Managing Recurrence

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Recurrent Ovarian Cancer

Ovarian Cancer Research Fund Alliance

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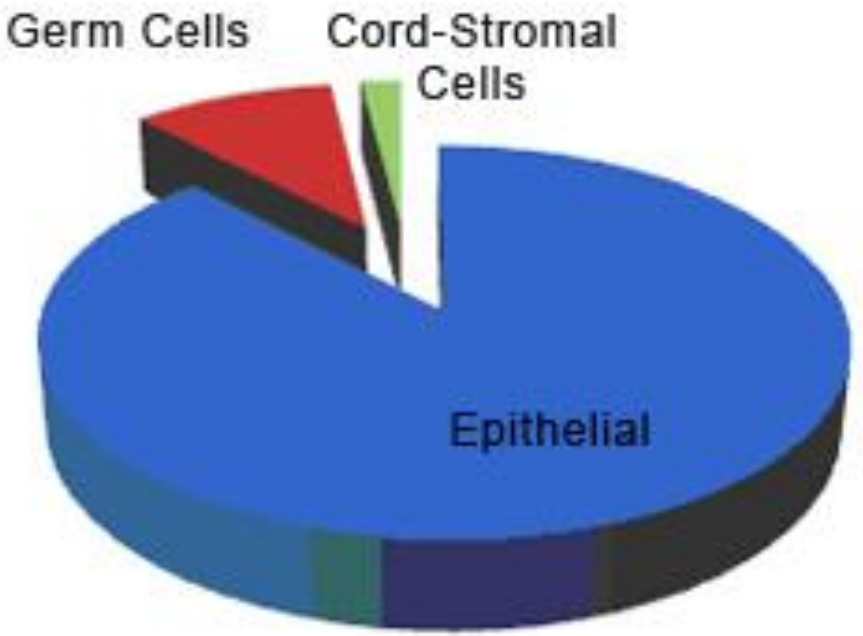
  University of New Mexico Comprehensive Cancer Center

Outline

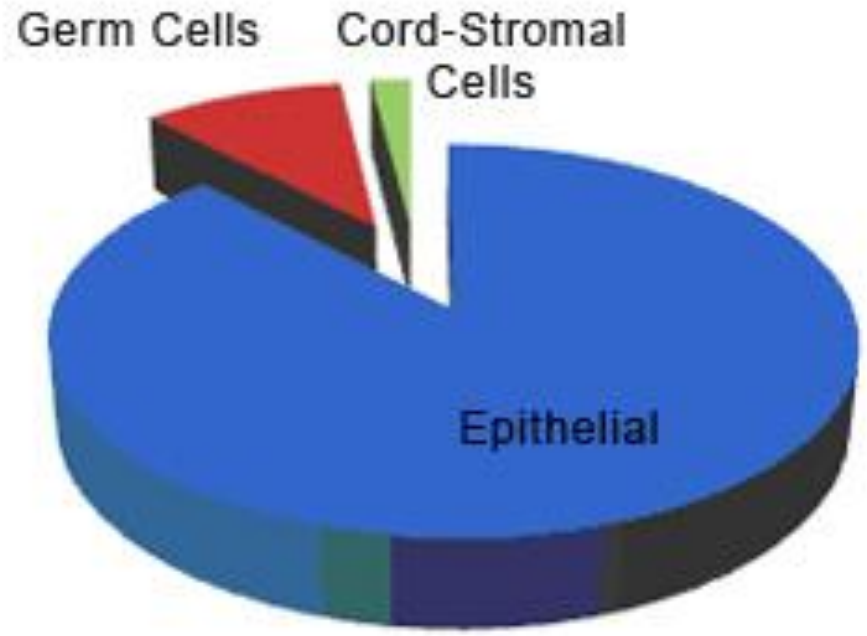
1. What are the chances that ovarian cancer will return after initial treatment?
2. What symptoms might suggest recurrent disease?
3. How is a recurrence diagnosed or confirmed?
4. What treatment options are available and what factors affect decisions about which to choose? **update on PARP-inhibitors and immune therapy**
5. Are there benefits to enrolling in a clinical trial?

Ovarian cancer subtypes

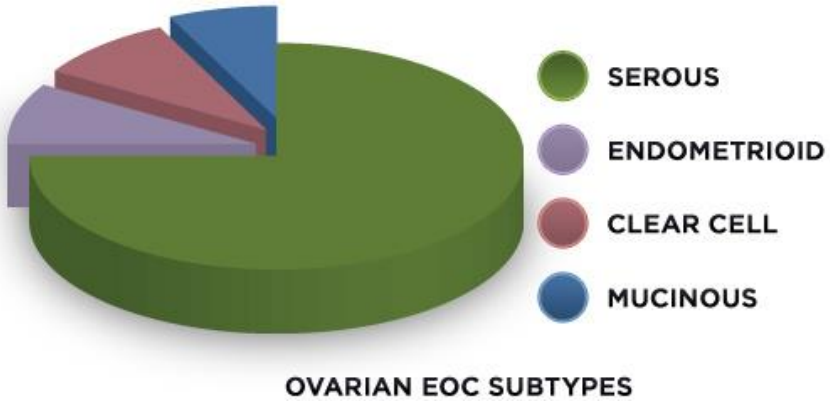


- Most ovarian cancers arise from the lining of the ovary –the epithelial layer
- Cancers arising from germ cells (eggs) or stromal cells are less common
- In this presentation, I will focus on epithelial cancers (ovarian, tubal, peritoneal)

Ovarian cancer subtypes



- Accumulating data indicates that serous ovarian cancers may actually develop in the fallopian tubes and then spread to the ovary.



Initial treatment: *curative intent*

Primary treatment:

- Debulking or cytoreductive surgery
- Chemotherapy
  - Neo-adjuvant chemotherapy (chemotherapy before surgery)
  - Primary adjuvant chemotherapy (chemotherapy after surgery)

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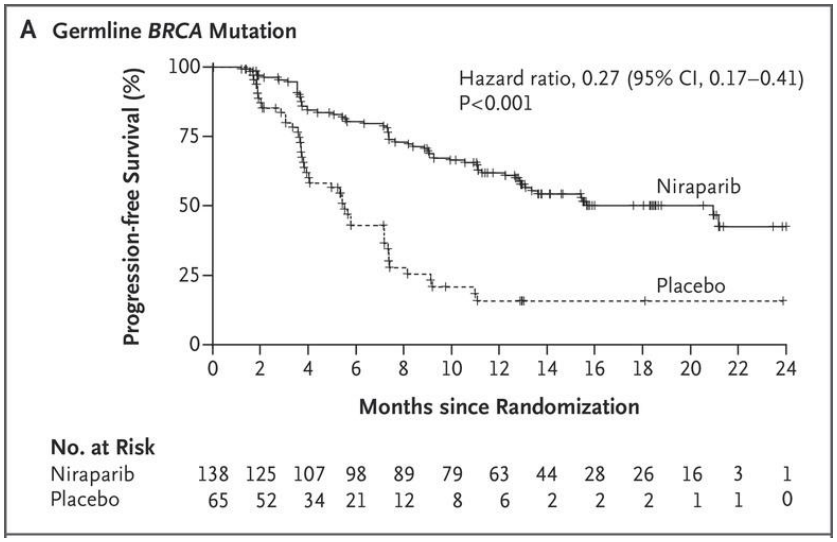
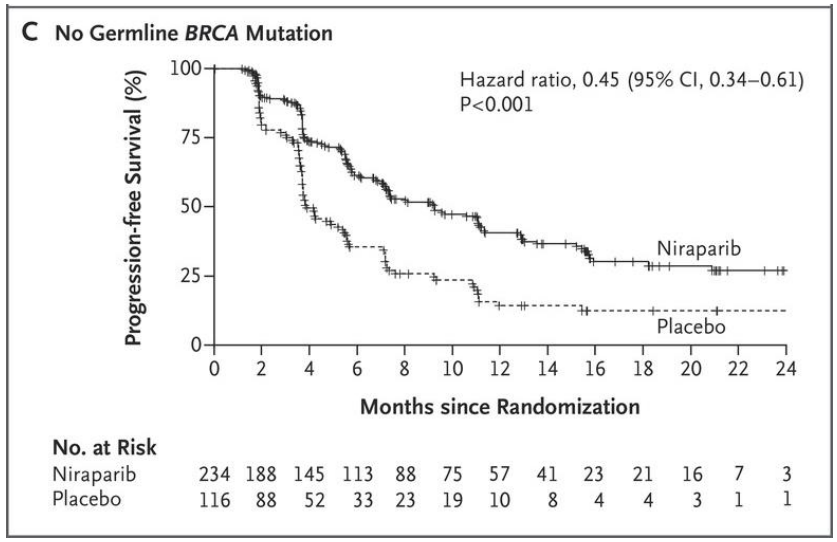
[Maintenance therapy: ongoing chemotherapy to reduce the risk of recurrence]

PARP-inhibitor maintenance therapy





N Engl J Med. 2016 Dec 1;375(22):2154-2164. Epub 2016 Oct 7.

- Improved progression-free survival in women with and without germline BRCA mutations
- Improved “PFS2” – survival in response to second-line chemotherapy

Initial treatment: *curative intent*

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- Debulking or cytoreductive surgery
- Chemotherapy
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  - Primary adjuvant chemotherapy (chemotherapy after surgery)

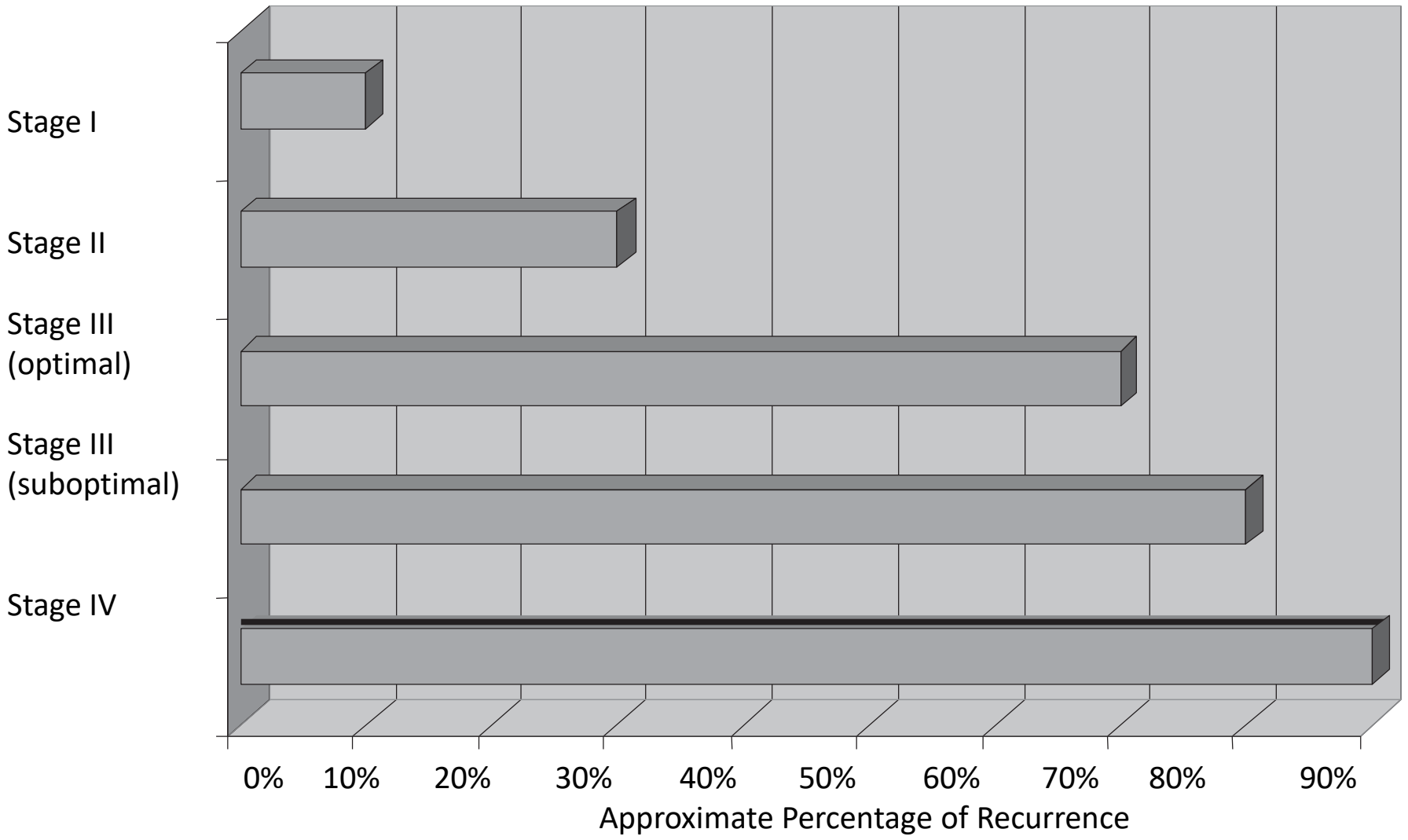
[Maintenance therapy: ongoing chemotherapy to reduce the risk of recurrence]

Cancer surveillance:

- 3-month intervals for two years
- 4-month intervals for the third year
- 6-month intervals for up to 10 years

What are the chances that ovarian cancer will return after initial treatment?

Ovarian cancer recurrence

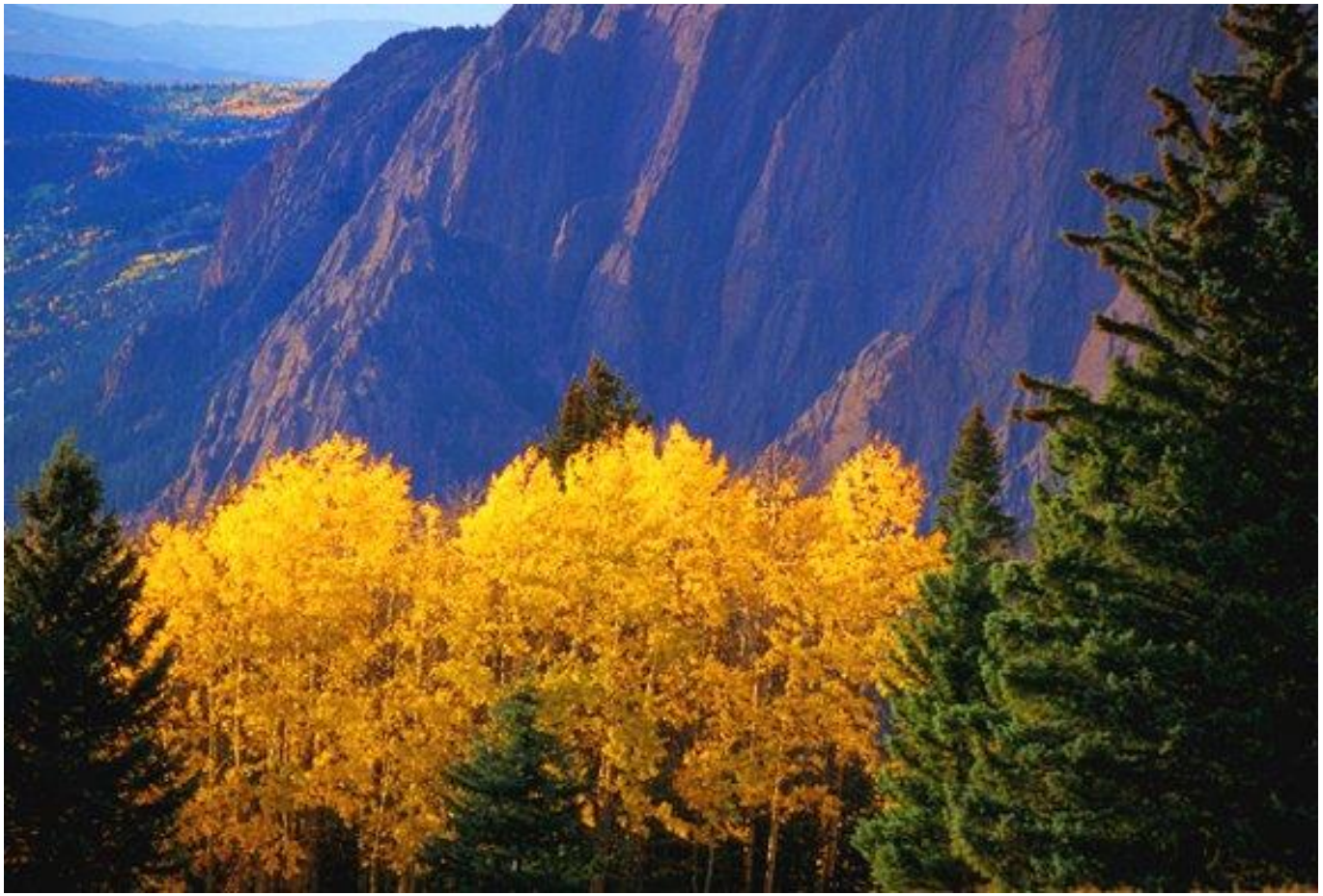


What symptoms might suggest recurrent disease?

Symptoms associated with ovarian cancer recurrence

- Bloating, abdominal fullness, increased girth, indigestion
- Pelvic pain
- Change in bowel or bladder habits
- Early satiety
- Vaginal discharge or bleeding
- Pain with intercourse
- Lymphedema / leg swelling
- Shortness of breath
- Nausea, vomiting

*Any new or persistent symptoms should be reported to your oncologist



How is a recurrence diagnosed or confirmed?

Physical exam

- Physical exam
  - Evaluation of lymph nodes
  - Chest exam for pleural fluid
  - Abdominal exam for masses, fullness, fluid accumulation, pain
  - Pelvic exam for masses or nodularity
  - Extremities for swelling, tenderness, range of motion

- 35% who presented with symptoms had a normal physical exam

CA125

- 61% of women are diagnosed with recurrence based on an elevated CA125 level
  - Rises in CA125 may precede symptomatic relapse by a median of 4.5 months (range 0.5-29.5 months)
  - Doubling of CA125 has a sensitivity of 86% and a specificity of 91% for detecting progression.
  - A second confirmatory value reduces the false-negative rate to <2%.
  - Even a rise within the normal range is associated with a high risk of relapse.

Imaging

- CT or MRI scan can be used to evaluate for recurrence
  - Imaging is indicated in response to new symptoms or a rise in CA125
  - Sensitivity ranges from 40-93%
  - It may be difficult to detect peritoneal or serosal disease
- PET sensitivity of 88-90%
- Directed biopsy may be performed to confirm recurrence

What treatment options are available and what factors affect decisions about which to choose?

Treatment goals for recurrent disease

- Recurrent ovarian cancer is unlikely to be cured with currently available chemotherapeutics, radiation or surgery.

Goal of treatment in the setting of recurrent disease is to prolong disease-free and overall survival and to palliate symptoms

- Options include surgery, chemotherapy, targeted therapeutics, immune therapy, hormones, radiation, observation

Surgery

- Secondary (or tertiary) debulking surgery
  - Rationale is based on benefit seen with primary debulking
  - Studies of secondary surgery are limited by patient selection

Generally, surgery is reserved for women with:

- Platinum-sensitive disease
- Limited sites of recurrence
- Long treatment-free intervals (>24 mos)
- Absence of ascites
- Good performance status

- As with primary surgery, the best outcomes are seen in patients who can be optimally debulked

- Minimally invasive options (robotic or laparoscopic surgery) may reduce morbidity for eligible women

Chemotherapy

- Most patients do respond to second-line chemotherapy
- Response to second-line chemotherapy is predicted by:
  - Tumor type, size, and number of disease sites
  - Duration of response to previous platinum-based regimen, platinum-free interval and treatment-free interval (TFI)
    - TFI <12 mos: Response Rate 24-35%
    - TFI >12 mos: Response Rate 52-62%

Platinum sensitivity

Most women with ovarian cancer receive a platinum drug (carboplatin, cisplatin, oxaloplatin) as part of their primary chemotherapy regimen.

The time to recurrence after platinum treatment determines "platinum sensitivity"

	Response to platinum	Likely secondary treatment	Examples
Platinum sensitive	>6 months without recurrence	Another platinum-based regimen	Carboplatin alone or in combination with another drug
Platinum resistant	< 6 months until recurrence	A non-platinum drug	Doxil, Taxol, Gemzar, Topotecan
Platinum refractory	Failure to achieve remission	A non-platinum drug	Doxil, Taxol, Gemzar, Topotecan

Clinical trials in platinum-sensitive patients with recurrent ovarian cancer

Study (number of patients)	Agents	Response Rate (%)	Median progression free survival (months)	Median overall survival (months)
ICON 4 (802)	Carboplatin Carboplatin + Taxol	54% 66%	9 12*	24 29*
AGO (366)	Carboplatin Carboplatin + Gemcitabine	31% 47%	5.8 8.6*	17.3 18
CALYPSO (976)	Carboplatin + Taxol Carboplatin + Doxil		9.4 11.3*	31.5
OCEANS (484)	Carboplatin + Gemcitabine Carbo+Gem+Avastin	57% 79%	8.4 12.4*	35.2 33.3

Response rates to second-line treatment are high among women with platinum – sensitive disease.

Coleman R, et al. Nat Rev Clin Oncol 5 Feb 2013

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Platinum-sensitive patients are usually treated with another platinum-containing regimen – often carboplatin in combination with a second drug.

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Most-frequently used agents in platinum-resistant disease

Agent	Response Rate (%)	Median progression free survival (months)	Median overall survival (months)	Side effects	
Doxil	10-20%	3-4	10-12	Hand-foot syndrome, mucositis	
Topotecan	12-18%	3-4	10-12	Myelosuppression	
Taxotere	22%	3.5	12.7	Myelosuppression	
Gemzar	15%	4-5	11.8-12.7	Myelosuppression	
Etoposide	6-27%	4-5	10-11	Myelosuppression	
Taxol	10-30%	4-6	13	Myelosuppression, neuropthy	
Avastin	21%	4.7	17	Hypertension, blood clots	

Because of the more limited prognosis associated with platinum-resistant disease, reducing toxicity becomes a primary goal, and typically single agent protocols are used.

Coleman R, et al. Nat Rev Clin Oncol 5 Feb 2013

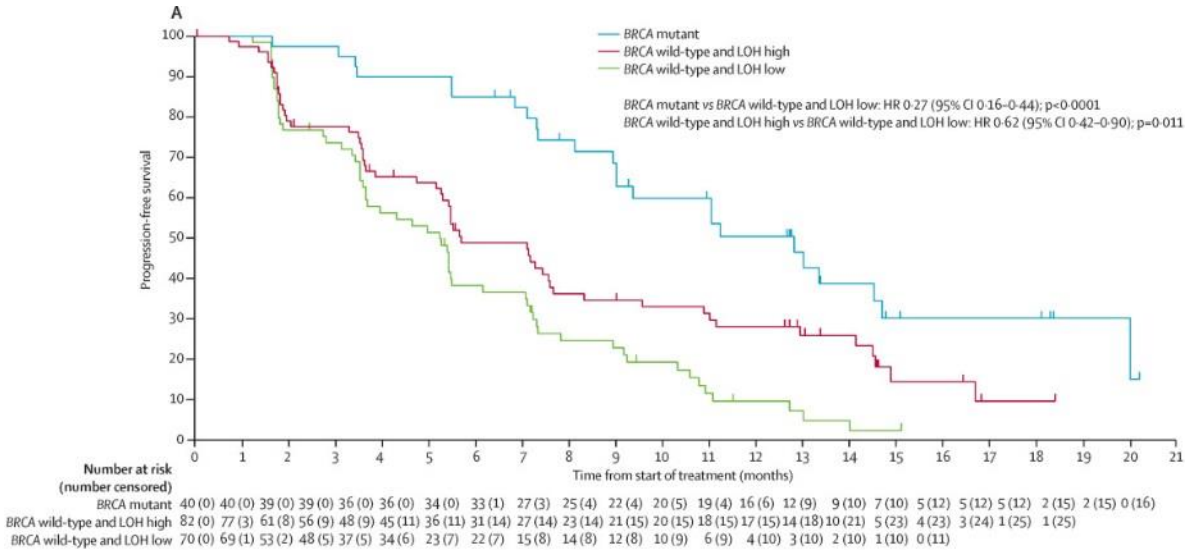
Targeted agents

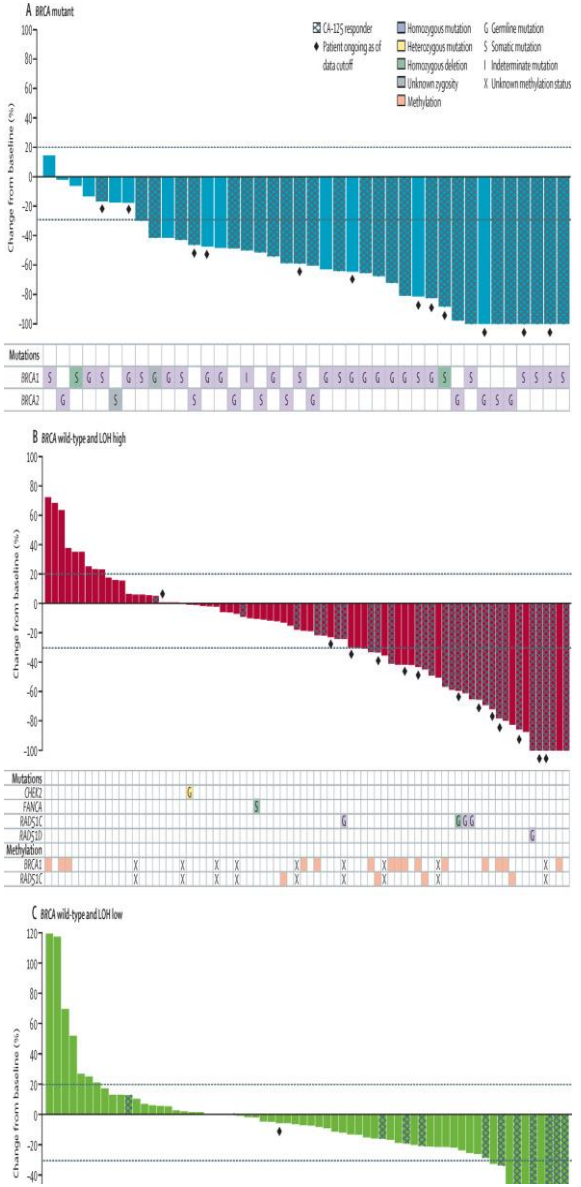
- Advantages:
  - Different (often more limited) toxicity profile
  - May be active in chemotherapy resistant disease
  - Better understood mechanism of action

- Bevacizumab (Avastin):
  - blocks blood vessel formation in tumors
  - Also has immune modulatory effects
  - response rate greater than 20% (6 mo PFS 28-40%)

- PARP-inhibitors:
  - block single-stranded DNA repair
  - best response is among women with BRCA gene mutations
  - response rates as high as 40% in recurrent EOC

PARP-inhibitors for recurrent ovarian cancer





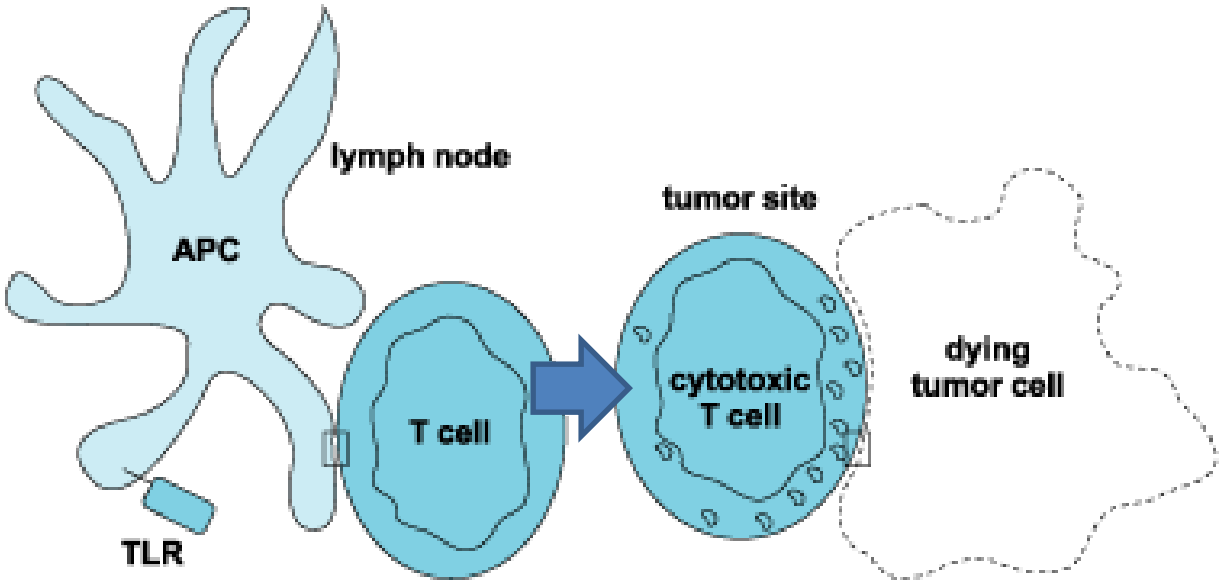
Immune therapy

- Advantages:
  - Toxicity profile is different than cytotoxic chemotherapy
  - Adaptive effects and potential for long-term benefit

- Currently available primarily through clinical trials

- Examples:
  - Cancer vaccines
  - T cell therapy
  - Immune checkpoint blockade antibodies

A model for the induction of an anti-tumor T cell response



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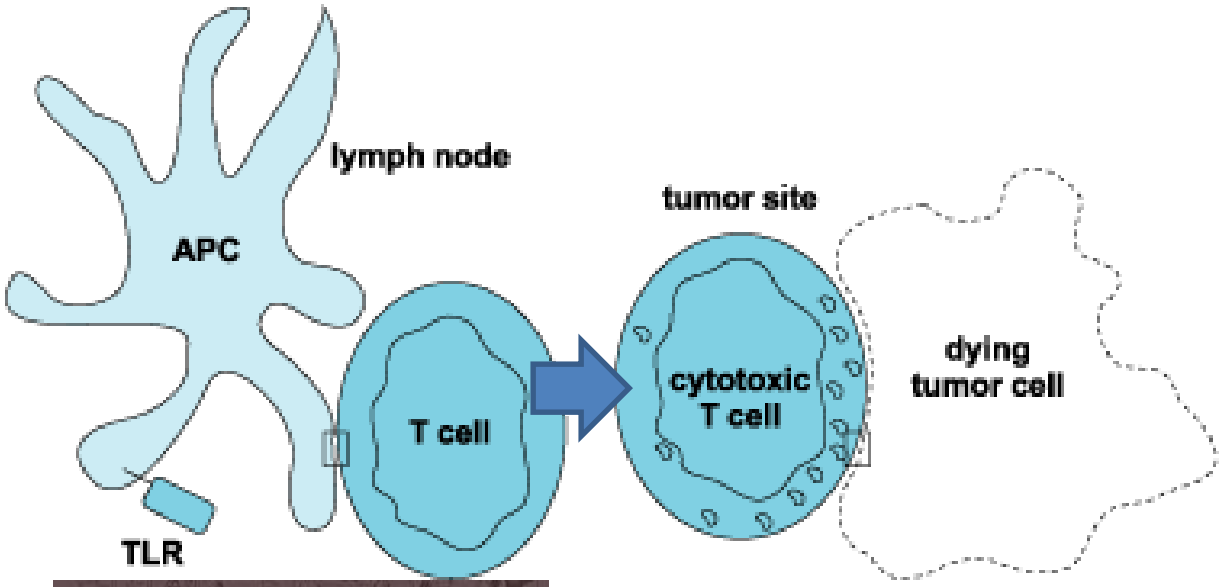

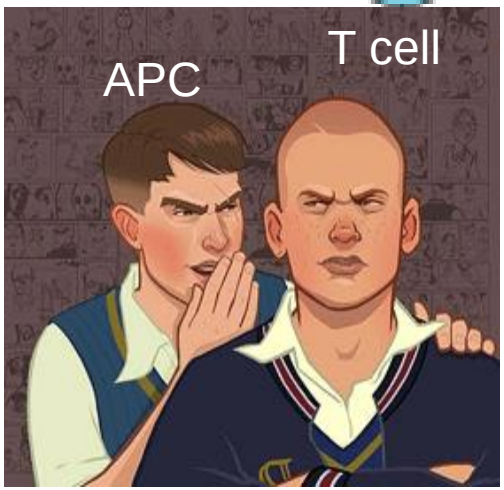

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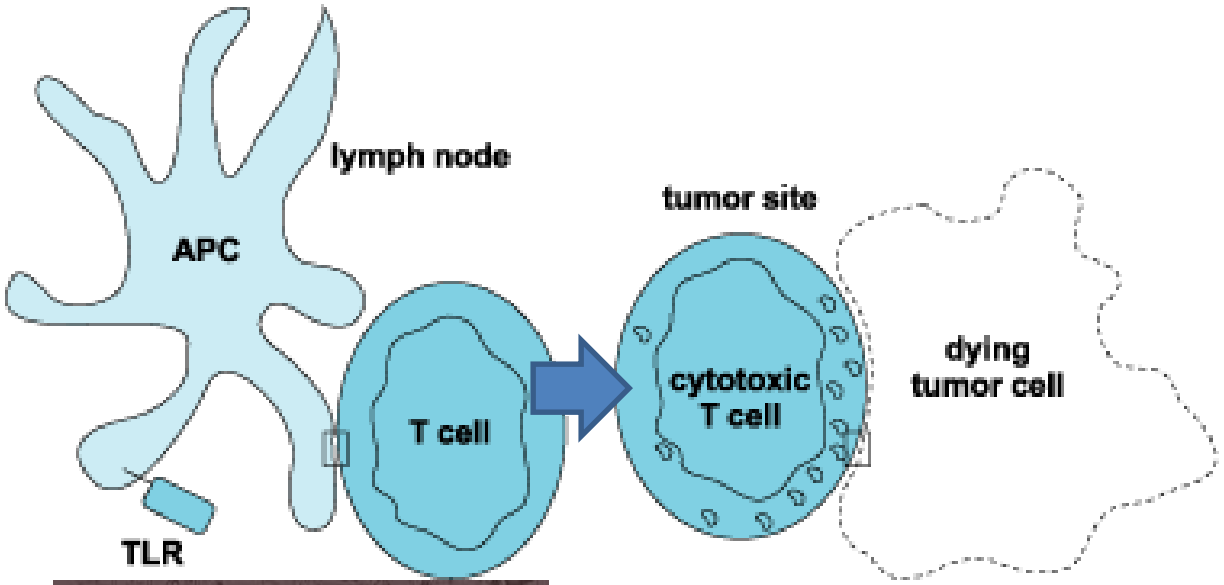
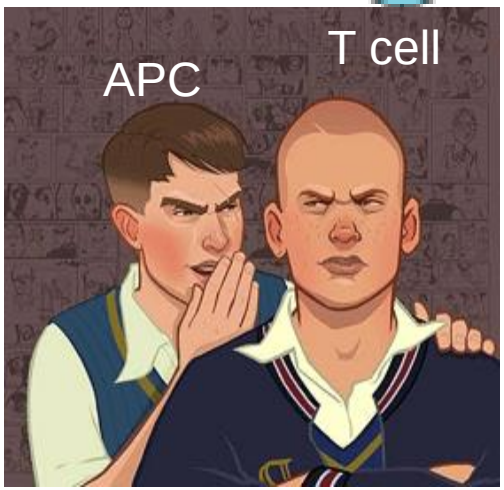
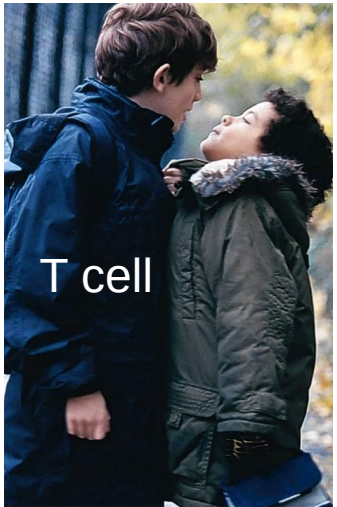
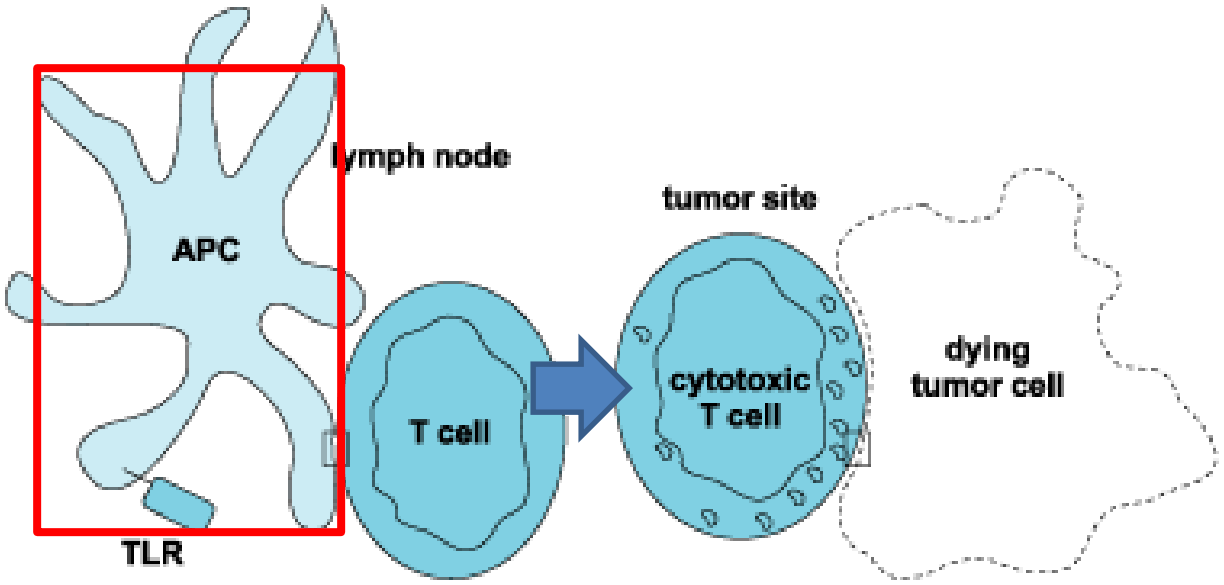
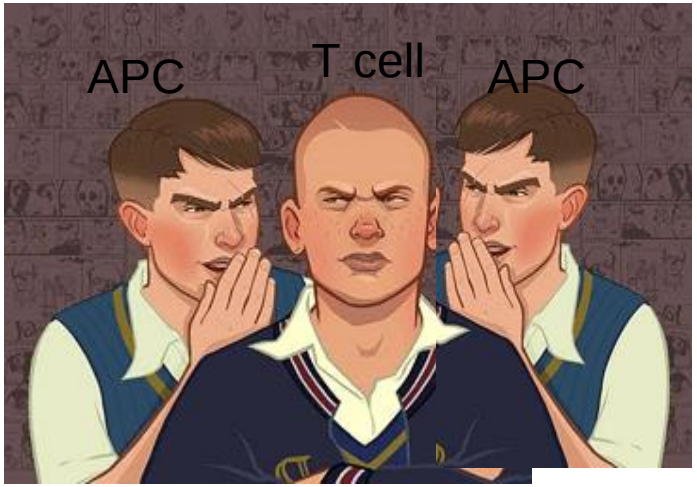






The goal of immune therapy is to amplify the anti-tumor T cell response





Example: Tumor vaccines

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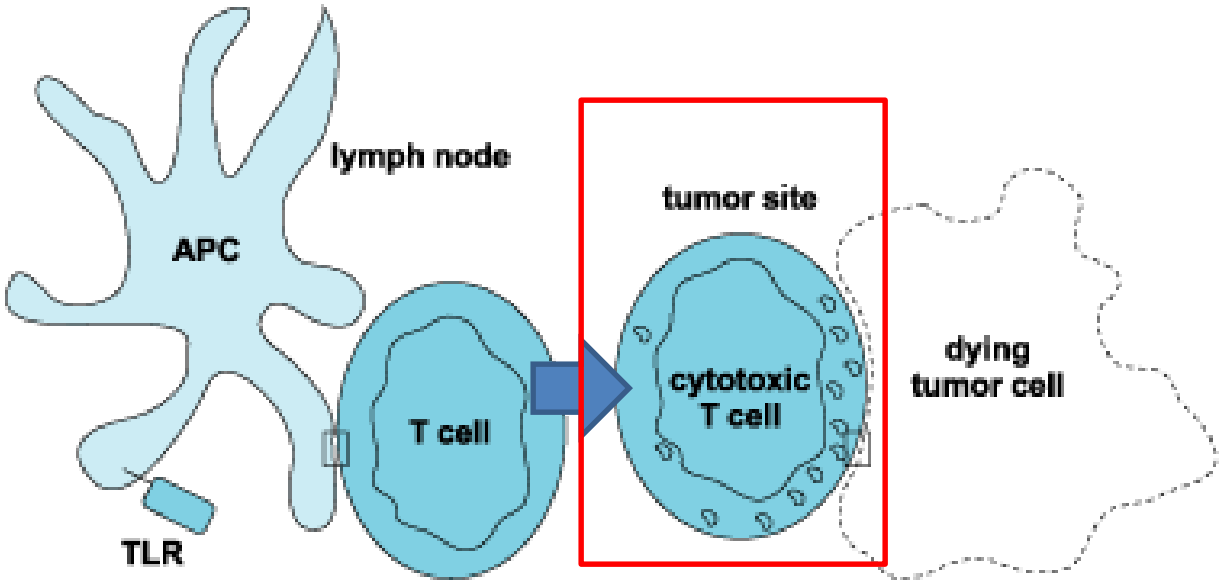
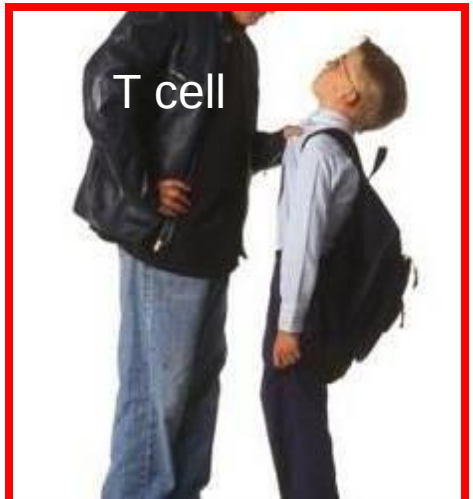


Examples:
Adoptive T cell therapy
CAR T cell therapy (Chimeric Antigen Receptor)
Immune checkpoint antibodies



Goals of immune therapy

- Elicit or boost an adaptive anti-tumor immune response
- Induce immune memory for protection against cancer recurrence
- Current interest in combining immune therapy with tumor-directed therapy or chemotherapy to optimize outcomes

Hormone therapy

- Advantages:
  - Lower toxicity
  - Oral administration
- Tamoxifen:
  - Response rate of 17-20% among women with recurrent ovarian cancer
- Fulvestrant (selective estrogen receptor modulator)
  - Maintained disease stability in 50-64% of patients, 30% at 90 days
- Aromatase Inhibitors
  - Modest objective RR of 8-15%, stability in 19-24%
  - Evidence for efficacy in low grade serous cancers

Radiotherapy

- Whole abdominal radiation therapy is associated with significant toxicity and has limited efficacy in the treatment of recurrent disease

- Localized radiation may be effective
  - Good for symptom control
  - Best for deposits in the pelvis, at the vaginal vault, on the abdominal wall.
  - Median remission of 4.8 months.

Observation -

When should treatment be initiated?

- Many oncologists believe that early diagnosis and treatment of recurrent disease improves outcomes for women with ovarian cancer
  - Better surgical outcomes
  - Smaller tumors are more susceptible to chemotherapeutics
  - Better symptom control

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Rustin GJ,et al, Lancet 2010

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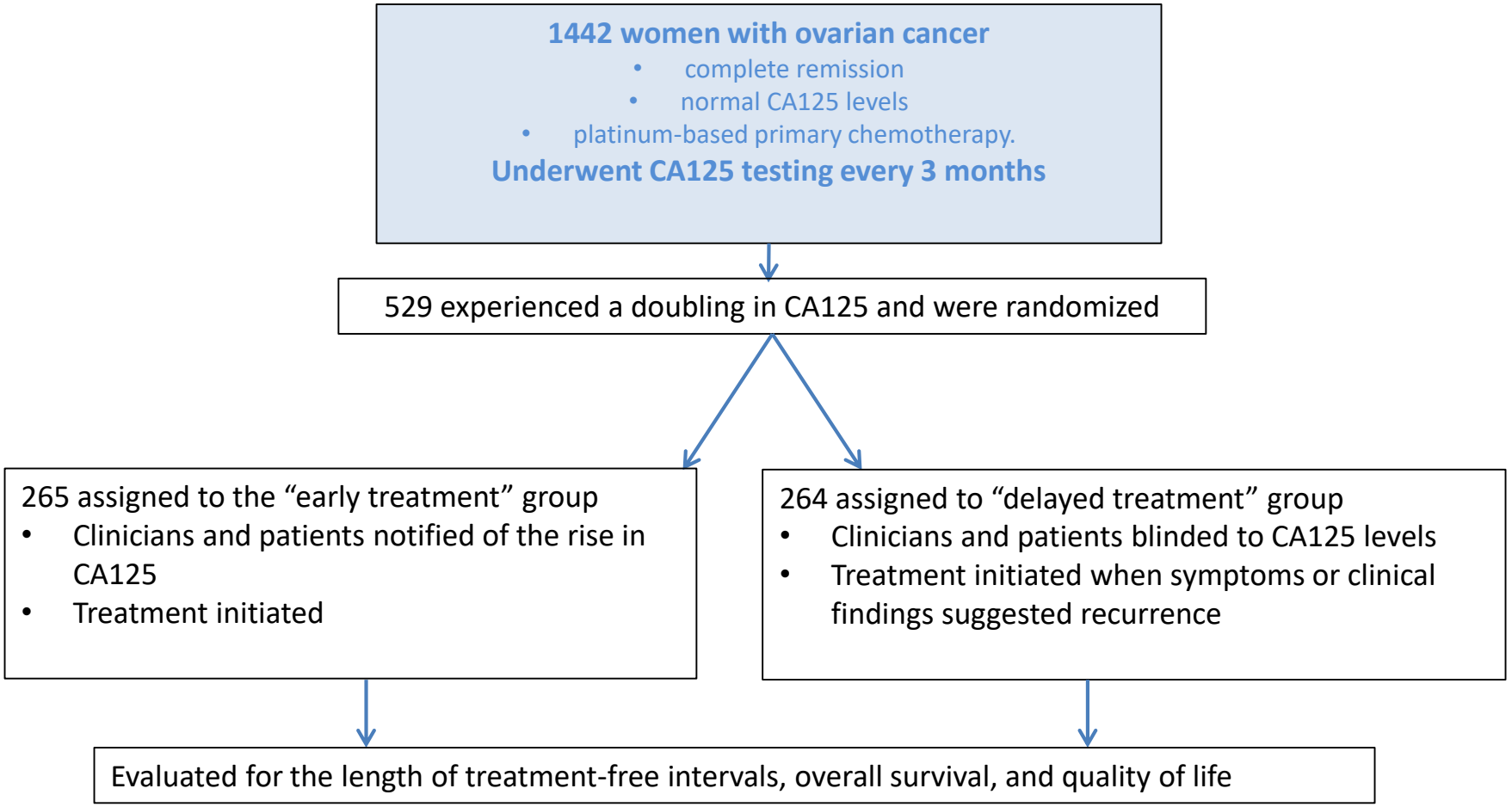

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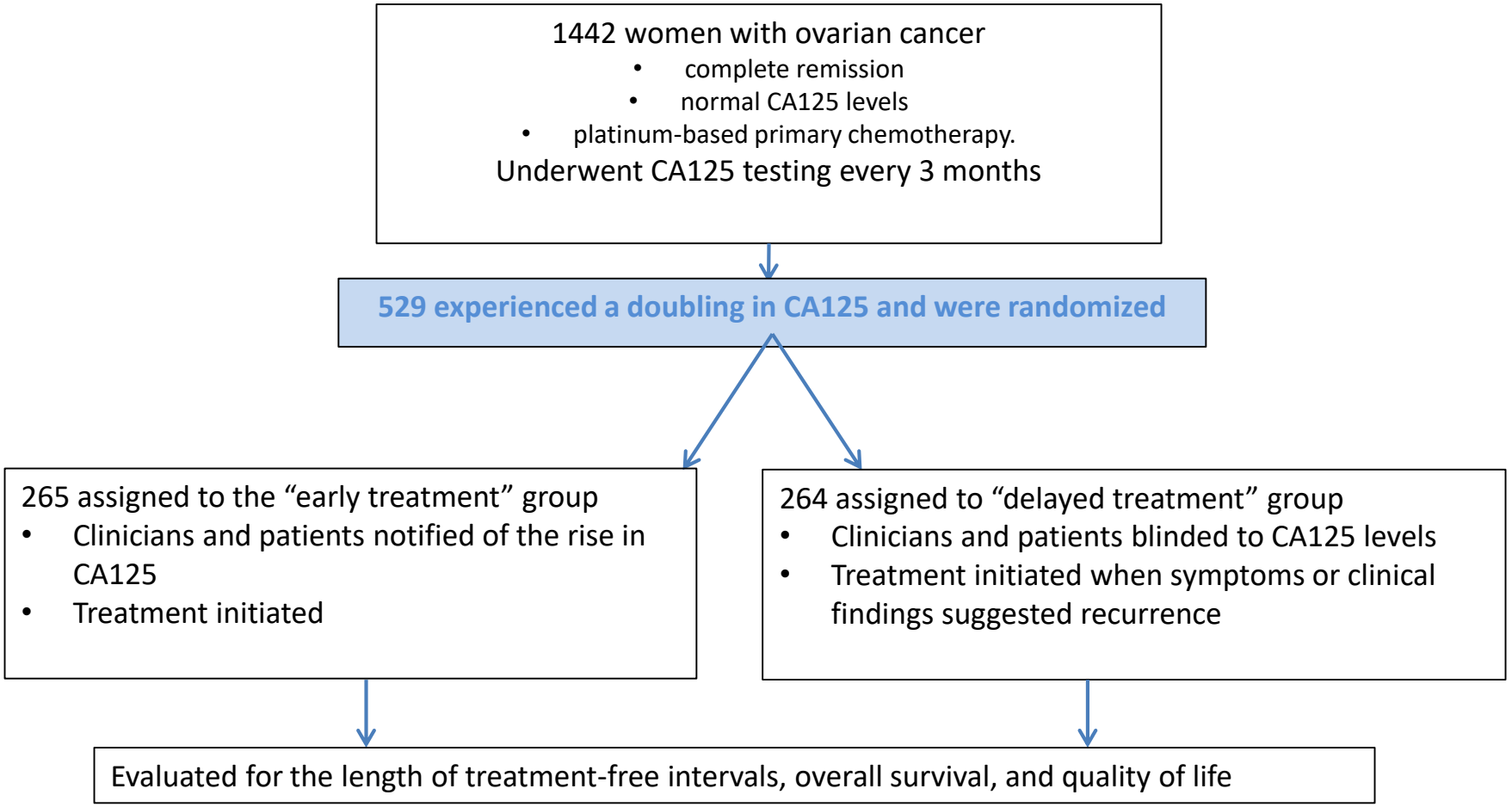

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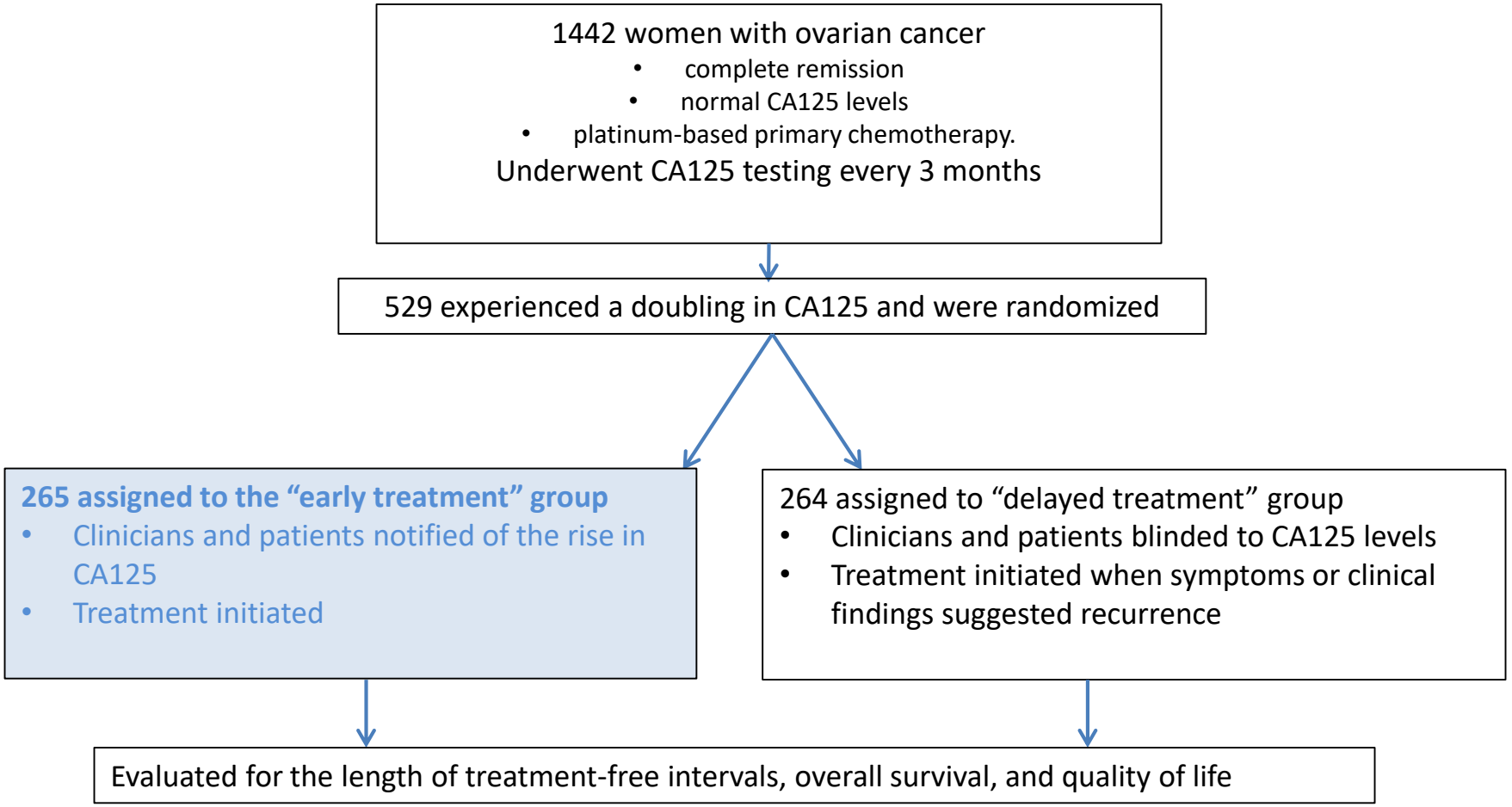

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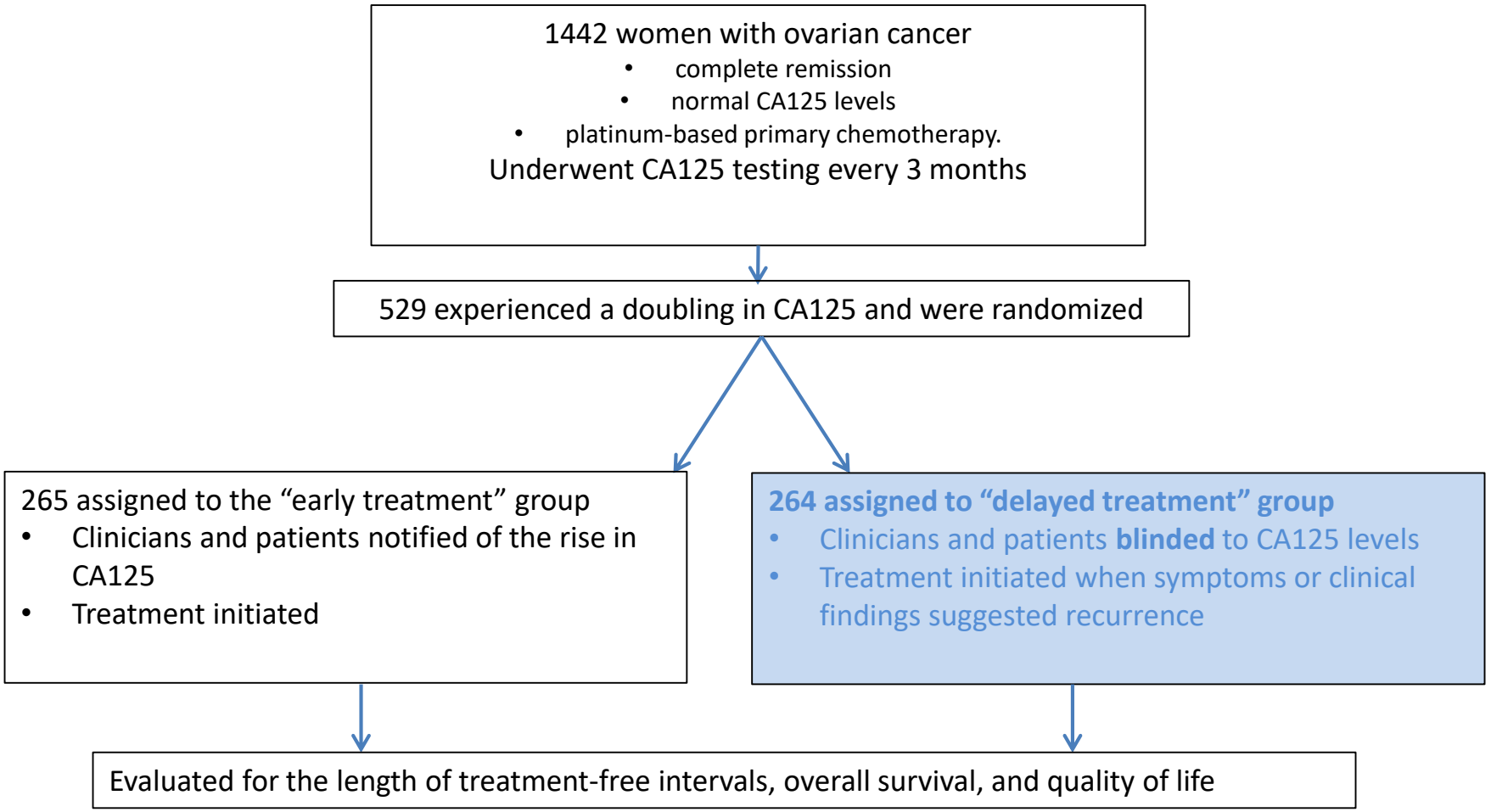

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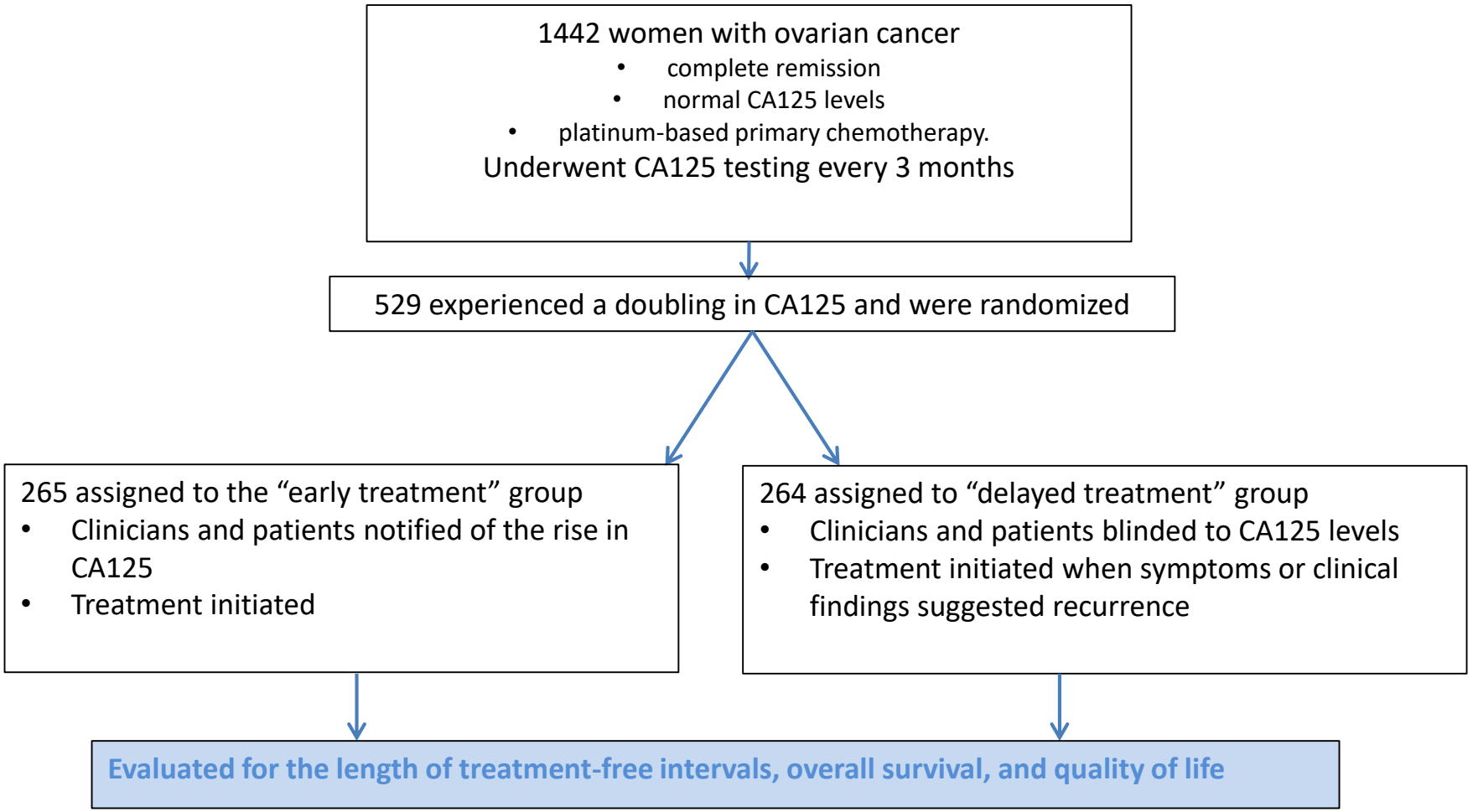

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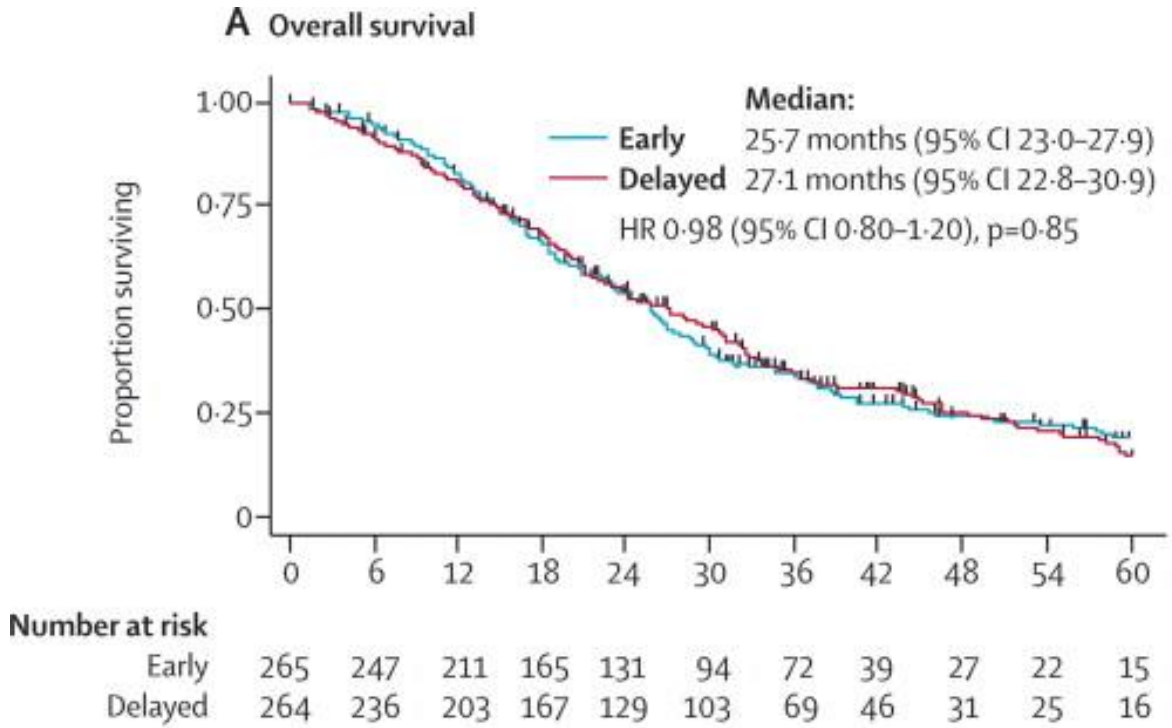
Results:



- No difference in overall survival
- Women in the early treatment group underwent more courses of chemotherapy
- Delayed treatment was associated with better quality of life scores.

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Are there benefits to enrolling in a clinical trial?

Standard health care vs. clinical trials

- Standard health care: interventions designed solely to enhance the well-being of the patient that have a reasonable expectation of success

- Research (Clinical trial): an activity designed to test a hypothesis, permit conclusions to be drawn, develop or contribute to generalizable knowledge

Clinical Trials

- Oversight and protection of subjects
  - Institutional Review Boards (IRB)
    - Protect the rights and welfare of research subjects
    - Include members of the community
  - Informed consent
    - Benefits, risks and discomforts
    - Alternatives to participation
    - *Must be voluntary and un-coerced*

- Strategies to optimize results
  - Randomization
    - Process by which participants are assigned to treatment groups
    - Placebo control is optimal to evaluate new treatments
  - Blinding
    - Single-blind: treating physician knows but patient doesn't
    - Double-blind: neither the treating physician nor the patient knows

Goals of clinical trials

Phase I Trials:

- Safety and tolerability
- Uncontrolled, unblinded
- Not randomized

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Phase III Trials:

- Therapeutic ratio (and continued safety) (Drug x compared to drug y)
- Control is placebo or standard of care.
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Phase IV Trials: post-marketing surveillance (safety)

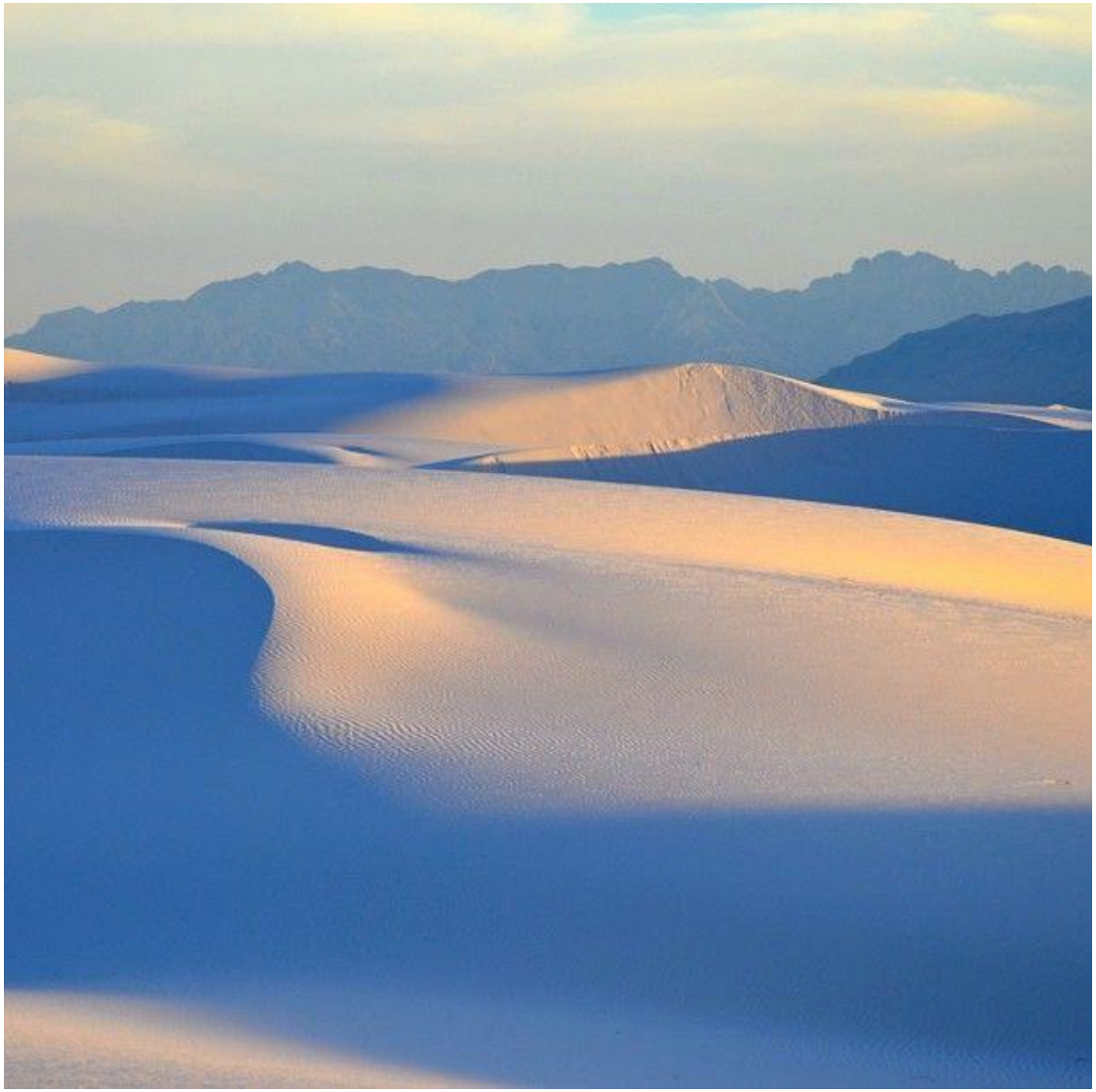
Benefits of clinical trials

	Advantages	Disadvantages
Phase I trials	Access to newest therapeutic agents	Dose escalation may mean that a lower dose is given to early participants
	Usually not randomized or blinded	Primary outcome is safety and tolerability
	Smaller studies, results may be available sooner	May or may not be given with known active agents
Phase III trials	Protocol already tested in prior phase I/II with evidence of efficacy	Often randomized Often blinded
	Often given with active agents; control arm is usually standard treatment	Large scale studies – may take years to learn results

- Additional benefits:
  - Oversight by a team of physicians, nurses, study personnel – both locally and often at a national level
  - Expanded options for treatment
  - Benefit to other women with ovarian cancer by advancing our understanding of treatment options and cancer biology

Questions to ask if you are considering enrolling in a clinical trial:

- What is the scientific rationale for conducting the trial?
- What are the objectives of the trial?
- In what phase is the trial? How many participants will there be?
- What are the eligibility requirements?
- What is the intervention, and what is its duration and schedule?
- What are the possible risks, side effects and benefits?
- What medical tests and follow-up tests will participants undergo? How often?
- What are the endpoints (measurable outcomes that indicate an intervention's effectiveness)?
- Who is sponsoring the trial?
- What is the contact information to inquire about the trial?



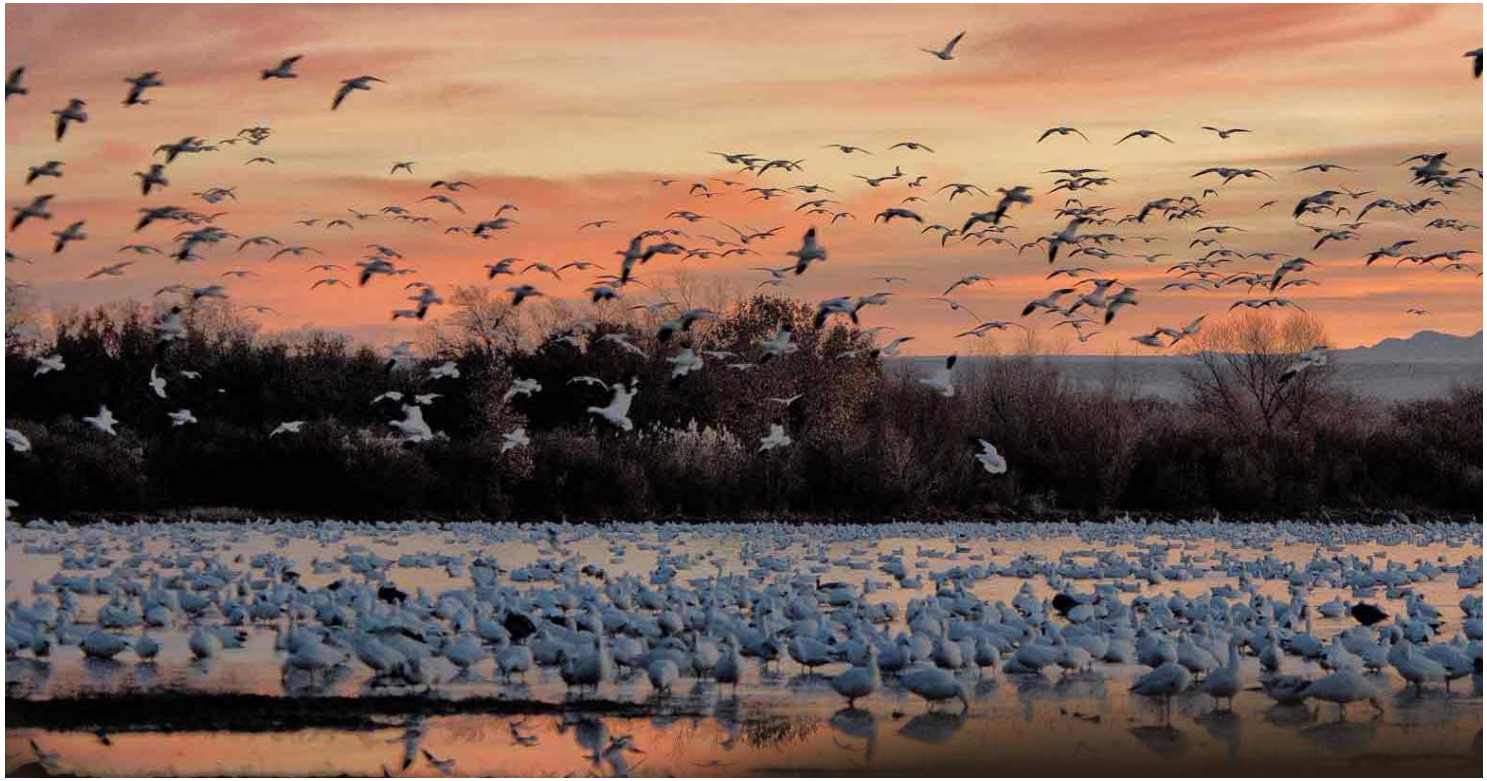
Summary

There are *many* options available to manage ovarian cancer recurrence

- Several factors affect choice of treatment including the presence of symptoms, response to prior treatment, availability of a clinical trial, patient preference

- Goal of treatment is to optimize quality of life and to prolong remission

- For more information about available clinical trials: **www.ocrf.org/clinicaltrials**



Thank you – questions?