Progress in Drug Development for Rare Epithelial Ovarian Cancers: The NRG Oncology Experience and Beyond

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Framework

- Scope of discussion: Rare EOC
  - Clear Cell Carcinoma
  - Low-Grade Serous Carcinoma
  - Mucinous Carcinoma
- All rare ovarian cancers are not created equal
- GOG established Rare Tumor Committee in 2005
- No rare EOC trials existed prior to that time
- Essentially no prospective data for rare subtypes

Challenges and Barriers

- Small number of cases
- Long accrual times
- Few interested investigators
- Less attention by scientific community
- Funding priority has been low
- Low priority for Pharma
- Fewer patient advocates
- Lack of standard bioinformatics methods and trial designs

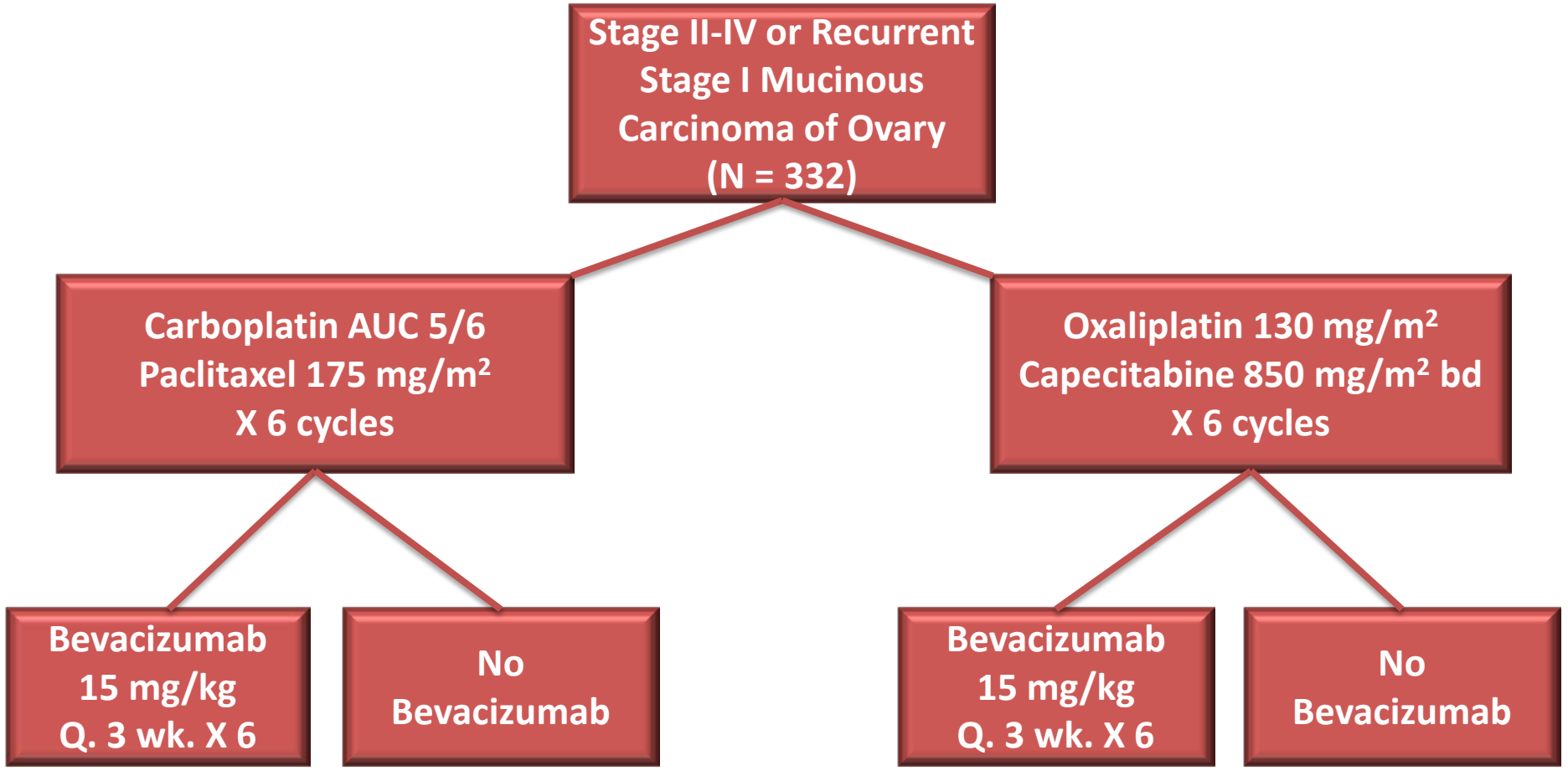
Clinical Features

Feature	Clear Cell	Low-Grade Serous	Mucinous
Incidence	5%	5%	10%
Stage Distribution			
Stages I/II	67%	10%	61%
Stages III/IV	33%	90%	39%
Biology	Aggressive	Indolent	Aggressive
Relative Chemoresistance	Yes	Yes	Yes
Outcomes in Early Stage	Similar to HGSC HR = .87	Unknown but thought to be excellent	Similar to HGSC HR = .87
Outcomes in Advanced Stage	Median OS = 21 mo Worse than HGSC HR = 2.2	Median OS = 101 mo Better than HGSC HR = ?	Median OS = 15 mo Worse than HGSC HR = 2.7

Mucinous Carcinoma:
Key Pathways & Potential Targets

- **Angiogenesis pathway**
- **HER-2/neu amplification (20%)**
- **MAPK (*KRAS* mutation, 40-50%)**

mEOC/GOG 241: A Randomized Phase III Trial of Capecitabine/Oxaliplatin vs. Paclitaxel/Carboplatin +/- Bevacizumab in Patients with Previously Untreated Mucinous Ovarian Cancer



mEOC/GOG 0241

- Target accrual = 330
- Closed early for slow accrual: Only 50 pts accrued (34 UK, 16 US)
- 40/50 cases available for central pathology review: Only 18 (45%) were diagnosed as primary mucinous ovarian cancer
- Neither of experimental regimens (Oxal/Cape vs. Pac/Carbo or Bev versus no Bev) clearly improved OS or PFS

Mucinous Carcinoma: Future Directions

- Advanced stage mucinous carcinoma is rarer than originally thought
- Path for progress: Smaller phase II trials or basket trials
- Prospective central pathology review is essential
- Potential trials:
  - Targeting KRAS mutations
  - Targeting HER-2/neu amplification
  - Immunotherapy: Pts whose tumors have high CD8+ tumor-infiltrating lymphocytes have improved survival
  - PI3K/mTOR + MEK inhibitors show synergistic anti-tumor effects preclinically
  - Oxaliplatin + dasatinib reduces cancer cell viability and promotes apoptosis in human mEOC cell lines

Clear Cell Carcinoma:
Key Pathways & Potential Targets

- ARID1A mutation 50%
- PI3K/AKT/mTOR pathway 30-40%
- Angiogenesis pathway
- PD-1 and PD-L1
- HNF-1β upregulation 100%
- IL6-HIF-1α pathway upregulation 50%
- MET amplification 20-30%
- HER-2 amplification 14%
- PPM1D amplification 10%
- Microsatellite instability (MSI) 7-18%

Clear Cell Carcinoma

Trial	Phase	Setting	No. Pts	Agent(s)	Results
JGOG3017	III	First-line	667	Irinotecan/Cisplatin vs Paclitaxel/Carboplatin	2-yr OS = 85.5% vs 87.4% (NS)
GOG 268	II	First-line	90	Paclitaxel/Carboplatin + Temsirolimus → Temsirolimus maintenance	54% with PFS > 12 mo No better than historical controls
GOG 254	II	Recurrent	35	Sunitinib	ORR = 6.7% Median PFS = 2.7 mo
NRG-GY-001	II	Recurrent	13	Cabozantinib	ORR = 0% Median PFS = 3.6 mo
Princess Margaret Cancer Centre Trial	II	Recurrent	40	ENMD-2076	ORR = 5% Median PFS = 3.7 mo

Clear Cell Carcinoma

Trial	Phase	Setting	No. Pts	Agent(s)	Results
GOG 283	II	Recurrent	35	Dasatinib	Pending analysis
NiCCC	Randomized II	Recurrent	--	Nintedanib vs SOC	Recruiting
NRG-GY-014	II (basket)	Recurrent	--	Tazemetostat	Not yet recruiting
NRG-GY-016	II	Recurrent	--	Pembrolizumab + Epacadostat	Not yet recruiting
ATARI/NCRI	II	Recurrent	--	AZD6738 +/- Olaparib	Not yet recruiting

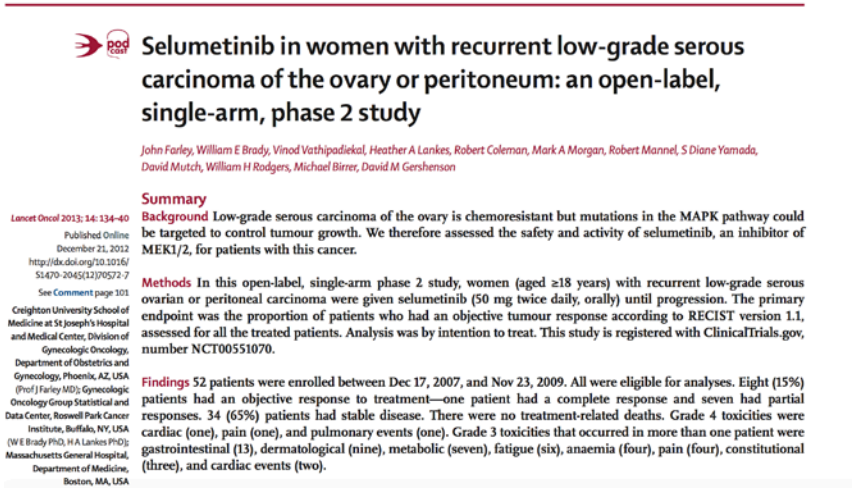
Clear Cell Carcinoma: Future Directions

- Continue to conduct phase II or basket trials
- Targets of most interest:
  - PD-1 or PD-L1
  - ARID1A mutation
  - PI3K/AKT/mTOR pathway
  - Angiogenesis pathway

Low-Grade Serous Carcinoma: Key Pathways & Potential Targets

- **MAP Kinase pathway**
  - **KRAS 20-40%**
  - **BRAF 5-10%**
  - **NRAS 15%**
- **Estrogen Receptor**
- **Angiogenesis pathway**
- **IGFR-1**

GOG 0239



Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study

John Farley, William E Brady, Vinod Vathipadiekal, Heather A Lankes, Robert Coleman, Mark A Morgan, Robert Mannel, S Diane Yamada, David Mutch, William H Rodgers, Michael Birrer, David M Gershenson

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See Comment page 101

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Summary

Background Low-grade serous carcinoma of the ovary is chemoresistant but mutations in the MAPK pathway could be targeted to control tumour growth. We therefore assessed the safety and activity of selumetinib, an inhibitor of MEK1/2, for patients with this cancer.

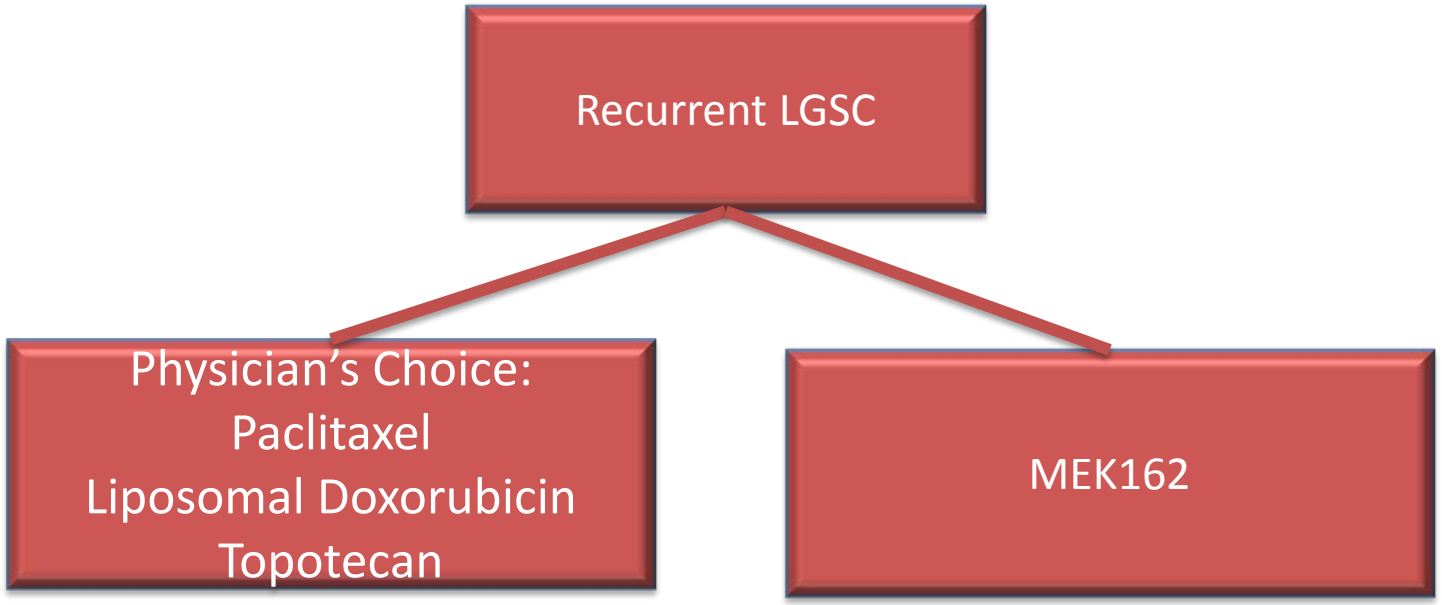
Methods In this open-label, single-arm phase 2 study, women (aged ≥18 years) with recurrent low-grade serous ovarian or peritoneal carcinoma were given selumetinib (50 mg twice daily, orally) until progression. The primary endpoint was the proportion of patients who had an objective tumour response according to RECIST version 1.1, assessed for all the treated patients. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00551070.

Findings 52 patients were enrolled between Dec 17, 2007, and Nov 23, 2009. All were eligible for analyses. Eight (15%) patients had an objective response to treatment—one patient had a complete response and seven had partial responses. 34 (65%) patients had stable disease. There were no treatment-related deaths. Grade 4 toxicities were cardiac (one), pain (one), and pulmonary events (one). Grade 3 toxicities that occurred in more than one patient were gastrointestinal (13), dermatological (nine), metabolic (seven), fatigue (six), anaemia (four), pain (four), constitutional (three), and cardiac events (two).

- Phase II study of selumetinib (MEKi) in 52 women with recurrent LGSC
- ORR = 15%
- Clinical benefit rate = 80%
- No correlation of outcome with KRAS/ BRAF mutations

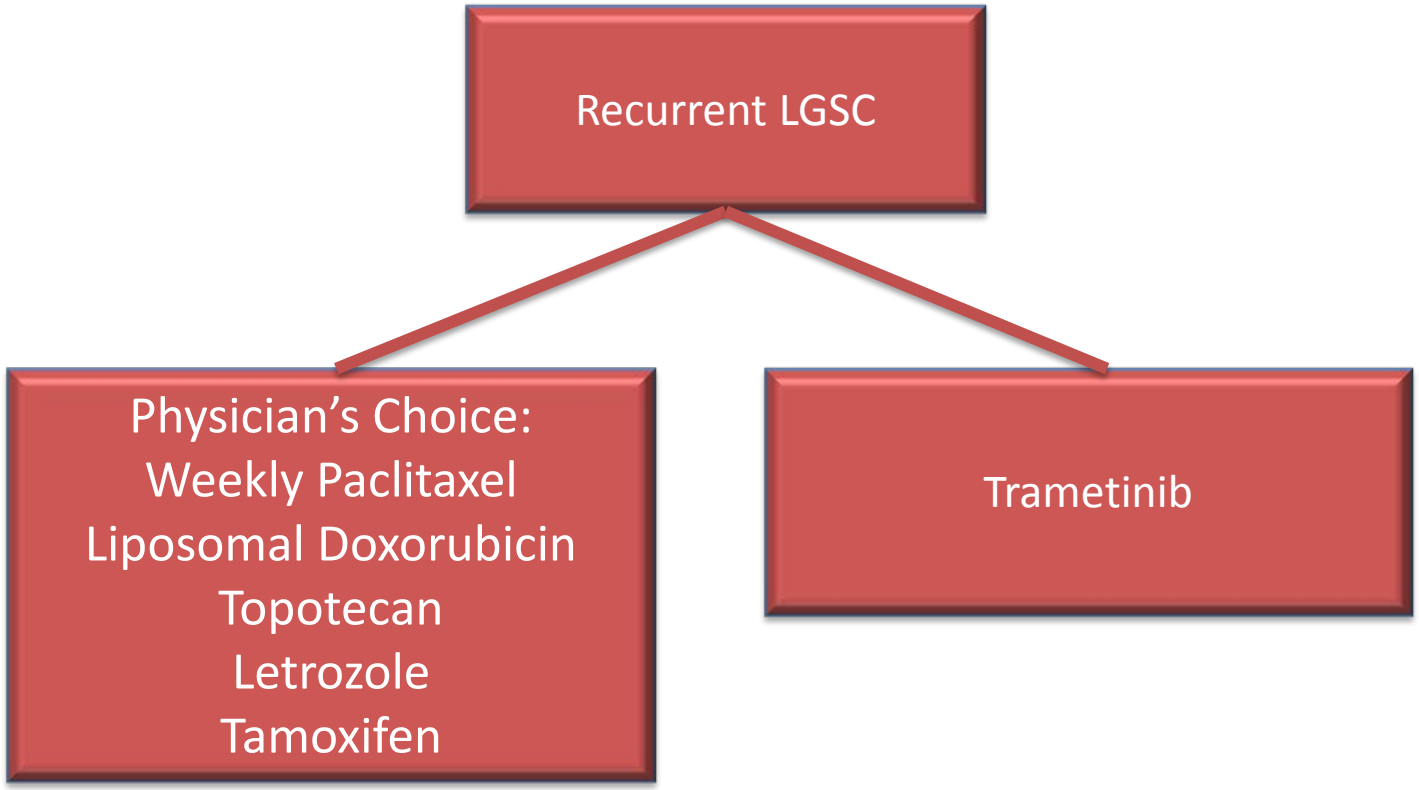
NCT01849874
MILO Trial

Randomized Phase III Trial



NCT02101788
GOG-0281

Randomized Phase III Trial



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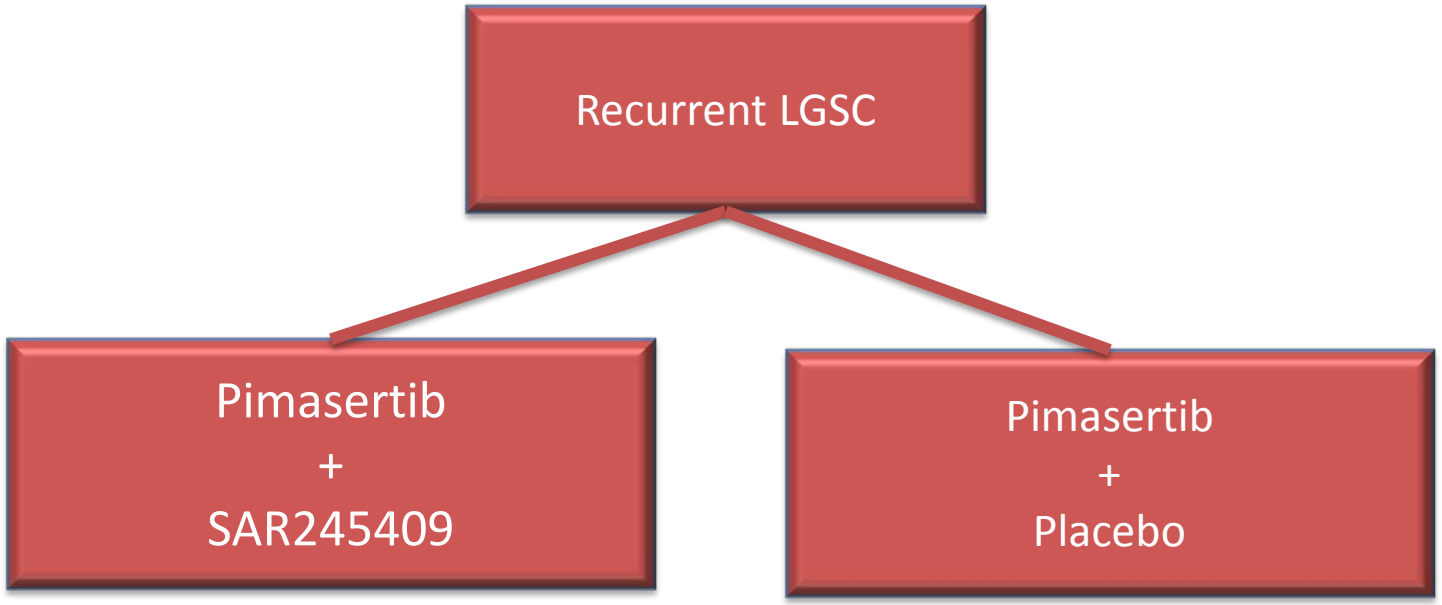
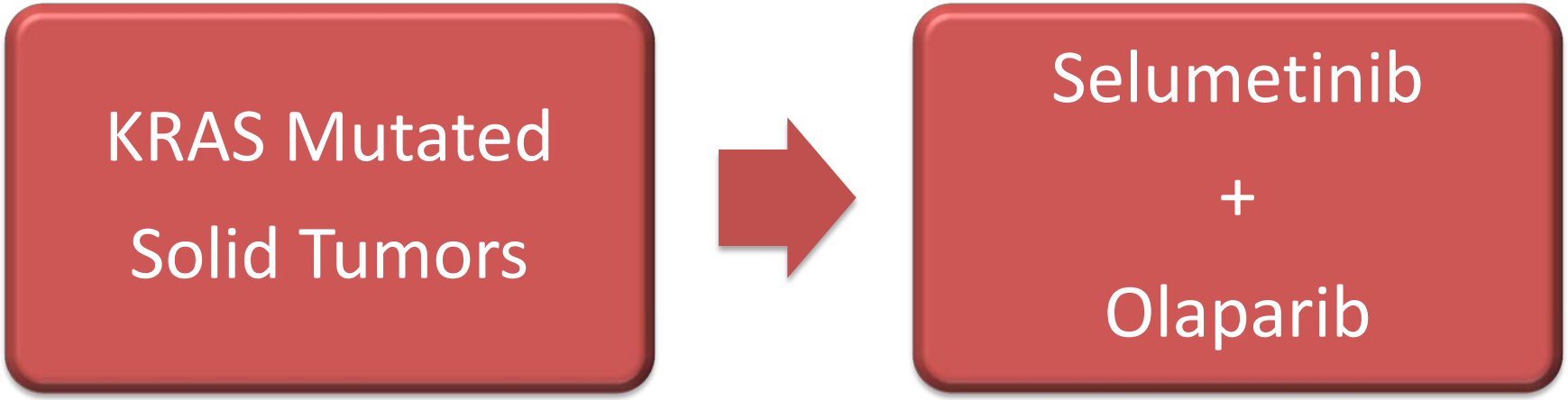
Randomized Phase II Trial



Phase I Study of Selumetinib + Olaparib in Women with KRAS Mutant Tumors (SOLAR)



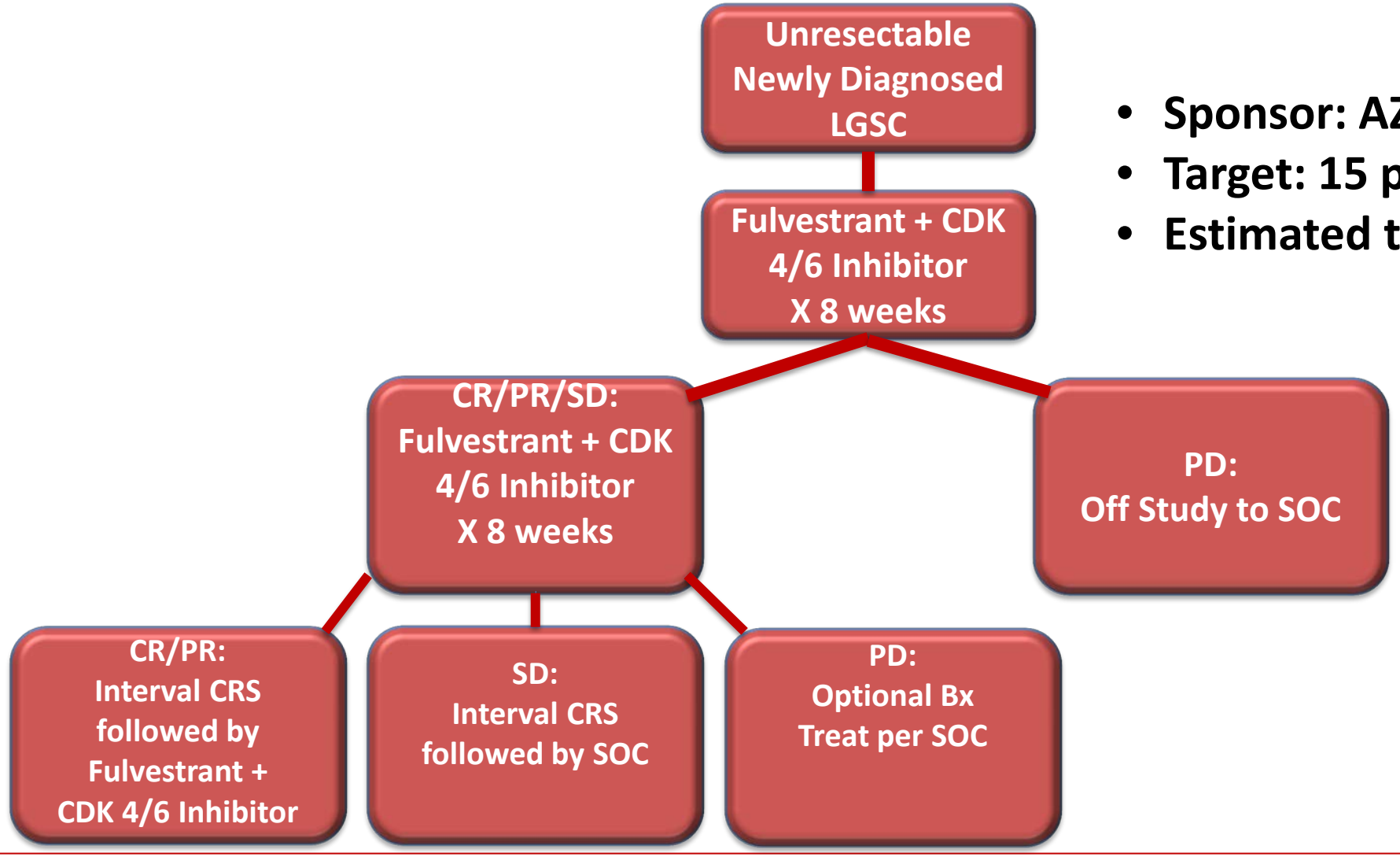
A Phase II Trial of Ribociclib + Letrozole in Women with Recurrent Low-Grade Serous Carcinoma

Recurrent
Low-Grade Serous Carcinoma

Letrozole 2.5 mg daily
+
Ribociclib 600 mg x 21d
then 7d off

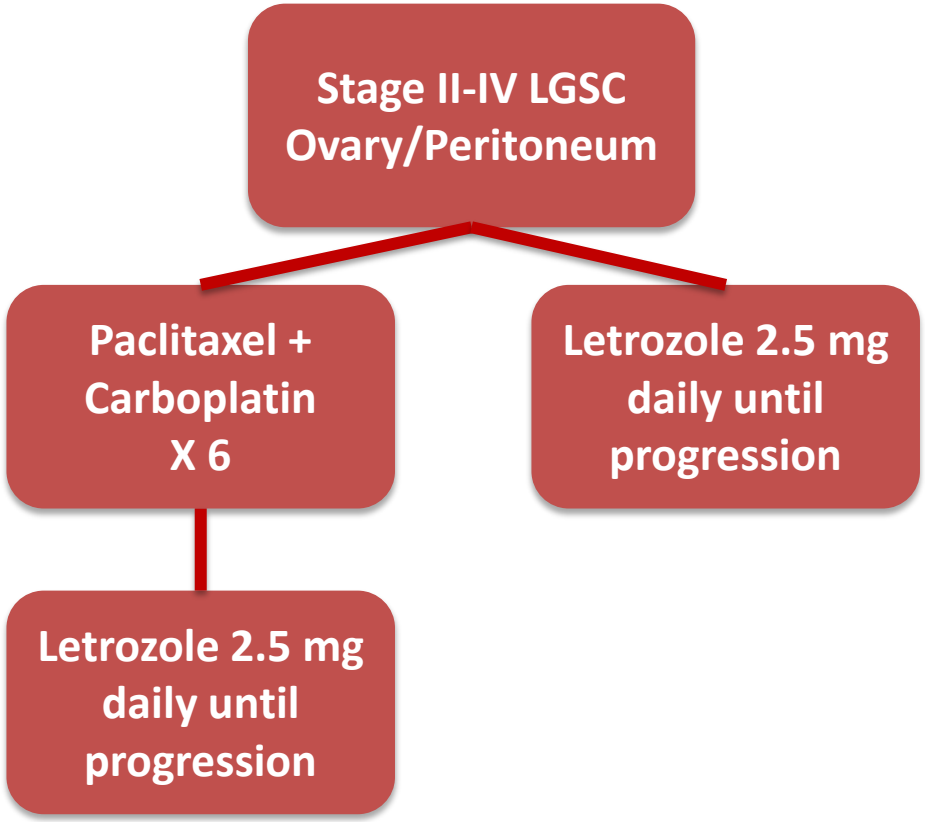
- **Sponsor: Novartis**
- **GOG Foundation Trial**
- **Target: 50 pts**
- **Estimated to activate Q3 2018**

Pilot Study of Neoadjuvant Fulvestrant + CDK 4/6 Inhibitor in Low-Grade Serous Ovarian Cancer



- **Sponsor: AZ**
- **Target: 15 pts**
- **Estimated to activate Q4 2018**

NRG-GY-019:
Randomized Phase III Trial of Paclitaxel/Carboplatin Followed by Maintenance Letrozole versus Letrozole Monotherapy in Stage II-IV Low-Grade Serous Carcinoma



- Sponsor: NCI (NRG Oncology)
- International phase III trial
- Primary Objective: PFS
- Target: 450 pts
- Estimated to activate Q2 2019

Low-Grade Serous Carcinoma: Future Directions

- Continue to study genomics of low-grade serous carcinoma
- Await findings from MEKi trials
- Conduct combination targeted aged trials
  - MEKi + PARPi
  - MEKi + Letrozole
  - MEKi + PI3Ki
  - MEKi + IGF-1R inhibitor
  - MEKi + Metformin
  - MEKi + BRAFi
- Activate trials focused on hormonal therapy