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Clinical Trials in Gynecologic Oncology: Past, Present, and Future

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Introduction

The Gynecologic Oncology Group has historically performed ground-breaking, practice-changing clinical trials in women's cancers. The current standard of care for initial treatment of ovarian, endometrial, cervical, and trophoblastic cancers was determined by clinical trials completed within this cooperative group structure. For example, trial GOG-0111 set the standard for combining platinum and taxane chemotherapy in ovarian cancer, and more recently GOG-0240 provided evidence for adding bevacizumab to chemotherapy for women with advanced cervical cancer (1,2). The landscape of clinical trial design has markedly changed in recent decades, with a clear emphasis on streamlining drug development towards specific patient populations and indications for investigational agents. Translational science in gynecologic cancers can set the stage for rapid and efficient introduction of new therapies for our patients. The gynecologic oncology community of researchers and clinicians is well positioned to enter into the new era of drug development, with breakthrough discoveries increasing each year. It is clear that we must incorporate smart clinical trial design to get the right drugs to the right patients expeditiously, so we can continue to improve outcome for women with gynecologic cancers.

Current FDA Guidance in Clinical Trials

The FDA has implemented four programs to improve efficiency of the drug development process. These designations include Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval (<https://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm>). The purpose of these expedited programs is to facilitate development and expedite review of drugs that treat serious conditions and fill an unmet medical need, with the goal of getting important new drugs to patients earlier. The seriousness of a condition is difficult to define, but is based on whether a drug can have an impact on measures of clinical benefit, such as survival, physical function, or progression of a disease to a more serious condition.

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The Fast Track designation is given to products that have the potential to address an unmet clinical need, provide therapy where none exists or that is potentially better than available therapy. A sponsor may request Fast Track designation at any time during drug development, and the Agency must provide a response to the request within 60 days. This designation is based on preliminary measures of efficacy in the serious condition, and must have a well-delineated development plan that addresses an unmet medical need. The plan should evaluate whether the agent has an ability to provide benefit while reducing toxicity, for example, or an ability to provide benefit in patients unresponsive to alternative treatment. Successful Fast Track designation allows early and frequent communication with FDA throughout the drug development process such as for discussion of endpoints, biomarker development, or other aspects of trial design to support drug approval. Additionally, Fast Track designation permits a sponsor to request “rolling review,” whereby completed sections of its biologics license application (BLA) or new drug application (NDA) may be submitted instead of submitting an entire completed application.

For a product to qualify for Breakthrough Therapy, it must hold the promise of demonstrating a substantial improvement over available therapy. This is based on the magnitude of the treatment effect in preliminary clinical studies, which must show an advantage compared to a historical control. For example, rucaparib was granted Breakthrough Therapy designation in April 2015, when clinical data from the ARIEL2 study showed that 65% of patients achieved a RECIST response. This is better than historical control with chemotherapy where response rates are <50% in the third line treatment of women with platinum-sensitive ovarian cancer. The Breakthrough designation allowed the FDA to expedite the review of this drug, and to closely guide the generation of evidence needed to support final approval, which was granted in December 2016. The endpoint must measure an effect on irreversible morbidity or mortality, or on symptoms that represent a serious consequence of the disease process. The FDA defines the most clinically significant endpoint for a cancer indication as overall survival. Endpoints could also include a validated surrogate endpoint, or even a pharmacodynamic biomarker, though these endpoints may not be sufficient in and of themselves for later marketing approval. For example, overall response rate and duration of response may be acceptable surrogates if they are closely linked to improving overall survival with an improvement in quality of life. The Breakthrough Therapy designation permits increased FDA guidance, and is thus more efficient if the drug development program starts in the phase 1 setting. Generally, the FDA recommends a preliminary discussion prior to submission of a Breakthrough Designation Request. Once submitted, a response is provided within 60 days.

Priority Review Designation shortens the review period before FDA takes action on an application to 6 months, from the 10 months under standard review. These applications are chosen on the basis of providing significant improvement to treatment safety or efficacy. Applicants may request priority review, but all applications get assigned a review designation by the Agency. Designation of “priority” does not alter the scientific or medical standard for approval, but does allocate more resources for the review of the benefit:risk assessment in order to shorten the review clock, with the goal of getting safe and effective drugs to patients faster. The Prescription Drug User Fee Act (PDUFA) was first enacted in 1992 in order to collect fees from drug companies applying for approval (www.fda.gov/

For Industry/User Fees/Prescription Drug User Fee). If the data in the application meet the criteria for Priority Review Designation, then the 6-month review period date is set from the time that the initial New Drug Application was completed (www.fda.gov/Drugs/DevelopmentApprovalProcess).

The Accelerated Approval mechanism, enacted in 1992 and modified in 2012, focuses on surrogate endpoints that may be demonstrated earlier than the clinical benefit endpoints used for regular approval. These endpoints could be biomarkers, radiographic images, or other measures that are considered reasonably likely to predict clinical benefit based on supportive scientific evidence. In this setting, reduction of tumor burden is considered reasonably likely to predict a clinical benefit, but can be measured well before learning whether a treatment allows patients to live longer. If considering accelerated approval, post-marketing clinical trials should be underway at the time of approval. These confirmatory trials must have a primary endpoint, such as overall survival, that clearly shows clinical benefit.

Implementing these Strategies

The FDA approved 80 new drug indications for non-hematologic malignancies between 2011-2016 (Table 1). Five of these were for gynecologic cancers. The bevacizumab approval was expanded to include three indications in gynecologic cancers: in combination with chemotherapy for cervical cancer, in combination with chemotherapy for platinum-resistant recurrent ovarian cancer, and combined with platinum-based chemotherapy for platinum-sensitive recurrent ovarian cancer. Two indications were based on clinical trials implemented by the Gynecologic Oncology Group/NRG Oncology. These include GOG-240, for the use of bevacizumab with chemotherapy in advanced cervical cancer; and GOG-213, for the use of bevacizumab with chemotherapy in platinum-sensitive recurrent ovarian cancer (2,3). Olaparib and rucaparib were initially approved for treatment of women with BRCA-mutated ovarian cancer. The first FDA indication for each of these drugs was based on biomarker-positive cancer: olaparib received its first approval for the treatment of women with germline BRCA mutation, with recurrent ovarian cancer after 3 or more lines of therapy; rucaparib was approved for the treatment of women with deleterious BRCA mutation (germline or somatic) associated advanced ovarian cancer who have been treated with 2 or more prior regimens.

Recently Completed Gynecologic Oncology Clinical Trials

During the time period 2011-2016, the Gynecologic Oncology Group/NRG Oncology published 58 peer reviewed articles reporting clinical trial results (Table 2) (3, 4-60). Six publications reported phase 3 clinical trial results. One of these led to an FDA-approved indication, for the addition of bevacizumab to chemotherapy in women with advanced cervical cancer. (Of note, GOG-0213 contributed to the 2016 approved indication for bevacizumab with chemotherapy in women with platinum-sensitive ovarian cancer; the publication was released in 2017 (3).) There were 12 phase 1 clinical trials reported, and the remainder were phase 2 studies. At least 15 of these publications concluded that the compound or regimen was tolerable and interpreted as having reasonable clinical activity justifying further investigation. Five of these trials have influenced practice in the

gynecologic oncology community, without a change in the FDA labeled indication. For example, GOG-0174 supported the use of pulsed dactinomycin in gestational trophoblastic neoplasia. In addition, the use of bevacizumab is considered acceptable treatment for women with recurrent endometrial cancer (GOG-0229E) and rare ovarian stromal tumors (GOG-0251). Nab-paclitaxel (Abraxane) was added to the armamentarium to treat recurrent ovarian cancer after GOG-0126R. For vulvar cancer, GOG-0205 added the use of weekly cisplatin with radiation. Two agents – veliparib (GOG-0280 and GOG-0077HH) and fosbretabulin (GOG-0186I) moved to the phase 3 setting. Thus, the cooperative group structure has longstanding impact on setting standards for optimal care of women with gynecologic cancer. The improvements come not only from testing new drugs for approval in gynecologic indications, but also for optimizing the use of drugs, with respect to schedule/timing of administration, or combination with other modalities of surgery and radiation.

Ongoing Clinical Trials in Gynecologic Oncology

Overall, there are 551 clinical trials enrolling women with ovarian cancer, 164 for endometrial cancer, and 230 for cervical cancer listed on clinicaltrials.gov (search date 10/12/2017; terms: ovarian cancer, endometrial cancer, uterine cancer, cervical cancer). Currently, the NRG Oncology cooperative group manages 17 potentially practice-changing clinical trials, with planned accrual of at least 80 patients each, for women with gynecologic malignancies (Table 3). Seven are phase 3 studies, 4 have phase 2/3 design, 2 are randomized phase 2 studies, and 5 are single arm phase 2 studies. The average accrual target per trial is 407 patients (range of 84-1052). The trial size is intentionally smaller than in past decades, with a shift toward the phase 2/3 design, to use information efficiently, and with a larger effect size sought, based on biomarker hypotheses. The rationale for limiting trial size is not simply based on financial constraints. More efficient trial design helps our patients by exposing fewer women to potentially harmful but ineffective drugs, or to placebo controls, and by accelerating approval of effective drugs for wider use in the community.

Gynecologic Oncology Clinical Trials in the Future

How can we expedite drug development for gynecologic oncology indications? The pattern of development for several recent drugs suggests a more seamless process is possible for moving promising regimens from early phase clinical trials to FDA approval. Phase 2 or even phase 1 trials have led to accelerated approval, making the drug available to patients while the confirmatory phase 3 study proceeds. One example is the phase 2 study for rucaparib. Its approval was based on the outcome of 106 patients with BRCA mutated in germline or in tumor (somatic), combined from two phase 2 clinical trials (Study 10, NCT01482715 and ARIEL2, NCT01891344). Women with ovarian cancer that had relapsed after 2 or more prior therapies received rucaparib 600mg twice daily, and 54% experienced objective tumor responses. This response rate was considered better than available therapies in the third line setting. While the true overall response rate (ORR) for third-line treatment of ovarian cancer patients with BRCA mutation is unknown, this was considered in the setting of the ORR of 63% reported for the combination of liposomal doxorubicin and carboplatin, when given in an earlier setting (second-line) (61), and has the additional benefit of sparing women from platinum toxicity. Safety data were assessed from 377

patients on these two trials, including women whose tumors did not contain BRCA mutation.

Similarly, the approval for olaparib capsules in 2014 was based on the outcome of 137 women with ovarian cancer and germline BRCA mutation who had received at least 3 prior treatment regimens. The overall response rate of 37% in this population was persuasive when compared to previously reported response rates of <20% after several lines of treatment, in the general population of women with ovarian cancer, unselected by BRCA mutation status. Notably, the FDA approvals for both rucaparib and olaparib specifically considered the responses in the patient population with a BRCA mutation in the germline or tumor tissue. This was justified by strong preclinical and clinical data linking BRCA mutations with increased responsiveness to PARP inhibitors.

As exemplified with PARP inhibitors, endpoints in phase 2 clinical trials are typically those other than overall survival. Instead, phase 2 studies seek a measurable effect that may correlate with clinical benefit. The “surrogate” endpoint should be reasonably likely to predict improved overall survival, when considering the accelerated approval pathway through the FDA. These might include overall response rate (ORR), duration of response (DOR), or a biomarker response linked to survival (such as in the case of cholesterol level and mortality from coronary artery disease). Landmark analyses, such as overall survival at 12 months, or PFS at 6 months, are not considered appropriate from the FDA standpoint of regulatory approval, though these endpoints may be useful to provide preliminary data on whether or not to develop an agent further. For example, GOG-0229N used the landmark of TPFS at 6 months to determine whether dalantercept should be moved forward in endometrial cancer patients (12). The statistical design called for 7 patients to reach the 6 month landmark without progressing or receiving non-protocol therapy. Since only 3 patients reached this landmark, the agent was not developed further. The 6-month TPFS would not have been useful for FDA approval considerations, but contributed to the decision that this was not a promising treatment for women with recurrent or persistent endometrial cancer. Also of note, CA-125 is not reliable as a surrogate in the FDA approval process for drugs treating ovarian cancer, given its variability across patients. ORR is considered the most objective endpoint and thus allowable for single arm trials; DOR should only be used in the setting of a randomized phase 2 trial.

The phase 2/3 trial design could expedite the transition from accelerated approval to regular approval. This design usually includes separate endpoints for the phase 2 and phase 3 parts, in order to maintain adequate power with a relatively small sample size. For example, the phase 2 part may have progression-free survival endpoint for statistical purposes, and the phase 3 would then have overall survival as the primary endpoint. Such a trial could be designed to use the overall survival data from patients in the phase 2 portion for the phase 3 endpoint, improving efficiency in patient accrual numbers without requiring alpha spending.

A challenge to the 2/3 design is the perceived increased time to complete accrual, compared to a straight phase 3 study, since enrollment must be halted in order to assess the phase 2 PFS endpoint. For example, GOG-286B trial of paclitaxel and carboplatin +/- metformin for women with advanced endometrial cancer has enrolled approximately 20 patients per month,

but will likely take over 40 months to complete accrual of all 540 patients, due to the pause for interim analysis of progression-free survival between the phase 2 and 3 portions. Because all patients will count towards final OS endpoint, however, only 540 women are needed for adequate power to determine whether metformin added to chemotherapy improves overall survival. In other cases where accelerated approval is sought after the phase 2 part, the drug is available to patients sooner, while the phase 3 part is ongoing for regular FDA approval. It is important to recognize that time may actually be saved in this instance, compared to starting with a phase 2 study, and then developing a second phase 3 clinical trial as an entirely new protocol.

The phase 2/3 design can be tailored when the efficacy of the individual arms in a randomized study is not well estimated, and ineffective arms can be eliminated from the full phase 3 study, improving patient safety and preventing randomization to ineffective treatment regimens. The ongoing study NRG-GY005 for women with platinum-resistant ovarian cancer is designed in this way. The phase 2 portion starts with 4 arms – olaparib, cediranib, olaparib+cediranib, and standard chemotherapy. It is designed to drop one or both single-agent arms for the phase 3 study if progression free survival is below the predefined targets. In contrast to this strategy, GOG-182 enrolled over 4000 women to a randomized phase 3 study without an accurate estimate of expected activity for each of the arms (62). It is possible that if study GOG-182 was instead designed as a phase 2/3 study, with accrual suspension after the phase 2 patients had enrolled, the same conclusion could have been reached with 1740 patients, thus exposing 2572 fewer women to toxic therapy without clear benefit (63). It is highly recommended that endpoints and statistical analysis plan should be discussed with FDA when planning the phase 2/3 design for trials with registration intent.

The development of pembrolizumab took the notion of “seamless” one step further, achieving accelerated approval from expansion cohorts on the phase 1 clinical trial, and for 2 separate indications (64). In 2014, the FDA granted pembrolizumab its first accelerated approval based on an ORR of 24% in 173 patients with metastatic melanoma who had relapsed after ipilimumab treatment. In 2015, a different expansion cohort within the same clinical trial resulted in accelerated approval for non-small cell lung cancer (NSCLC) based on 61 patients with PD-L1 expressing tumors (65). Accelerated approval from the phase 1 setting attains the goal of making drugs available to patients early, with strong preliminary evidence of safety and activity, while the definitive clinical trial proceeds to confirm results and gain full FDA approval.

Biomarker-Driven Clinical Trials

It is striking to note that the highest number of new FDA approved indications during the 2011-2016 time frame was in non-small cell lung cancer (NSCLC), with 15 new approvals. Remarkably, 9 of these are linked to biomarker-selected patients. For example, the ALK genomic rearrangement was instrumental in selecting patients for the approval of alectinib, ceritinib, and crizotinib in NSCLC. Accelerated approvals were more likely with biomarker-selected trials, with 9 of the 13 accelerated approvals for any solid tumor given to biomarker-driven indications, compared to 4 accelerated approvals with no molecular marker. Slightly lower numbers of patients were required for both accelerated and regular

approvals in biomarker-selected trials. It should be noted that if the biomarker is infrequent in the population, however, then a larger number of people will be screened in order to enroll sufficient patients carrying the biomarker, something that could slow the trial process. Accelerated approvals in biomarker-driven trials considered an average of 172 patients, while accelerated approvals in non-marker indications had an average of 184 patients. Regular approvals followed a similar trend, with an average of 554 patients considered for biomarker-selected indications, and 585 for non-biomarker indications.

Clinical trials that enroll biomarker selected patients may complete faster and have greater differences thus leading to earlier FDA review. This can more rapidly introduce therapeutic options for patients who have the greatest likelihood of benefit. Such a marker should have strong preliminary evidence – both preclinical and clinical – of statistically predicting the effect of the product under study (66,67). A predictive biomarker is one that identifies patients most likely to respond to a particular therapy. This is distinct from a prognostic marker, that indicates the survival of a patient irrespective of treatment. The predictive biomarker can be used for the selection and/or stratification of patients enrolling on the clinical trial, and must have a validated assay performed in a CLIA-qualified laboratory (68). Examples include somatic or germline BRCA1 or 2 mutation for rucaparib, or PD-L1 expression for pembrolizumab in lung cancer. Each of these clinical trials also gained co-approval for the companion diagnostic used for patient selection. Companion diagnostics are under the purview of Center for Devices and Radiologic Health (CDRH), as they are considered a device required for the safe and effective use of a drug.

Single arm, non-stratified biomarker cohorts have been used for gaining both accelerated and regular approval. In most instances, however, for full regular approval it is necessary to demonstrate that the biomarker-expressing cohort has a better outcome with the product under study compared to a group that does not express the biomarker. In this situation, a stratified trial design is appropriate instead of a single-arm study (69). The stratified design will enroll all patients and stratify to arms based on expression of the biomarker. Patients may all receive the experimental product, or may be randomized to experimental versus standard treatment. The number of patients required for sufficient power to show a difference between groups will depend on the magnitude of the difference expected, as with standard phase 3 trial design. Alternatively, it may be more useful to show that the biomarker-expressing group does better with the product compared to standard therapy. Here, an enrichment design would be implemented. Only patients with biomarker-positive disease are included, and randomized to receive the experimental product or standard treatment. This design is typically used when biomarkers have very strong evidence for selecting patients who will benefit from the product. The SOLO1 and SOLO2 clinical trials are examples of an enrichment design, where only women with BRCA mutation were enrolled, and randomized to olaparib or standard of care (placebo) in the maintenance setting following standard chemotherapy (70). A disadvantage is that there will be no data gathered on potential benefit of the product to patients whose cancer does not express the biomarker, and thus the biomarker will not have direct evidence of clinical utility.

Conclusion

With current trends in clinical trials for gynecologic oncology, it is critical to re-think our approach to clinical trial design in order to maximize efficiency of patient accrual, and make the newest drugs available to patients as early as possible. Clinical trials in today's environment should be smarter and more nimble, with “seamless” transition from early phase to later phase testing. Focused trials with efficient use of clinical data have the highest potential to help our patients in the future. Moving promising agents forward with a biomarker for patient selection is most expedited when the marker has strong preclinical and early clinical evidence that predicts a large margin of increase over best available therapy. There have never been more promising agents, or more detailed scientific inquiry into the field of gynecologic cancers as there is today. It is critical to encourage our physician scientists to lead novel insights into new clinical trials focused on key biological drivers and vulnerabilities in women's cancers, translating from the bench to personalized therapies. Riding the wave of enthusiasm to increase access to clinical trials for our patients, we must learn from the past and embrace the present – better science, smarter data analysis, streamlined FDA communication – so we can continue to give our patients hope for the future.

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Highlights

Groundbreaking clinical trials have historically been run through cooperative groups.

Recent trial design accelerates approval of new agents from phase 1 or 2 settings.

Biomarkers are essential to move research forward expeditiously.

Our clinician scientists are well positioned to drive new discoveries to patients.

Table 1

Year	Drug	Combination	Indication	Approval Type	Other Status	Endpoint	#Patients	Biomarker
2016	rucaparib		ovarian cancer	accelerated	BT, PR, OD	ORR, DOR	106	BRCA
2016	crizotinib		NSCLC		BT, PR	ORR, DOR	50	ROS1
2016	palbociclib	fulvestrant	breast cancer		PR, BT	PFS	521	ER/PR+, HER2 neg
2016	pembrolizumab		NSCLC	regular*	BT, PR	PFS, OS	1338	PD-L1
2016	olaparumab	doxorubicin	soft tissue sarcoma	accelerated	FT, BT, PR	OS	133	
2016	atezolizumab		urothelial carcinoma	accelerated	BT, PR	ORR, DOR	310	
2016	lenvatinib	everolimus	renal cell carcinoma			PFS	153	
2016	everolimus		NET - GI or lung			PFS	302	
2016	nivolumab		head and neck (SCCHN)			OS	361	
2016	cabozantinib		renal cell carcinoma		BT, FT, PR	PFS	375	
2016	eribulin		liposarcoma		PR	OS	446	
2016	atezolizumab		NSCLC			OS	1137	
2016	bevacizumab	carboplatin, paclitaxel, gemcitabine	ovarian cancer, platinum-sensitive			OS	1157	
2015	pembrolizumab		NSCLC	accelerated		ORR	61	PD-L1
2015	nivolumab	ipilimumab	melanoma	accelerated		PFS, ORR	142	BRAF V600 wild-type
2015	palbociclib	letrozole	breast cancer	accelerated	BT	PFS	165	ER/PR+, HER2 neg
2015	alectinib		NSCLC	accelerated	BT, PR	ORR, DOR	225	ALK
2015	osimertinib		NSCLC	accelerated	BT	ORR	411	EGFR T790M
2015	gefitinib		NSCLC			ORR	106	EGFR (L858R; del exon 19)
2015	cobimetinib	venurafenib	melanoma			PFS, OS	495	BRAF V600E or V600K
2015	trametinib	dabrafenib	melanoma			OS	1127	BRAF V600E or V600K
2015	dinutuximab	GM-CSF, IL-2, and RA	neuroblastoma			EFS, OS	226	
2015	sonidegib		basal cell carcinoma			ORR	230	
2015	nivolumab		NSCLC-squamous			OS	272	
2015	lenvatinib		thyroid cancer			PFS	392	

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Year	Drug	Combination	Indication	Approval Type	Other Status	Endpoint	#Patients	Biomarker
2015	nivolumab		renal cell carcinoma		BT, FT, PR		410	
2015	irinotecan liposome	5FU + LV	pancreas			OS	417	
2015	talimogene		melanoma			ORR	436	
2015	trabectedin		liposarcoma or leiomyosarcoma			PFS	518	
2015	nivolumab		NSCLC			OS	582	
2015	trifluridine/tipiracil		colorectal cancer			OS	800	
2015	ipilimumab		melanoma			RFS	951	
2015	ramucirumab	FOLFIRI	colorectal cancer			OS	1072	
2015	necitumumab	gem/cis	NSCLC -squamous			OS	1093	
2014	trametinib	dabrafenib	melanoma	accelerated		ORR, DOR	162	BRAF V600E or V600K
2014	ceritinib		NSCLC	accelerated		ORR, DOR	163	ALK
2014	olaparib		ovarian cancer			ORR	137	BRCA
2014	nivolumab		melanoma	accelerated	BT	ORR, DOR	120	
2014	pembrolizumab		melanoma	accelerated	BT	ORR	173	
201	lanreotide		NET - GEP			PFS	204	
4								
2014	ramucirumab		gastric or GEJ adenocarcinoma			OS	355	
2014	bevacizumab	paclitaxel, pegylated liposomal doxorubicin, or topotecan	ovarian cancer -platinum-resistant			PFS	361	
2014	bevacizumab	Paclitaxel and cisplatin or paclitaxel and topotecan	cervical cancer			OS	452	
2014	ramucirumab	paclitaxel	gastric or GEJ adenocarcinoma			OS	665	
2014	ramucirumab	docetaxel	NSCLC			OS	1253	
2013	erlotinib		NSCLC			PFS	174	EGFR (L858R or del exon 19)
2013	afatinib		NSCLC			PFS	345	EGFR (L858R or del exon 19)
2013	crizotinib		NSCLC	regular*		PFS, ORR	347	ALK
2013	pertuzumab	trastuzumab and docetaxel	breast cancer			pCR	417	HER2
2013	ado-trastuzumab emtansine		breast cancer			PFS, OS	991	HER2

Year	Drug	Combination	Indication	Approval Type	Other Status	Endpoint	#Patients	Biomarker
2013	Ibrutinib		mantle cell lymphoma			ORR	111	
2013	lenalidomide		mantle cell lymphoma			ORR, DOR	134	
2013	denosumab		giant cell tumor of bone			ORR	304	
2013	sorafenib		thyroid carcinoma			PFS	417	
2013	Ra 223 dichloride		prostate cancer			OS	809	
2013	bevacizumab	FOLFIRI or FOLFOX	colorectal cancer			OS	820	
2013	Abraxane	gemcitabine	pancreas			OS	861	
201	everolimus		astrocytoma	accelerate		ORR	28	TSC
2				d				
2012	everolimus		renal angiomyolipoma			ORR, DOR	118	TSC
2012	imatinib		GIST	regular *		OS	397	KIT
2012	everolimus		breast cancer			PFS	724	ER/PR+, HER2 neg
2012	pertuzumab	trastuzumab + docetaxel	breast cancer			PFS	808	HER2
2012	cetuximab	FOLFIRI	colorectal cancer			OS	1210	KRAS mutation n negative
2012	vismodegib		basal cell carcinoma			ORR	204	
2012	cabozantinib		thyroid cancer, medullary			PFS	330	
2012	axitinib		renal cell carcinoma			PFS	361	
2012	pazopanib		soft tissue sarcoma			PFS	369	
2012	regorafenib		colorectal cancer			OS	760	
2012	abraxane	carboplatin	NSCLC			ORR	1052	
2012	enzalutamide		prostate cancer			OS	1199	
2012	ziv-aflibercept	FOLFIRI	colorectal cancer			OS	1226	
2011	crizotinib		NSCLC	accelerated		ORR	255	ALK
2011	vemurafenib		melanoma			OS	675	BRAF V600E
2011	sunitinib		NET - pancreatic			PFS	171	
2011	vandetanib		thyroid cancer, medullary			PFS	331	
2011	everolimus		NET - pancreatic			PFS	410	
2011	cetuximab	platinum and 5-FU	head and neck (SCCHN)			OS	442	
2011	ipilimumab		melanoma			OS	676	

Year	Drug	Combination	Indication	Approval Type	Other Status	Endpoint	#Patients	Biomarker
2011	abiraterone		prostate cancer			OS	1195	
2011	peginterferon alfa-2b		melanoma			RFS	1256	

* previously accelerated; BT, breakthrough therapy; PR, priority review; OD, orphan drug; FT, fast track

Table 2

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Public ation year	Trial Number	Drug	Combination	Indication	Ph ase	Endpoint	Secondary	# Pati ents	Biomarker
2016	GOG-0076HH	veliparib	paclitaxel, cisplatin	cervical cancer	1	MTD	ORR, PFS, OS	34	
2016	GOG-0262	paclitaxel weekly	carboplatin +/-bevacizumab	ovarian cancer	3	PFS		692	
2016	GOG-9927	veliparib	carboplatin, doxorubicin, bevacizumab	ovarian cancer	1	MTD		39	
2016	GOG-0187	paclitaxel		ovarian stromal tumors	2	ORR		31	
2016	GOG-9925	motolimod	pegylated liposomal doxorubicin (PLD)	ovarian cancer	1	MTD		297	
2016	GOG-0186I	fosbretabulin *	bevacizumab	ovarian cancer	2	PFS	ORR	107	
2015	GOG-0229H	selumetinib		endometrial cancer	2	ORR	PFS, OS	54	
2015	GOG-9920	IP/IV taxol	doxorubicin, carboplatin	endometrial cancer	1	MTD	PFS	21	
2015	GOG-0229N	dalantercept		endometrial cancer	2	T-PFS at 6 mo	ORR	28	
2015	GOG-0229J	cediranib		endometrial cancer	2	ORR	PFS, OS	53	
2015	GOG-0229L	trebananib		endometrial cancer	2	ORR	PFS, OS	32	
2015	GOG-0280	veliparib *		ovarian cancer	2	PFS	OS	50	BRCA
2015	GOG-0250	bevacizumab	gemcitabine and docetaxel	Uterine leiomyosarcoma	3	OS	PFS	107	
2015	GOG-0127W	veliparib	topotecan	cervical cancer	2	PFS		27	
2014	GOG-0076GG	penmetrexed	cisplatin	cervical cancer	2	ORR	PFS, OS	55	
2014	GOG-0240	bevacizumab **	cisplatin/paclitaxel or topotecan/paclitaxel	cervical cancer	3	OS	ORR	452	
2014	GOG-0219	tirapazamine	cisplatin	cervical cancer	3	PFS	OS, tolerability	402	
2014	RTOG 0417	bevacizumab	cisplatin and radiation	cervical cancer	2	OS	LRE, PAF, DE, DFS	49	
2014	GOG-0251	bevacizumab ***		stromal tumors	2	ORR	PFS	36	
2013	GOG-0239	selumetinib		ovarian cancer	2	ORR	PFS	52	
2014	GOG-0170P	Ritolumab (AMG 102)		ovarian cancer	2	ORR	PFS, OS, AE	31	
2014	GOG-0229K	nintedanib		endometrial cancer	2	EFS	AE	37	
2014	GOG-0131H	ixabepilone		recurrent LMS	2	ORR		26	
2014	GOG-0248	temsirolimus	metformin and tamoxifen	endometrial cancer	2	ORR, AE		71	
2013	GOG-0229C	gefitinib		endometrial cancer	2	ORR	PFS, AE	29	

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Public ation year	Trial Number	Drug	Combination	Indication	Ph ase	Endpoint	Secondary	# Pati ents	Biona rker
2013	GOG-0170L	Motesanib		ovarian cancer	2	ORR	PFS, AE	22	
2013	GOG-0229G	bevacizumab	temsirolimus	endometrial cancer	2	ORR		53	
2012	GOG-	Iniparib	paclitaxel and carboplatin	uterine	2	ORR		22	
	0232C			carcinosarcoma					
2012	GOG-0127V	nab-paclitaxel		cervical cancer	2	ORR, PFS, OS		37	
2012	GOG-0229F	affibercept		endometrial cancer	2	PFS	OS	49	
2012	GOG-0126T	belinostat	carboplatin	ovarian cancer	2	ORR	PFS, OS	29	
2012	GOG-0170G	lapatinib		ovarian cancer	2	PFS	ORR	25	
2012	GOG-0170N	urokinase-derived peptide (A6)		ovarian cancer	2	ORR	PFS	31	
2012	GOG-9916	docetaxel	IP carbo, IP taxol	ovarian cancer	1	MTD		40	
2012	GOG-0229D	lapatinib		endometrial cancer	2	PFS	ORR	30	
2012	GOG-0230B	thalidomide		Uterine carcinosarcoma	2	ORR	PFS, OS	45	
2012	GOG-0087M	trabectedin		uterineleiomyosarcoma	2	ORR		20	
2012	GOG-0205	cisplatin weekly ***	radiation	vulvar cancer	2	ORR		58	
2012	GOG-9918	cetuximab	cisplatin and radiation	cervical cancer	1	MTD	ORR	64	
2012	GOG-9910	p53 vaccine		ovarian cancer	2	immune response	PFS, OS	21	
2012	GOG-9913	topotecan	cisplatin and radiation	cervical cancer	1	MTD		11	
2011	GOG-0227E	cetuximab		cervical cancer	2	ORR	PFS, OS	35	
2012	GOG-0170M	dasatinib		ovarian cancer	2	ORR	PFS, OS	34	
2011	GOG-0229E	bevacizumab ***		endometrial cancer	2	PFS, ORR		56	
2011	GOG-0170I	temsirolimus		ovarian cancer	2	PFS	ORR	60	
2011	GOG-0218	bevacizumab	paclitaxel and carboplatin	ovarian cancer	3	PFS	OS	1873	
2011	GOG-0126R	nab-paclitaxel ***		ovarian cancer	2	ORR	PFS	51	
2011	GOG-0188	fulvestrant		endometrial cancer	2	ORR	PFS, OS	67	
2011	GOG-9921	intrapritoneal	cisplatin and paclitaxel	ovarian cancer	1	feasibility		21	
2011	GOG-0076DD	cetuximab	cisplatin	cervical cancer	2	ORR		69	
2011	GOG-9916	paclitaxel	IP carbo, IP taxol	ovarian cancer	1	MTD		90	
2011	GOG-0146Q	topotecan	daily *** vs. weekly	ovarian cancer	2	PFS	OS	80	

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Public ation year	Trial Number	Drug	Combination	Indication	Ph ase	Endpoint	Secondary	# Pati ents	Biona rker
2011	GOG-9915	docetaxel	radiation	ovarian cancer	1	ORR	PFS	13	
2011	GOG-0170F	sorafenib		ovarian cancer	2	PFS		70	
2011	GOG-0186F	trabectedin	docetaxel	ovarian cancer	2	ORR		71	
2011	GOG-0174	weekly methotrexate	vs. pulsed dactinomycin ***	GTN	3	CR		216	
2011	GOG-0129Q	gemcitabine		endometrial cancer	2	ORR	PFS	23	
2011	GOG-0170J	enzastaurin		ovarian cancer	2	ORR, PFS	OS	27	

* ongoing phase 3 study;
** FDA approval;
*** accepted into practice, no FDA label change

Table 3

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Protocol Number	Study Title	Phase	Accrual Target
GOG-0213 (NCT00565851)	A Phase III Randomized Controlled Clinical Trial of Carboplatin and Paclitaxel (or Gemcitabine) Alone or in Combination with Bevacizumab (NSC #704865, IND #113912) Followed by Bevacizumab and Secondary Cytoreductive Surgery in Platinum-Sensitive, Recurrent Ovarian, Peritoneal Primary and Fallopian Tube Cancer. NCI-Supplied Agents: Bevacizumab (NSC #704865, IND #113912)	3	1052
RTOG-0724 (NCT00980954)	Phase III Randomized Study of Concurrent Chemotherapy and Pelvic Radiation Therapy with or without Adjuvant Chemotherapy in High-Risk Patients with Early-Stage Cervical Carcinoma Following Radical Hysterectomy	3	285
GOG-0263 (NCT01101541)	Randomized Phase III Clinical Trial of Adjuvant Radiation Versus Chemoradiation in Intermediate Risk, Stage I/IIA Cervical Cancer Treated with Initial Radical Hysterectomy and Pelvic Lymphadenectomy	3	534
GOG-0264 (NCT01042522)	A Randomized Phase II Trial of Paclitaxel and Carboplatin vs. Bleomycin, Etoposide, and Cisplatin for Newly Diagnosed Advanced Stage and Recurrent Chemo-naïve Sex Cord-Stromal Tumors of the Ovary	2	128
ANZGOG-0902-GOG-0274 (NCT01414608)	A Phase III Trial of Adjuvant Chemotherapy Following Chemoradiation as Primary Treatment for Locally Advanced Cervical Cancer Compared to Chemoradiation Alone: The OUTBACK Trial	3	780
GOG-0270 (NCT01500512)	GROningen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS-V) II: An Observational Study	Other	600
GOG-0277 (NCT01533207)	A Phase III Randomized Trial of Gemcitabine (NSC# 613327) Plus Docetaxel (NSC# 628503) Followed by Doxorubicin (NSC# 123127) Versus Observation for Uterus-Limited, High Grade Uterine Leiomyosarcoma	3	216
GOG-0275 (NCT01535053)	A Phase III Randomized Trial of Pulse Actinomycin-D Versus Multi-Day Methotrexate for the Treatment of Low-Risk Gestational Trophoblastic Neoplasia	3	384
GOG-0281 (NCT02101788)	A Randomized Phase II/III Study to Assess the Efficacy of MEK Inhibitor GSK1120212 in Patients with Recurrent or Progressive Low-Grade Serous Ovarian Cancer or Peritoneal Cancer	2/3	250
GOG-0286B (NCT02065687)	A Randomized Phase II/III Study of Paclitaxel/Carboplatin/Metformin (NSC#91485) Versus Paclitaxel/Carboplatin/Placebo as Initial Therapy for Measurable Stage III or IVA, Stage IVB, or Recurrent Endometrial Cancer	2/3	540
NRG-GY003 (NCT02498600)	Nivolumab with or without Ipilimumab in treating patients with persistent or recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer	2	96
NRG-GY004 (NCT02446600)	A Phase III Study Comparing Single-Agent Olaparib or the Combination of Cediranib and Olaparib to Standard Platinum-Based Chemotherapy in Women with Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	3	450
NRG-GY005 (NCT02502266)	A Randomized Phase II/III Study of the Combination of Cediranib and Olaparib Compared to Cediranib or Olaparib Alone, or Standard of Care Chemotherapy in Women with Recurrent Platinum-Resistant or -Refractory Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (COCOS)	2/3	680
NRG-GY006 (NCT02466971)	A Randomized Phase II Trial of Radiation Therapy and Cisplatin Alone or in Combination with Intravenous Triapine in Women with Newly Diagnosed Bulky Stage IB2, Stage II, IIIB, or IVA Cancer of the Uterine Cervix or Stage II-IVA Vaginal Cancer	2	188

Protocol Number	Study Title	Phase	Accrual Target
NRG-GY007 (NCT02713386)	Ruxolitinib phosphate, Paclitaxel, and Carboplatin in Treating Patients with Stage III-IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	2	162
NRG-GY008 (NCT02728258)	Copanlisib in Treating Patients with Persistent or Recurrent Endometrial Cancer	2	84
NRG-GY009 (NCT02839707)	Pegylated Liposomal Doxorubicin hydrochloride with Atezolizumab and/or Bevacizumab in Treating Patients with Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	2/3	488

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