Grade 3 Significant TILs	Endometrioid Grade 3 Lymph vascular space invasion(LVSI) substantial MELF-type invasion Significant TILs lower uterine segment involvement	Serous Grade 3 LVSI	Endometrioid Grade 1–2 Squamous differentiation ER/PR (+)
Clinical features	EarlyStage (IA/IB) Early onset Young age	Correlated with Lynch Syndrome	Advanced stageLate onset	High BMI
Therapeutic method	Benefit from immunotherapy No significant difference in adjuvant treatment	benefit from immunotherapy	Adjuvant radiotherapy and chemotherapy	P13K/Akt pathway inhibitor

PORTEC-4a: Molecular Profile-based Versus Standard Adjuvant Radiotherapy in Endometrial Cancer : started 2016

- multicenter, phase III RCT in endometrial cancer with high-intermediate risk features.

- Aims to investigate the role of an integrated clinicopathological and molecular risk profile to determine if participants should receive no adjuvant therapy, vaginal brachytherapy or external beam radiotherapy based on a favourable, intermediate or unfavourable profile compared to standard adjuvant vaginal brachytherapy.

- To Measure Vaginal recurrence rates as primary outcomes; 5y-RFS, QOL, Toxicities, OS as Secondary outcomes

TRIALS IN ENDOMETRIAL CANCERS

2.1. Endometrial cancer (EC)								
Tumor types	Therapeutic drugs of experimental group	Gov number	Type of study	Number of participants (n)	Biomarkers	ORR(%,95% CI)	Trial phase	PFS (months)
EC	dostarlimab	NCT02715284 (20)	Single arm	104	dMMR	42.3%(30.6-54.6)	II	_
EC	pembrolizumab	NCT02628067 (21)	Single arm	24	PD-L1,TMB	13%(2.8-33.6)	I	_
Advanced EC	pembrolizumab	NCT02628067 (22)	Single arm	90	MSI-H/dMMR	48%(37-60)	II	_
Solid tumors including EC	pembrolizumab	NCT02628067 (23)	Single arm; Cohort TMB-H and cohort Non-TMB-H	790	TMB-H (n=102) Non-TMB-H (n=688)	29%(21-39); 6%(5-8)	II	_
Advanced EC	pembrolizumab plus lenvatinib	NCT03517449 (24)	Randomized controlled double-blind	827	dMMR	_	III	7.2 vs. 3.8, PFI-stratified HR:0.56 (95% CI, 0.47 -0.66; P<0.001).
EC, CC	Pembrolizumab +radiation+immune/ environmental-targeting compounds	NCT03192059 (25)	Single arm;3-cohort	EC:25 CC:18	–	–	II	–
EC	pembrolizumab	NCT02899793 (26)	Single arm	Lynch-like cancers:25	TMB	100%(-)	II	–
EC	dostarlimab	NCT02715284 (27)	Single arm. Cohort A1: dMMR/MSI-H and A2: pMMR/MSS	A1:n=129 A2:n=161	dMMR/MSI-H	A1:43.5%(34.0-53.4) A2:14.1%(9.1-20.6)	II	–

Tumor types	Therapeutic drugs	Study registration number	Type of study	Number of participants	Trial phase	Treatment period
MSI-H/dMMR EC,squamous cell carcinoma of cervix,vulva	Pembrolizumab	CTR20200103	Single arm	1200	III	Second-line therapy
Advanced EC	Durvalumab + carboplatin, paclitaxel +Olaparide (PARP inhibitor)	CTR20210547	Randomized controlled double-blind	699	III	First-line/Initial therapy
Advanced EC	Pablizumab combined with carboplatin, paclitaxel+ radiotherapy	CTR20211275	Randomized controlled double-blind	990	III	First-line/Initial therapy
EC	Pabolizuma(anti-PD-1)+lenvatinib (anti-VEGF)	CTR20191858	Randomized controlled double-blind	875	III	First-line therapy
EC,cervical carcinoma,OC	PM8002 injection (Immunosuppression+anti-VEGF)	CTR20202497	Single arm	246	IIa	First-line therapy failure
Advanced EC	Sintilimab+fruquintinib(anti-VEGF)	CTR20190514	Single arm	323	Ib/II	First/second-line therapy failure
Advanced EC	IMP7068 (WEE1 inhibitor)	CTR20212068	Single arm	150	II/III	First/second-line therapy failure
Advanced EC	TQB2450 injection (anti-PD-1) +Anlotinib Hydrochloride(anti-VEGF)	CTR20213383	Single arm	196	I	First/second-line therapy failure
Advanced EC	KN035 injection(anti-PD-1) +lenvatinib(anti-VEGF)	CTR20212718	Single arm	108	II	First/second-line therapy failure

TRIALS IN CERVICAL CANCERS

Table 1. Clinical trials in CC

Author	Trial/Phase	Setting	Pts *N*	Treatment	Results	Grade 3-4 AEs Pts *N* (%)
Lheureux et al., 2015 [25]	NCT01693783 Phase I-II	Metastatic, recurrent	42	Ipilimumab 10mg/kg q3w for 4 cycles If CR/PR/SD 4 → cycles ipilimumab 10mg/kg q12w every 12 weeks	ORR 8.8%	-diarrhea *n* = 4 (9.5) -colitis *n* = 3 (7.1)
Chung et al., 2019 [11]	KEYNOTE-158 Phase II	PD-L1 positive advanced	98 (82, PDL1 CPS ≥ 1)	Pembrolizumab 200 mg q3w	ORR 12.2% 14.6% in PD-L1 positive Total population: Median PFS 2.1 Mo. Estimated PFS rate at 6 Mo. 25.0% Median OS 9.4 Mo. 6-month estimates OS 75.2% 12-month estimates OS 41.4% PD-L1 positive: Median PFS 2.1 Mo. Median OS 11 Mo. 6-month estimates OS 80.2% 12-month estimates OS 47.3%	Treatment related: -increased ALT *n* = 3 (3.1) -increased AST *n* = 2 (2.0) Immune-mediated: -hepatitis *n* = 2 (2.0) -severe skin reactions *n* = 2 (2) -adrenal insufficiency *n* = 1 (1)

TRIALS IN CERVICAL CANCERS

Author	Trial/Phase	Setting	Pts *N*	Treatment	Results	Grade 3-4 AEs Pts *N* (%)
Wendel Naumann et al., 2019 [12]	CheckMate 358 Phase I-II	HPV-associated tumors, recurrent or metastatic cervical, vaginal, vulvar cancers	24 (19 cervical, 5 vaginal-vulvar cancer)	Nivolumab 240 mg q2w	ORR: 26.3% (cervical) 20.0% (vaginal-vulvar) DCR: 68.4% (cervical) 80.0% (vaginal-vulvar) Median PFS 5.1 Mo. 26.3% progression free patients at 12 Mo. In cervical cohort: Median OS 21.9 Mo., 12-month OS rate 77.5% 24-month OS rate 49.8%	Cervical cohort: -diarrhea *n* = 1 (5.3) -hepatocellular injury *n* = 1 (5.3) -pneumonitis *n* = 1 (5.3) Vaginal/vulvar cohort: none

Pts *N*: patient number; PFS: progression free survival; Mo.: month

2.2 Cervical cancer (CC) and ovarian cancer (OC).							
Tumor types	**Therapeutic drugs of experimental group**	**Gov number**	**Type of study**	**Number of participants(n)**	**Biomarkers**	**ORR(%,95% CI)**	**Trial phase**
CC	dostarlimab	NCT02383212 (28)	Single arm	155	PD-L1	42.3%(30.6-54.6)	II
CC	camrelizumab (anti-PD-1) +apatinib (anti-VEGF)	NCT03816553 (29)	Single arm	45	TMB-H	55.6%(40.0-70.4)	II
OC	Pembrolizumab+ziv-aflibercept(anti-VEGF)	NCT02298959 (30)	Single arm	30	_	16.7%(7-32)	Ib
epithelial OC	nivolumab +ipilimumab	NCT02498600 (31)	Randomized controlled double-blind	Experimental :51 Control :49	–	PFS(month):2 vs3,PFI-stratified HR: 0.53(95%CI,0.34-0.82)	II
Refractory OC	intraperitoneal Olvi-Vec virotherapy	NCT02759588 (32)	Single arm	12	_	ORR:9%(-) Stable disease:64%	Ib

- From the Cancer Genome Atlas Network, detailed genomic analyses revealed amplifications of PD-L1 and PD-L2 in cervical cancer tissues.
- Radiation therapy impacts tumor immune microenvironment and modulates immune system. Several clinical trials are ongoing, with combination regimen of concurrent chemoradiation therapy plus ICIs (pembrolizumab or durvalumab) for advanced cervical cancer patients.
- Other immunological approaches include adoptive cell therapy, which involves the systemic infusion of therapeutic T cells.

Response Rates with Single-Agent Checkpoint Blockade in Gynecologic Malignancies

Target	Antibody	Sample Size	Objective response rate (ORR)	Disease control rate (including CR, PR, SD)
Recurrent Ovarian Cancer				
CTLA-4	Ipilimumab [96]	n=39	10.3%	--
PD-1	Nivolumab [54]	n=20	15%	45%
	Pembrolizumab	n=26 [55]	11.3%	38.4%
		n=376 [56] (100 evaluable)	8% - CPS ≥ 1: 10.2% - CPS ≥ 10: 17.1%	37.2% - CPS ≥ 1: 38.1% - CPS ≥ 10: 41.5%
PD-L1	BMS 936559 [97]	n=17	6%	18%
	Atezolizumab [98]	n=9	22%	22%
	Avelumab [57]	n=125	9.6%	52%
Uterine Cancer				
PD-1	Pembrolizumab	n=9, (MMR-deficient) [70]	56%	88.9%
		n=23 [71]	13%	26.1%
	Nivolumab	n=22[99]	23%	--
PD-L1	Avelumab[73]	n=15 (MMR-deficient)	26.7%	53.3%
		n=16 (MMR-proficient)	6.25%	31.3%
Cervical Cancer				
CTLA-4	Ipilimumab [90]	n=34	2.9%	32.4%
PD-1	Nivolumab [89]	n=19	26.3%	68.4%
	Pembrolizumab [88]	n=98	12.2%	30.6%

CR: complete response, PR: partial response, SD: stable disease, CPS: combined positive score

VACCINE THERAPY FOR OVARIAN CANCERS

- New York esophageal squamous cell carcinoma-1 (NY-ESO-1) has demonstrated durable cellular and humoral immune responses in a majority of patients with NY-ESO-1-positive tumors.

- Several studies evaluating the effect of NY-ESO-1 vaccination in ovarian cancer patients demonstrate vaccine-elicited CD4+ and CD8+ T cell responses, persistence of NY-ESO-1+ lymphocytes and survival benefit among NY-ESO-1 vaccinated patients compared to non-vaccinated patients. (**NCT01567891, NCT002650986, NCT03017131**).

- Preliminary investigation using autologous dendritic cell-based vaccine with whole tumor lysate for 25 patients with recurrent ovarian cancer demonstrated ORR of 8%.

- In **CAN-003 phase II study**: mucin 1 targeted-dendritic cell maintenance therapy in recurrent EOC, improved OS in patients in remission after second-line therapy with vaccination compared to controls (42 vs. 26 months, p = 0.004)

VACCINE THERAPY FOR CERVICAL / ENDOMETRIAL CANCERS

- Role of ACT in endometrial cancer has largely remained uninvestigated. Currently one ACT-based clinical trial recruiting patients with metastatic endometrial cancer (NCT01174121).

- Evaluation of therapeutic vaccination of preinvasive cervical lesions using a DNA vaccine, pNGVL4a-CRT/E7(detox) demonstrated regression in 30% of patients with increased CD8+ T cell infiltration among women who received intralesional administration.

- Clinical trial using ACT published by Stevanovic and colleagues using single infusion of HPV E6 and E7 reactive tumor infiltrating lymphocytes after lymphodepletion. Five of 18 patients experienced objective response.

Stevanović S, et al. Journal of Clinical Oncology. 2015;33(14):1543.

Adoptive Cellular Therapy Clinical Trials in Gynecologic Malignancy

	Trial Number	Category	Target	Pretreatment Conditioning	Immunomodulators
Ovarian Cancer					
	03412526	TIL	broad	Fludarabine, Total body radiation (2 Gy)	IL-2
	03158935	TIL	broad	Cyclophosphamide, Fludarabine	IL-2 Pembrolizumab
	00101257	PBL - CD4 NY-ESO-1 reactive	NY-ESO-1	Cyclophosphamide	–
	03318900	PBL - CD8 tetramer	PRAME	Cyclophosphamide	IL-2, Anti-CD137 (utomilumab)
	03585764	CAR	Folate receptor	Cyclophosphamide, Fludarabine	–
	03017131	TCR - CD8	NY-ESO-1	Cyclophosphamide	IL-2, Decitabine
	02096614	TCR - CD8	MAGE-A4	Cyclophosphamide, Fludarabine	–
	03691376	TCR - CD8 TCR - CD4	NY-ESO-1	Melphalan	IL-2, Decitabine, Hematopoietic stem cells (HSC)
Cervical Cancer					
	03108495	TIL	broad	Cyclophosphamide, Fludarabine	IL-2
	02111850	TCR - CD4	MAGE-A3	Cyclophosphamide, Fludarabine	IL-2
	02379520	PBL – HPV-16/18 E6, E7 reactive	HPV-16, 18	Cyclophosphamide, Fludarabine	Nivolumab
Solid Tumors – including Ovary					
	01174121	TIL	broad	Cyclophosphamide, Fludarabine	IL-2, Pembrolizumab
	02876510	PBL - CD8 tetramer	8 targets 12 HLA	Cyclophosphamide	IL-2, Atezolizumab
	03054298	CAR	Mesothelin	Cyclophosphamide, Fludarabine	IL-2
	02713984	CAR	HER2	Cyclophosphamide, Fludarabine	IL-2
	02830724	CAR	CD70	Cyclophosphamide, Fludarabine	IL-2
	02650986	TCR - CD8	NY-ESO-1	Cyclophosphamide	IL-2
	03132922	TCR - CD8	MAGE-A3	Cyclophosphamide, Fludarabine	IL-2
	03139370	TCR - CD4	MAGE-A3/A6	Cyclophosphamide, Fludarabine	IL-2
	03412877	TCR - neoantigens	Neoantigens	Cyclophosphamide, Fludarabine	IL-2
Solid Tumors – including Uterine					
	01174121	TIL	broad	Cyclophosphamide, Fludarabine	IL-2, Pembrolizumab
Solid Tumors – including Cervix					
	02111850	TCR - CD4	MAGE-A3	Cyclophosphamide, Fludarabine	IL-2

TIL: tumor infiltrating lymphocytes, PBL: peripheral blood lymphocytes, CAR: chimeric antigen receptor, TCR: T cell receptor, IL-2: interleukin-2. Reference: https://clinicaltrials.gov, Accessed Oct 1 2019.

CONCLUSIONS

- According to current clinical evidence, **PARP inhibitors have made a remarkable progress in treatment of OC depending on the identification of disease with HRD** (e.g., BRCAm).

- **As for EC, given the identification of hormone-dependent histological type and POLE/MSI molecular subtypes**, the activity of PI3K/AKT/mTOR, PD-1, and hormone receptor-targeted therapies **might be promising** in treatment of patients with EC.

- Some studies suggesting higher benefit in MSI-H and POLE mutated tumors, others reporting efficacy regardless of molecular profile, especially when ICIs are combined with oral TKIs with antiangiogenic properties.

- Since CC is mostly associated with persistent infection of virus, **immune targeted therapies** (anti-PD-1/PD-L1 agents) **show promise**.

DEPARTMENT OF RADIATION ONCOLOGY

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THANK YOU

(UNITS OF TATA MEMORIAL CENTRE)