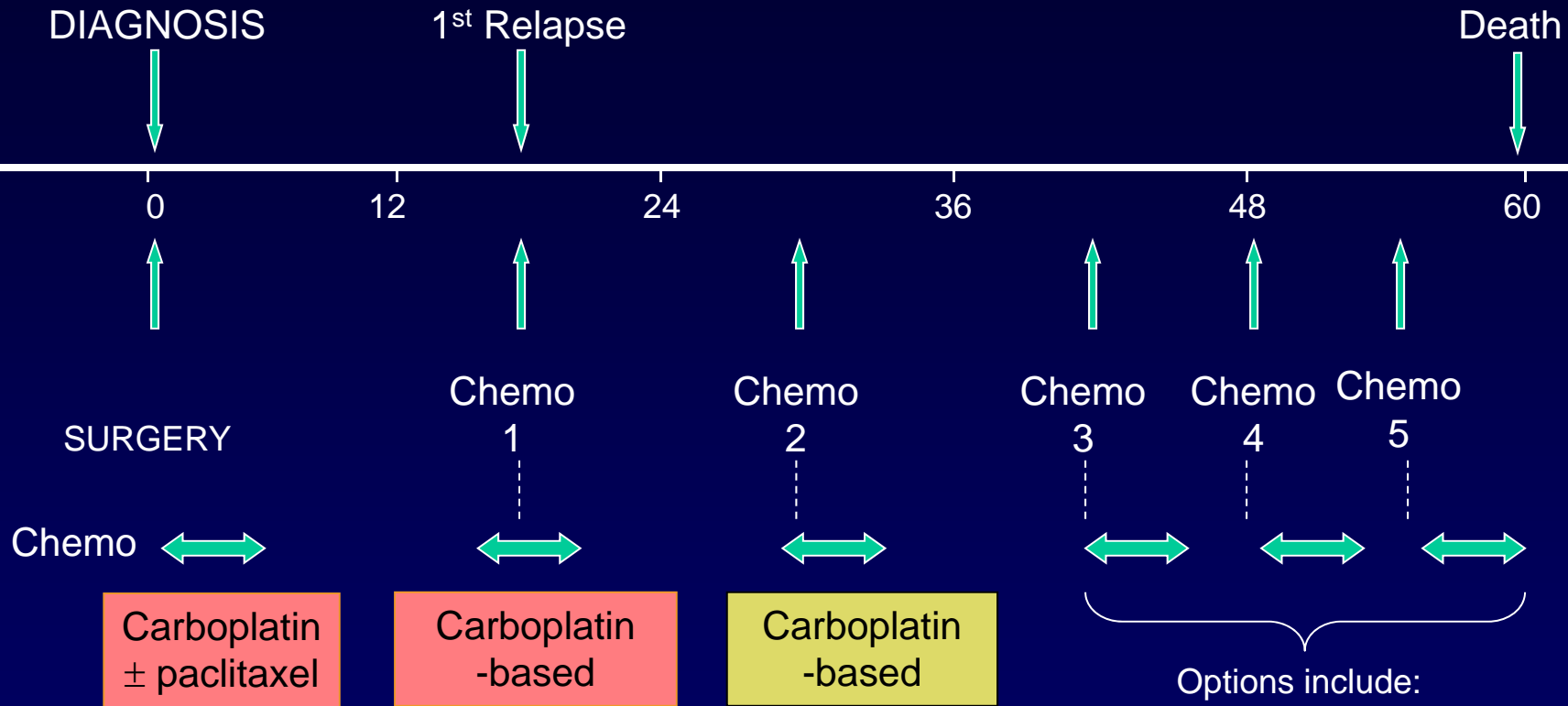


Targeted Therapy For Ovarian Cancer – Beyond Angiogenesis

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OVARIAN CANCER—The Typical Patient



Thus: For typical patient, duration of survival after 1st relapse exceeds initial time to relapse.

Options include:
Repeat paclitaxel (weekly), doxorubicin, topotecan, etoposide, potentially phase I trial

New Treatment Options in Ovarian Cancer

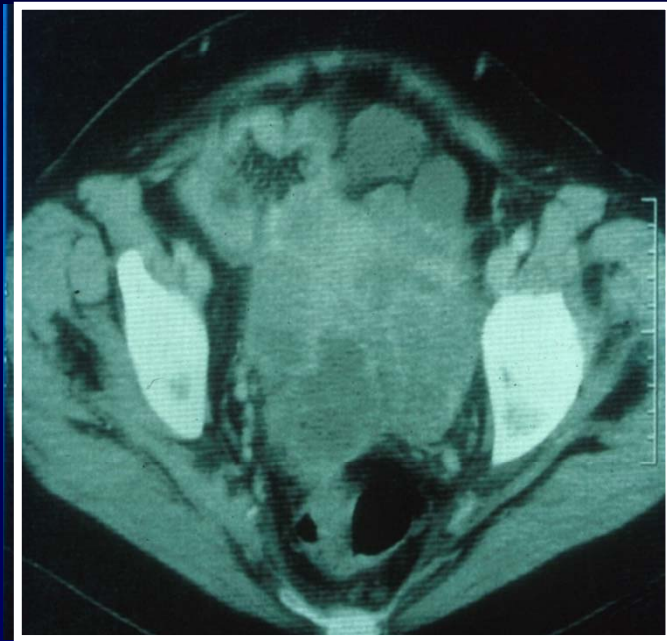
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- “Molecular targeted” agents
 - Monoclonal antibodies
 - Small molecules
- Novel cytotoxics

Major issues:

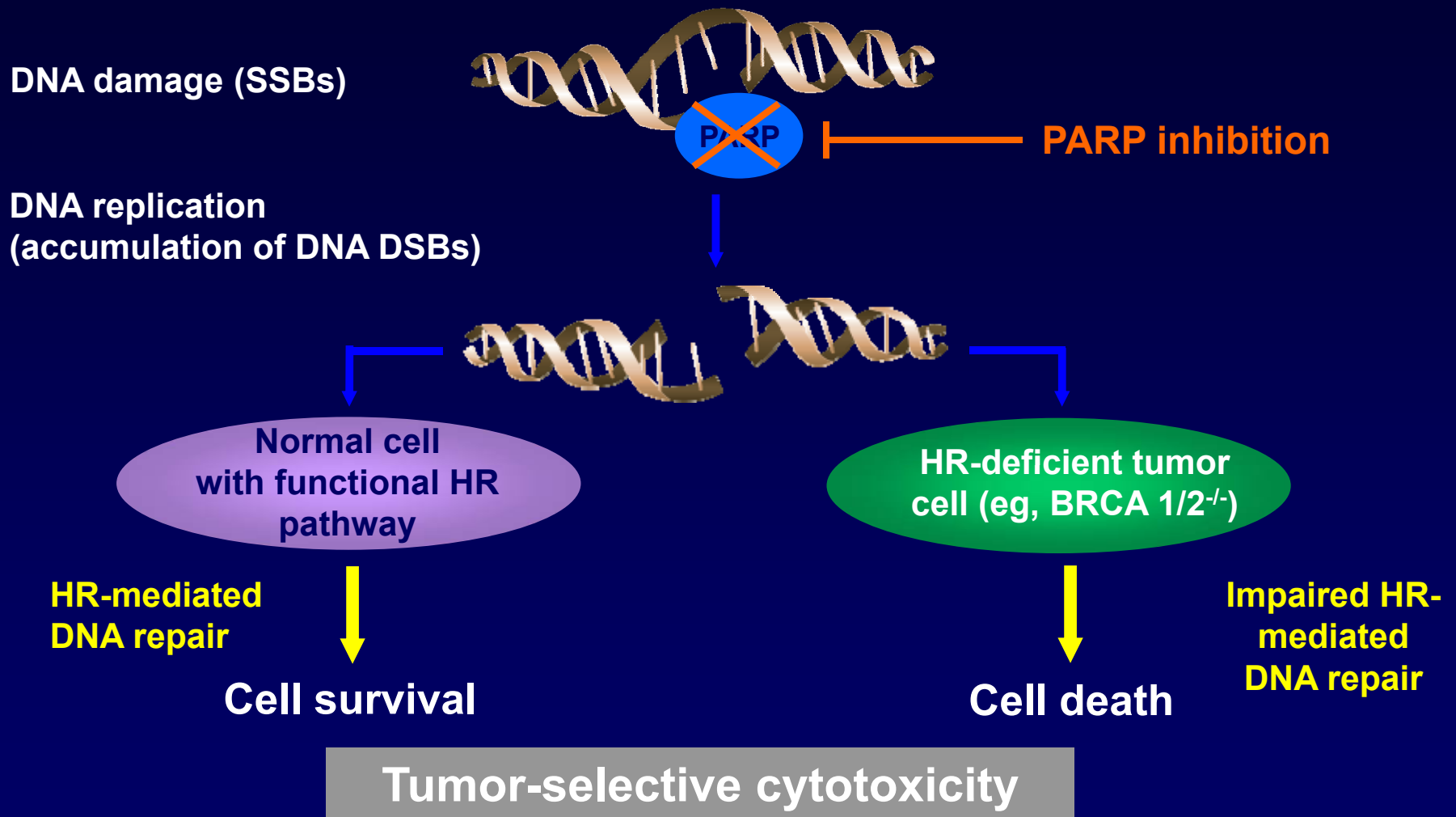
- Can we select those patients who will benefit most?
- Is a single agent, or combination approach preferable?

Selected Rational Targets In Ovarian Cancer



- VEGF receptor and ligand
 - PI3K/AKT pathway
 - Alpha folate receptor
-
- And the dysfunctional BRCA gene!

PARP Inhibition and Tumor-Selective Synthetic Lethality



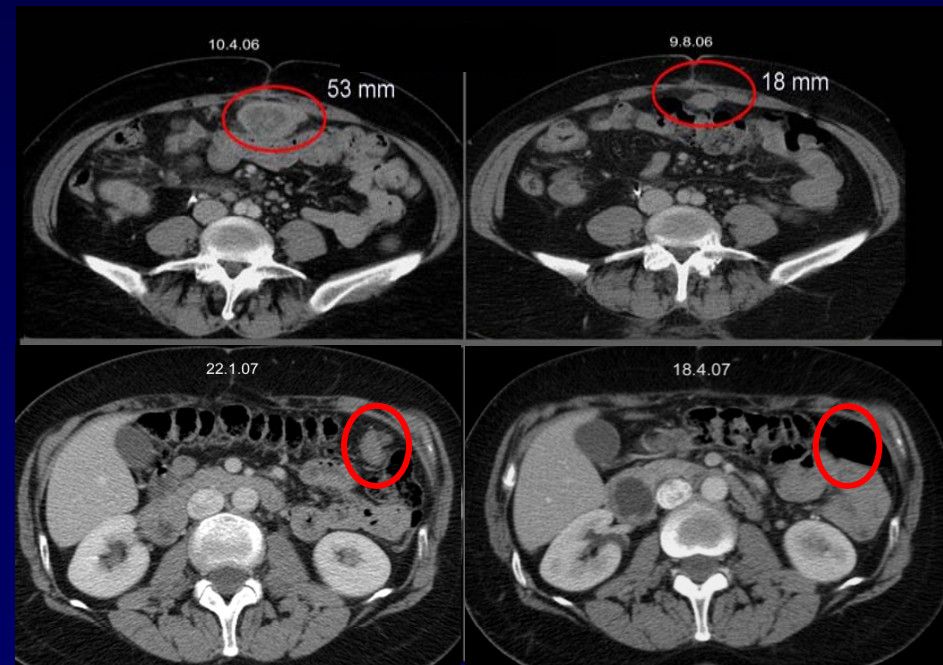
DSB, double-strand break; HR, homologous recombination; SSB, single-strand break

Farmer H, et al. *Nature*. 2005;434(7035):917-921. Bryant HE, et al. *Nature*. 2005;434(7035):913-917. McCabe N, et al. *Cancer Res*. 2006;66(16):8109-8115.

Olaparib

A Novel, Orally Active PARP Inhibitor

- A phase I trial identified olaparib (AZD2281; KU-0059436) 400 mg bid as the maximum tolerated dose¹ with a 50% (23/46 patients) combined response rate (RECIST and CA125) in BRCA-mutated ovarian cancer²
- Most common toxicities: CTCAE grade 1 and 2 nausea and fatigue
- Significant PARP inhibition and tumor response at olaparib doses 100-400 mg bid



1. Fong PC, et al. *N Engl J Med.* 2009;361(2):123-134.
2. Fong PC, et al. *J Clin Oncol.* 2010. In press.

Response to Olaparib by Platinum-Free Interval

	Total	Platinum Sensitive	Platinum Resistant	Platinum Refractory
Number of evaluable patients	50	13	24	13
Responders by RECIST	14 (28%)	6 (46%)	8 (33%)	0 (0%)
Responders by GCIG CA125	17 (34%)	8 (62%)	7 (29%)	2 (15%)
Responders by either RECIST or GCIG criteria	20 (40%)	8 (62%)	10 (42%)	2 (15%)
SD (>4 cycles)	3 (6%)	1 (7%)	1 (4%)	1 (7%)
Median duration of response in weeks	28 w	28 w	28 w	NE

- All patients received olaparib 200 mg bd
- Includes 4 patients who received <1 cycle (4 week)

International Phase II Trial of Olaparib in Associated Ovarian Cancer

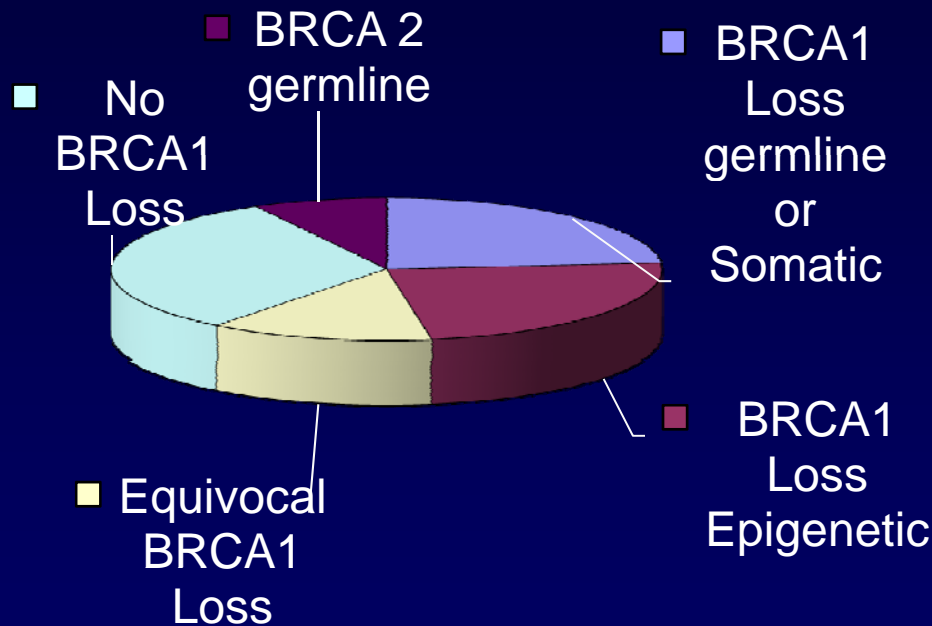
57 patients (BRCA 1 39; BRCA 2 18) received either 400 mg bd or 100 mg bd in 2 sequential cohorts – (med. 3 prior CT)

33 pts at 400 mg bd	RECIST response	11 (33%)
	Clinical benefit (incl. CA125 response)	22 (66%)
24 pts at 100 mg bd	RECIST response	3 (13%)
	Clinical benefit (incl. CA125 response)	10 (42%)

Conclusion:

- Level of efficacy confirmed, med. response duration 9.5 months
- Favorable toxicity profile confirmed
- 400 mg bd appears to be more active than 100 mg bd
- **Recently completed randomized trial (vs doxorubicin) will compare 400 mg bd + 200 mg bd doses**

Potential of PARP Inhibitor (Single Agent) In Sporadic Ovarian Cancer



What proportion of ovarian cancer patients will have BRCA1/2 dysfunction, either due to mutation of either gene or for other reasons, eg, methylation of this or related genes?

- Approx 15% of sporadic ovarian cancers have mutation of either gene; in serous histological subtypes, proportion is 18%.
- Approx 15% to 20% more cases have BRCA dysfunction, through methylation, etc.
- Approx 10% have FANCF methylation

At least half the cases of serous ovarian cancer could benefit from targeted single agent treatment
- How can these be identified?

Patient Selection for Single-Agent Treatment With Olaparib

Predictive biomarker:

- Immunohistochemistry, with BRCA 1/2 antibodies
- Functional (*ex vivo*) test for loss of HR (RAD 51 foci-formation)
- Molecular signature (gene array)

and/or: background of

- Repeated response to platinum-based chemo
- Prolonged survival (>5 years)
- Serous histology

Olaparib In Sporadic Cancer—An Anecdote

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Further Development of Olaparib—A Maintenance Trial

Patients with serous ovarian cancer, responding to second-line or third-line platinum-based chemo, with CR/PR (penultimate treatment-free interval >6 months)

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Olaparib 400 mg bd until disease progression

Placebo until disease progression

n = 250

Endpoint: PFS

- Recruitment now complete
- Results expected late 2010

- BRCA mutation not necessary

Key Issues for Future Developments of PARP Inhibitors

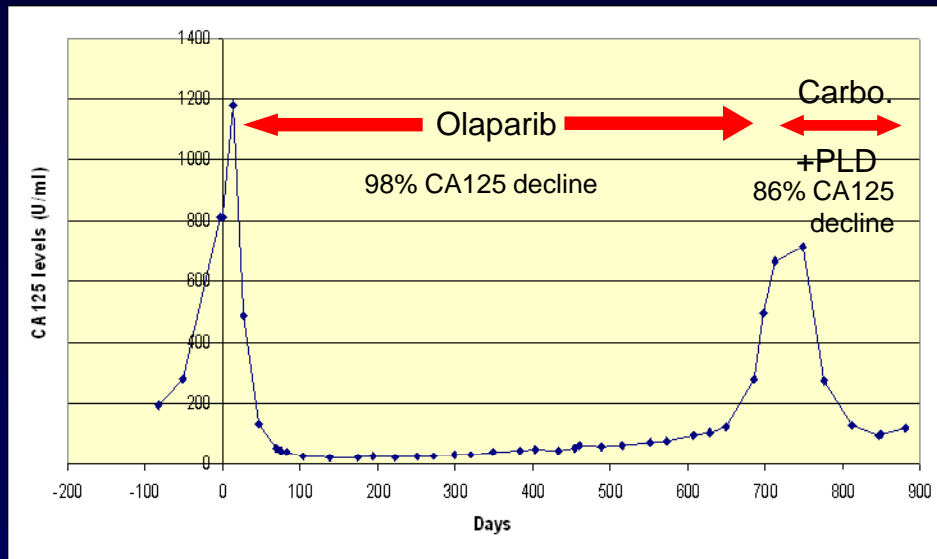
- Is a single-agent or combination approach preferable?
- Single-agent treatment utilises tumor selective synthetic lethality, with no issues of additional toxicity
- Combination with DNA-damaging chemotherapy, eg, temozolamide or platinum, reverses resistance in experimental models
- But: Clinically, myelotoxicity is usually enhanced by chemo/PARPi combination, and optimal duration of PARPi not yet defined
 - **Exception: Randomized trial in triple-negative breast cancer with BSI-201**
- Randomized trials in ovarian cancer (at least 4 now planned) will need careful interpretation

Key Issues for Future Developments of PARP Inhibitors in Ovarian Cancer

- What determines resistance to (single agent) PARP inhibitor treatment?
 - Recent data indicate return of BRCA function through intragenic deletion of mutation (in BRCA2) (Edwards et al. *Nature*. 2008)
 - Will this impact on response to further chemotherapy, particularly platinum or taxane?

Chemosensitivity Post Olaparib

Anecdote:



- In preliminary analysis of 26 olaparib-treated patients, response to subsequent carboplatin and/or paclitaxel-based treatment seen in significant proportion

- Initial prolonged response to olaparib, then radiologic and CA125 progression
- Subsequent response to carboplatin/pegylated liposomal doxorubicin

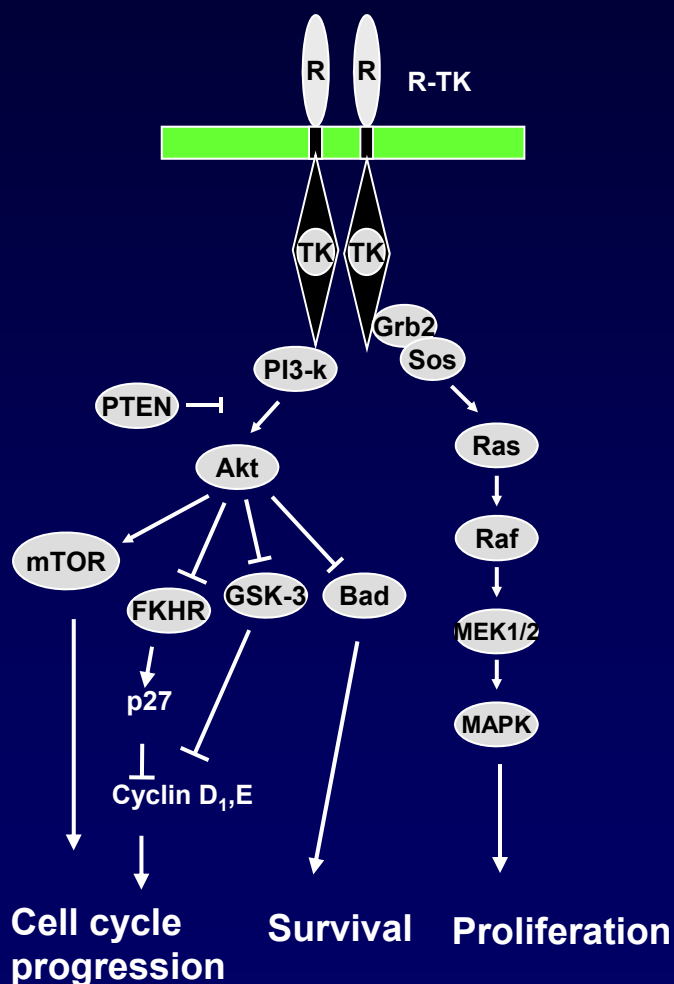
PLD, pegylated liposomal doxorubicin

PARP Inhibitors in Ovarian Cancer

Summary:

- Compelling clinical data with olaparib indicate efficacy in BRCA-related cancer
- Potential role of single-agent therapy in sporadic ovarian cancer (and TNBC) requires urgent assessment
- In this context, tests for “BRCAness” (HR loss) need rapid development
- Combination approach merits further study, but regimens require careful consideration of dose/ schedule of both chemo and PARPi, with appropriate patient selection
- 4 other PARP inhibitors in current or planned studies in ovarian cancer (mostly combination)
- **Tumor-selective synthetic lethality represents an important step forward in cancer treatment**

PI3 Kinase/Akt Pathway and Ovarian Cancer



- Key to normal cellular functions including glucose metabolism
- In cancer cells, it promotes growth factor-mediated cell survival and blocks apoptosis
- **PIK 3CA (gene encoding P110 α – key catalytic subunit) is amplified in 40% of ovarian cancer (Shayesteh et al, 1999) and mutations also present (<10% overall)**

PI3 Kinase/Akt Pathway and Ovarian Cancer

PI3K/AKT

- Plays an important role in drug resistance to both paclitaxel¹ and platinum² through negative effect on apoptosis
- Inhibitors can reverse resistance to both agents, particularly in models with increased pathway activity

What's in the clinic? Several agents, mostly phase I

- Range of small molecular weight inhibitors including new structures
- Occasional responses (mainly CA125) noted in ongoing phase I trials
- Combination studies planned or underway, and patient selection strategies under discussion
- PI3 KINASE
- PKB/AKT
- mTOR
- New TORC 1/2 inhibitor
- HSP90 inhibitors

Phase I Trial of an Oral PI3K Kinase Inhibitor: Clinical Activity in Ovarian Cancer

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Clinical Activity in Ovarian Cancer (Cont)

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Are There Other Novel Targets? One Possible: The Alpha Folate Receptor

Alpha folate receptor:

- Cell-membrane linked high affinity folate transporter
- Acts by receptor-mediated endocytosis
- Restricted expression in normal tissue (placenta, kidney, choroid plexus)
- **Overexpressed in various epithelial tumors, particular ovary**
- Potential to target new cytotoxics, eg, TS inhibitor, ONX 0801

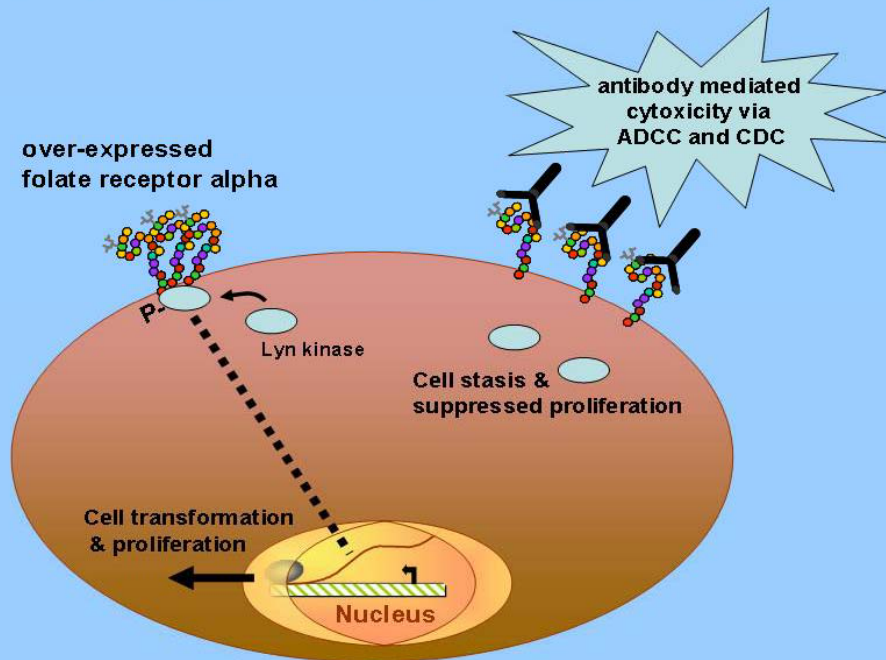
	% Tumors Overexpressing
Ovary	92%
Uterus	91%
Mesothelioma	70%
Kidney	50%
Stomach	38%
Lung	33%
Colon	22%
Choroid plexus	80% (epend)
Brain	80% (metastases)

α -FR overexpression in fresh clinical tumor material as measured by IHC¹⁻³

1. Garin-Chesa P, et al. *Am J Pathol.* 1993;142(2):557-567. 2. Weitman SD, et al. *Cancer Res.* 1992;52(23):6708-6711. 3. Bueno R, et al. *J Thorac Cardiovasc Surg.* 2001;121(2):225-233.

The Alpha Folate Receptor (FR) And Ovarian Cancer—A Therapeutic Antibody Approach

Farletuzumab: Bi-modal mechanism of action

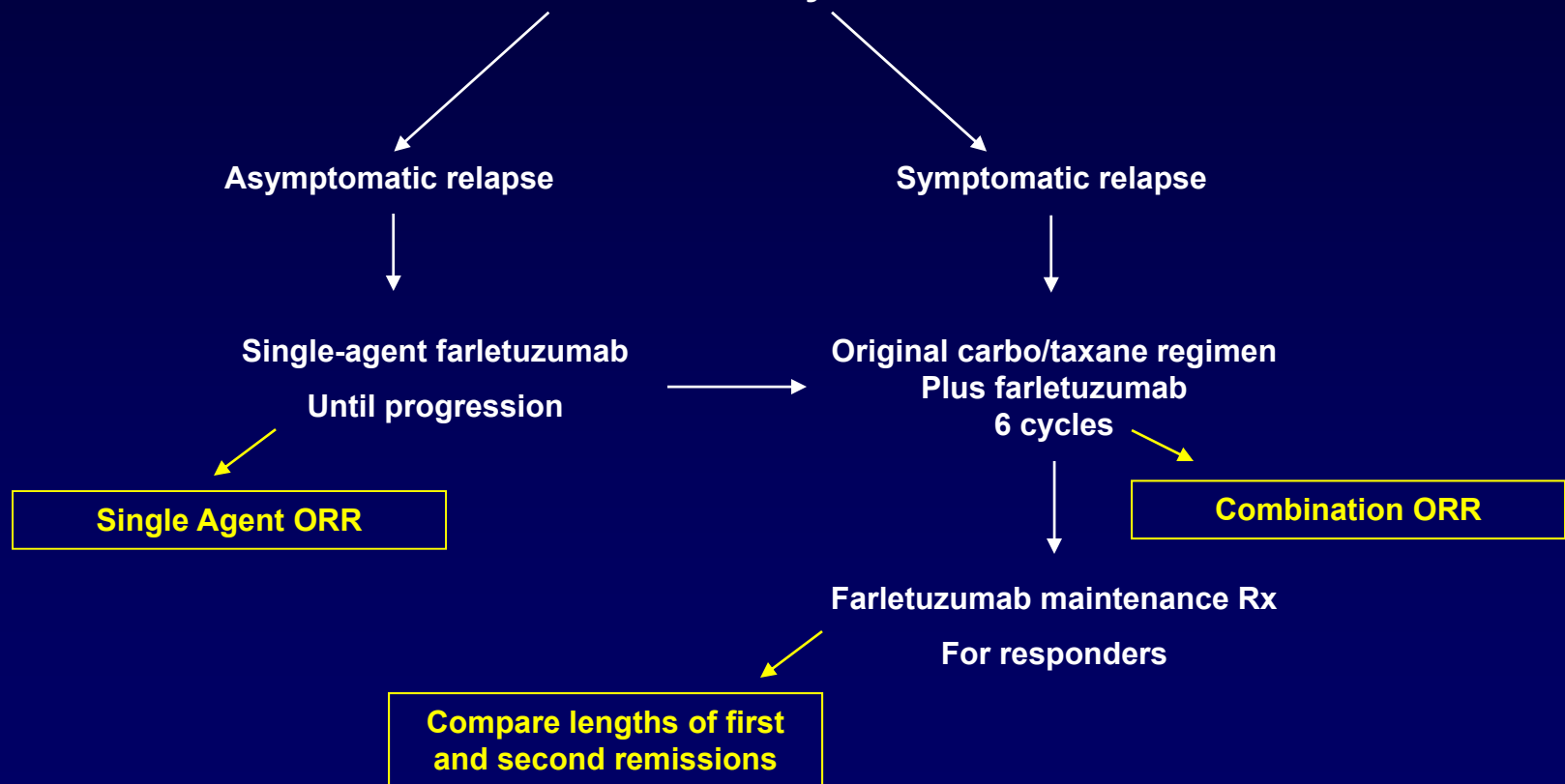


• Farletuzumab

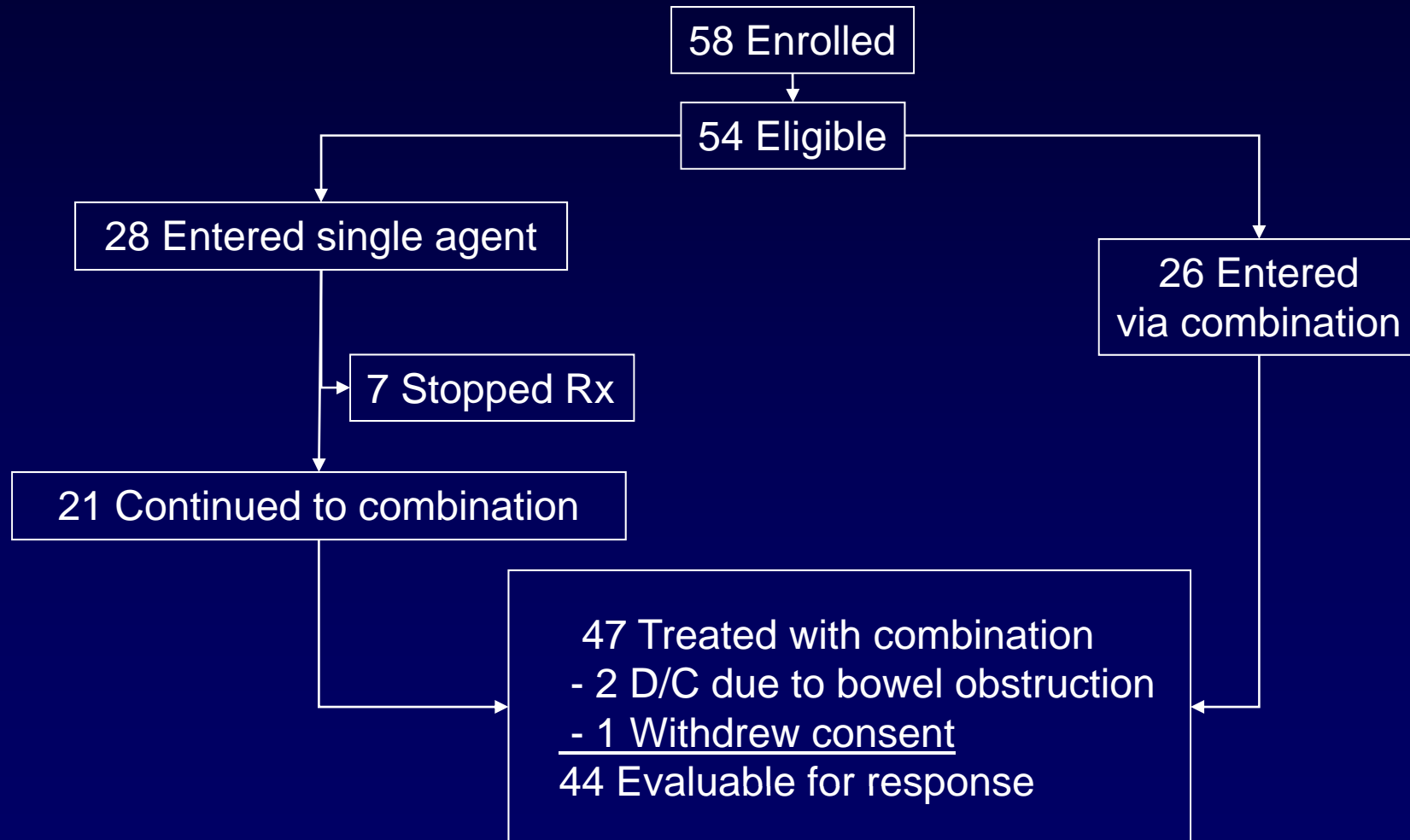
- Humanized MoA against FR with experimental antitumor activity in resistant models, particularly in combination with chemo
- In phase I trial, significant tumor uptake seen using radiolabelled MoA with favorable toxicity profile up to 400 mg/m² IV q7 days x 4 (MTD not reached)

Farletuzumab Phase II: Design

Patients with EOC experiencing first platinum sensitive relapse
After first remission of 6-18 months duration
Evaluable disease by CA125



Farletuzumab Phase II: Disposition



Farletzumab—Phase II Trial

Single agent (n = 28)

- 28 completed 9 weeks
 - No RECIST response
 - CA125 response is 2
 - 6 patients remained on treatment 16-32 weeks

Combination therapy

- 44 evaluable patients
 - 70% RECIST overall response
 - 89% CA125 complete response
 - Median PFS 10.3 months
 - In 9 cases (21%) duration of second response longer than first

Farletuzumab Phase II:

Comparison of Progression-Free (PF) Interval: 2nd vs 1st

9 subjects, farletuzumab + carboplatin + taxane
Data as of 18 Aug 2009

Subject	1 st PF Interval, months	2 nd PF Interval, months	Status
302	11.7	34.1 +	Still responding
804	16.8	29.8 +	Still responding
802	26.4	28.9	Off-study
801	11.9	23.3	Off-study
1102	16.1	24.1 +	Still responding
809	11.8	19.1	Off-study
305	13.8	13.8	Off-study
905	12.8	13.1	Off-study
2804	11.3	11.8 +	Still responding

Farletuzumab

- First clinical evidence of potential role for alpha-folate receptor–targeted therapy
- Monoclonal antibody with dual mechanism of action has potential in combination with chemotherapy and as maintenance
- 2 randomized trials in relapsed patients ongoing:
 - In platinum-sensitive disease: paclitaxel/carboplatin ± farletuzumab
 - In platinum-resistant disease: Weekly paclitaxel ± farletuzumab

Further Potential for Molecular Targeted Treatment in Ovarian Cancer Based on Molecular Genetic Changes

- **Type I disease (low grade invasive/mucinous/endometrioid)**
 - **Frequent mutations of KRAS, BRAF, PTEN**
 - **Clinical trials with RAF inhibitors (and PARPi) underway**
- **Granulosa cell tumors**
 - **Recent data suggesting efficacy of bevacizumab (and possibly HDAC inhibitors—these may have more application in combination therapy based on preclinical data)**

Novel Agents in Ovarian Cancer

Summary

- Clinical data indicate that most promising targets are:
 - Angiogenesis
 - HR deficiency (BRCA 1/2, etc)
- Clinical data now needed for:
 - PI3K/AKT/mTOR pathways
 - Alpha folate receptor
 - Others
- Key to success will be:
 - Patient selection
 - Patient selection
 - Patient selection