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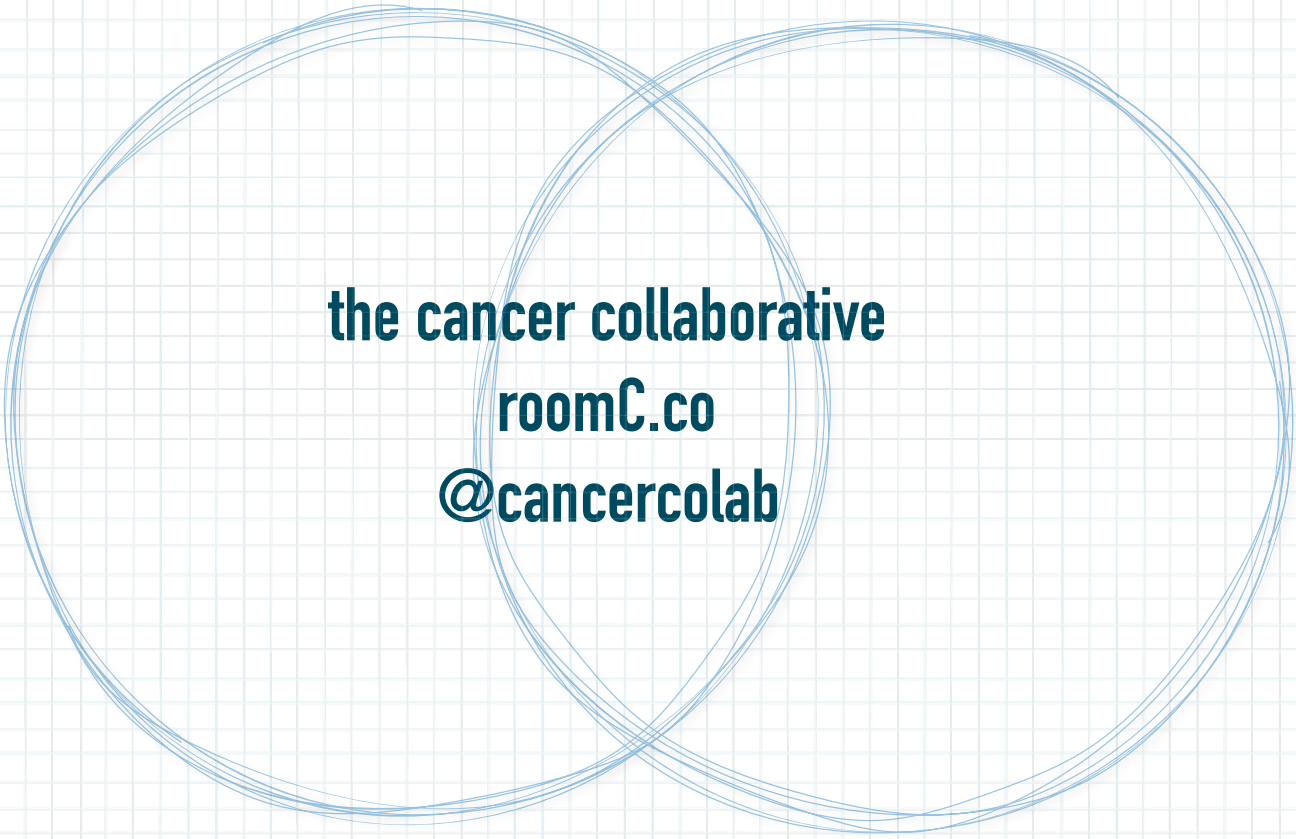
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# table of contents

# caring for every patient. learning from every patient

the theme of this year's ASCO meeting is intended to drive home the message that every patient deserves equal access to the highest quality care and the opportunity to participate in research, and not just some patients but EVERY patient- and to make sure that we, as clinicians, decision makers, payors, advocates and manufacturers use every single opportunity to do better until suffering from cancer is no longer part of our world.

the only way to truly learn from every patient is to engage with patients and each and every encounter with a patient is an opportunity to think about the different interventions, the different services that are necessary and the opportunity to think about how we can do this better for patients, for their families for healthcare systems and ultimately for society.

the ASCO theme should get everyone asking themselves how can we improve patient | scientist | clinician | decision maker collaboration and not only asking how can we learn from every patient, but how do we then translate these learnings so that we can make the greatest impact for patients from improving quality of life, to survivorship, better drug development, better decision making and finally even a cure?

“

what a powerful vehicle for progress we would have if every person challenged by a cancer diagnosis had access to the care that they need.
think about how powerful it would be if every person’s experience could contribute to making a better future.

*monica bertagnolli,*
*ASCO president*
*the presidential address, ASCO 2019*

# breast cancer

## MONALEESA-7 phase III

both peri- and pre-menopausal women with hormone receptor [HR]–positive HER2-negative advanced breast cancer demonstrated an estimated OS rate at 42 months of 70.2% when treated with ribociclib [kisqali] plus endocrine therapy compared with 46.0% for placebo and endocrine therapy. adding ribociclib, a CDK4/6 inhibitor, to endocrine therapy and ovarian suppression in premenopausal hormone receptor positive metastatic breast cancer resulted in a 29% relative reduction in risk of death.

## Young-PEARL phase II

OS now seen in the first-line setting with the addition of CDK4/6, and with endocrine therapy in combination with CDK4/6 showing a 6 month improvement in PFS when compared to chemotherapy [capecitabine]. **these results should be used to ensure that women receive access to CDK4/6 inhibitors up front and their use is not delayed to the second line setting where it is also approved**.

## FAKTION phase II trial

the addition of capivasertib, an AKT inhibitor, to fulvestrant demonstrated a more than doubling in PFS in patients with endocrine receptor positive advanced breast cancer compared to the fulvestrant alone arm. FAKTION tested the addition of capivasertib to fulvestrant for women with hormonally driven metastatic breast cancer. the addition of an AKT inhibitor led to an improvement in PFS of almost 6 months [4.8 vs 10.3 months], and although not statistically significant, a trend to improved survival as well. this leads to the growing body of evidence that inhibiting the PI3K/mTOR/AKT pathway in breast cancer translates to improved outcome. women received benefit regardless of whether they were one of the 40% that had activation in this pathway or not. this is in contrast to the body of data for PI3K inhibitors [such as the recently approved alpelisib] and underscores the importance of biomarker endpoints in trials and continued blood and tissue collection for such assays.

## IMpassion130 phase III

investigators looked at the addition of atezolizumab to nab-paclitaxel in first-line metastatic triple-negative breast cancer [TNBC]. OS update with improvement from 18 months to 25 months in persons with PD-L1–expressing TNBC, supporting the prior FDA accelerated approval. this is a clear standard-of-care option for correctly identified patients. women eligible for atezolizumab can be identified currently

through the use of the SP142 assay. any expression in tumour immune cells qualify women to receive this drug.

### NALA phase III

combining neratinib with capecitabine showed a 24% reduction in the risk of disease progression or death compared with lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer who had previously received two lines of HER2-targeted therapy. the objective response rate [ORR] was 33% in the neratinib arm versus 27% in the lapatinib group. the clinical benefit rate was 45% versus 36%, respectively. fewer patients required intervention for CNS metastases with neratinib plus capecitabine, suggestive of a delay in CNS progression. the trial results suggest that neratinib and capecitabine is an effective option for treating patients with progressive HER2-positive metastatic breast cancer.

## GI cancers

### POLO phase III

randomized, controlled trial compared maintenance olaparib versus placebo in patients with a germline BRCA1or BRCA2 mutation and metastatic pancreatic cancer who initially received first-line, platinum-based chemotherapy. demonstrated that the PARP inhibitor olaparib led to significantly improved PFS in patients with germline BRCA-mutated metastatic pancreatic cancer versus placebo. while OS data were not yet mature, PFS was significantly longer in the olaparib arm [7.4 months vs 3.8 months]. **this study is the first biomarker-driven study in pancreatic cancer.** while it is ultimately useful only for the very small proportion of pancreatic cancer patients with a germline BRCA1or BRCA2 mutation, the median duration of response [DOR] for those patients who received olaparib was about 25 months versus about 4 months for placebo.

**POLO trial marks a major advance for a patient population that has remained a clinical unmet need.** the POLO study ignited debate about the meaning of progression free survival [PFS] versus overall survival [OS], in terms of the ultimate endpoints of longevity and quality of life [QoL]. the trial surfaced a small subset of patients with defects in DNA repair damage pathways on whom the effects of PARP inhibition can be more rigorously studied. the presentation also dove-tailed beautifully with the recent NCCN recommendation that all patients with pancreatic adenocarcinoma should undergo BRCA testing.

## IDEA phase III

prospective, pre-planned pooled analysis, data from patients with high-risk stage II colorectal cancer in 4 concurrently conducted randomized phase III trials were analyzed for an interaction between duration and regimen. patients received investigator's choice of FOLFOX or CAPOX but were randomized to duration of therapy. this study suggested non-inferiority for 3 months versus 6 months of CAPOX, but inferiority of 3 months versus 6 months of FOLFOX. CAPOX for 3 months is likely sufficient for these patients. high-risk stage II disease might be too broad a category and might be a different entity than stage III disease.

## KEYNOTE-062 phase III

patients with PD-L1–positive, HER2-negative, advanced gastric or gastroesophageal junction [G/GEJ] cancer had non-inferior overall survival [OS] with frontline pembrolizumab compared with standard chemotherapy. the PD-1 inhibitor showed a clinically meaningful improvement in OS among patients with tumours that had high levels of PD-L1 expression: at 2 years, 39% of patients in this subgroup were alive versus 22% of those on standard chemotherapy. in addition, the agent showed an improved safety profile compared with chemotherapy. the ORR was higher among those who received pembrolizumab in addition to chemotherapy.

in patients with advanced gastric/gastroesophageal cancer, pembrolizumab should replace chemotherapy in the first-line treatment of this population.GU cancers

## TITAN phase III

patients with metastatic castration-resistant prostate cancer showed an increased rate of OS at 2 years when treated with apalutamide plus androgen deprivation therapy [ADT] versus ADT alone [82.4% vs 73.5%]. TITAN showed that the combination of apalutamide [a second-generation non-steroidal anti-androgen] and ADT improved radiographic PFS compared to ADT alone. the benefit was consistent across treatment subgroups, most importantly the benefit seemed to be the same regardless of volume of disease and prior docetaxel use.

survival was increased in patients with metastatic hormone-sensitive prostate cancer [mHSPC] who were treated with enzalutamide plus standard of care compared to those treated with other non-steroidal anti-androgens plus standard of care. the trial showed that the combination of enzalutamide and ADT improved both clinical PFS. compared to standard non-steroidal anti-androgens (bicalutamide, nilutamide, or dlutamide) and ADT, including in both low- and high-volume disease patients.

**overall, both TITAN and ENZAMET are practice changing phase III randomized, controlled trials which both suggest that the addition of more potent androgen-targeted therapies improves outcomes in patients with mHSPC in both low- and high volume-disease patients.** the role of concurrent docetaxel with apalutamide and enzalutamide needs to be further investigated given the potential for less benefit and more toxicity with such a combination.

EV-201 enfortumab vedotin [EV], an antibody drug conjugate targeting nectin-4, showed very strong data in this phase II trial of patients with advanced urothelial carcinoma. according to the results from cohort 1, the subgroup of patients who had been treated by both platinum-based chemotherapy and immune checkpoint inhibitors, for whom few therapeutic options are currently available, 44% of patients with locally advanced or metastatic urothelial cancer achieved a response with EV. this includes 12% of patients who reached a complete response [CR]. the responses were relatively durable with a median DOR of 7.6 months, median PFS of 5.8 months, and OS of 11.7 months.

these are exciting results for advanced urothelial carcinoma and this agent is currently being investigated in other settings, including combinations and cisplatin-ineligible immune checkpoint-treated patients.

# gynecologic cancers

## SOLO3 phase III

the PARP inhibitor olaparib reduced the risk of disease progression or death by 38% in patients with platinum-sensitive, relapsed, germline BRCA1/2-mutant ovarian cancer who were previously treated with ≥2 prior lines of chemotherapy. compared to chemotherapy, olaparib led to a PFS of 13.4 months versus 9.2 months. by independent review, the ORR was 72% with the PARP inhibitor compared with 51% with chemotherapy. the CR and PR rates were 9% versus 3% and 63% versus 49% with olaparib versus chemotherapy, respectively.

## ENGOT-OV24 phase II

the combination of PARP inhibitor niraparib plus bevacizumab led to a significant increase in PFS versus niraparib alone in patients with platinum-sensitive recurrent ovarian cancer. there is a clear benefit to the addition of an anti-angiogenic to PARP, especially in those patients who do not harbour a BRCAmutation in their tumour. patients who received the combination therapy had a median PFS of 11.9 months versus 5.5 months in those who received niraparib alone. in addition, there was a similar benefit from the combination treatment in patients who had previously received a platinum-free interval [PFI] of 6 to 12 months [11.3 vs 2.2 months], or >12 months [13.1 vs 6.1 months].

# hematologic cancer

## CLL

### CLL14 phase III

venetoclax plus obinutuzumab demonstrated a lengthening in progression-free survival [PFS] time for patients with previously untreated chronic lymphocytic leukemia [CLL] compared with obinutuzumab plus chlorambucil. trial results show that the chemotherapy-free combination reduced the risk for disease worsening or death by 65% compared with obinutuzumab plus chlorambucil. the percentage of patients with PFS at 2 years was significantly higher with the addition of venetoclax to obinutuzumab, compared with chlorambucil [88.2% vs 64.1% ]. median PFS reported by investigators was not yet reached in either arm; however, IRC assessment of PFS was consistent. similarly, the investigators observed this benefit among those with TP53 deletion, mutation, or both and in patients with unmutated immunoglobulin heavy-chain genes. the venetoclax-obinutuzumab group also demonstrated clinical benefit across secondary endpoints, including ORR [84.7% vs 71.3%] CR including incomplete marrow recovery [49.5% vs. 23.1%]; and higher rates of MRD-negativity [56.9% vs. 17.1%] and peripheral blood [75.5% vs. 35.2%] 3 months after treatment. the results of this trial represent a major advance in improving outcomes in chronic lymphocytic leukemia.

## multiple myeloma

### ICARIA-MM phase III

PFS was significantly improved with the triplet regimen of isatuximab, pomalidomide, plus low-dose dexamethasone in patients with relapsed/refractory multiple myeloma compared to pomalidomide with dexamethasone alone. Isatuximab is an anti-CD38 monoclonal antibody. the triplet arm had a near doubling of both ORR and PFS from 35.3% to 60.4% and 6.47 to 11.53 months, respectively. this is the first randomized trial of a pomalidomide/dexamethasone plus an anti-CD38 antibody and may lead to the FDA approval of isatuximab in this combination.

### COLUMBA phase III

a subcutaneous formulation of daratumumab showed similar efficacy to the original intravenous formulation of daratumumab in patients with relapsed/refractory multiple myeloma. there was also a reduction in the treatment burden with the subcutaneous flat dose. this study showed that the subcutaneous route of administration was not inferior to intravenous and greatly reduced administration time from as much as 7 hours to 5 minutes. this should have significant impact for clinic staff and, ultimately, improvement in patients' QoL.

# lung cancer

## IMpower150 phase III

the addition of immunotherapy to bevacizumab and a chemotherapy doublet improved progression-free survival [PFS] in patients with non small cell lung cancer [NSCLC] and baseline liver metastases. the 4-drug combination that included atezolizumab (A) plus bevacizumab, carboplatin, and paclitaxel [BCP] resulted in a median PFS of 8.2 months as compared with 5.4 months for patients treated with BCP alone. median OS was 13.3 months with ABCP and 9.4 with BCP. according to the data, patients with liver metastases had a greater survival benefit with ABCP than did patients without liver metastases. ABCP is an important new treatment option for patients with advanced nonsquamous NSCLC, particularly those with liver metastases.

## GEOMETRY phase II

promising responses have been seen with 2 highly selective, investigational MET inhibitors–tepotinib and capmatinib [INC280]– in both the first- and second-line setting for patients with MET exon 14 [METex14]-altered advanced non-small cell lung cancer [NSCLC]. capmatinib showed an objective response rate [ORR] by independent review [IR] of 67.9% in treatment-naive patients with METex14-altered NSCLC.

## VISION phase II

tepotinib has shown durable clinical activity in patients with NSCLC harbouring METex14 mutations, detected by liquid biopsy or tissue biopsy ORR by IR with tepotinib was 58.8% in untreated patients with NSCLC and an METex14 alteration determined by liquid biopsy. across all lines of treatment, the ORR by IR in liquid biopsy-identified METex14-positive tumours was 50%. by line of therapy, the ORR by IR was 58.8% in the first-line and 53.3% in the second-line in the liquid biopsy-identified patient.

MET exon 14 skipping mutations have been identified in approximately 3-4% of NSCLC cases and are associated with a poor response to currently available therapies. prior studies exploring MET inhibition have primarily examined multikinase inhibitors, such as crizotinib and cabozantinib. both capmatinib and tepotinib are more selective for MET, with IC50 measures of 0.6 nM and 3.0 nM, respectively, as compared with 7.8 nM and 22.5 nM, respectively, for cabozantinib and crizotinib. the FDA has granted designations to help speed up the development of both agents, based on the early promise.

### Lung Cancer Mutation Consortium [LCMC3] phase II

investigators reported that the PD-L1 inhibitor atezolizumab induced a major pathological response [MPR] in 19% of patients and a pathologic complete response [pCR] in 5% of patients in the primary efficacy population who went on to complete surgical resection.

### NEOSTAR phase II

combined MPR and pCR rates in the intention-to-treat [ITT] population were 17% among patients who received nivolumab and 33% in those who took the PD-1 inhibitor plus the CTLA-4 inhibitor ipilimumab. more than 50% of patients with stage I to III resectable NSCLC relapse and perioperative chemotherapy has been associated with an absolute 5-year overall survival benefit of only 5% versus surgery alone. the advantages of administering immune checkpoint inhibitor therapies in the neoadjuvant setting include an opportunity to address micrometastases earlier in the disease process, the potential for increasing patient compliance with systemic therapy, and the use of pCR as an early surrogate for overall survival.

### AMG 510 phase I

half of patients with KRAS G12C–positive advanced non–small cell lung cancer [NSCLC] achieved a response from treatment with the investigational KRAS G12C inhibitor, AMG 510. there are no approved targeted agents for KRAS G12C found in approximately 13% of lung cancers, 3% of colorectal and appendix cancers, and 1% to 3% in other solid tumours. AMG 510 is a novel, first-in-class, small molecule that specifically and irreversibly inhibits KRAS G12C by locking it in an inactive GDP-bound state. all 5 NSCLC patients who achieved a PR are still on treatment. four other patients with NSCLC achieve stable disease. among the NSCLC responders, the duration ranged from 8.4 to 25.1 weeks.

### NCT02454972 phase II basket trial

investigators evaluated the safety and efficacy of lurbinectedin in patients across advanced solid tumours, including SCLC, head and neck cancer, neuroendocrine tumours, biliary tract cancer, endometrial cancer, BRCA1/2-mutant metastatic breast cancer, carcinoma of unknown primary site, germ cell tumours, and ewing's family of tumours. single agent lurbinectedin induced an overall response rate [ORR] of 35.2% in the second-line setting for the treatment of patients with small cell lung cancer [SCL]). lurbinectedin as second-line treatment in SCLC emerges as a new promising drug for this unmet clinical need.

*in August 2018, the FDA granted lurbinectedin an orphan drug designation for the treatment of patients with SCLC. the designation facilitates the development and review of therapies in areas of high unmet medical need.*

# melanoma

## NCT02211131 phase II

according to findings from a randomized trial, neoadjuvant talimogene laherparepvec [T-VEC], an oncolytic immunotherapeutic, led to a significant improvement in the 1-year recurrence free survival rate compared to surgery alone [33.5% vs 21.9%] in patients with resectable advanced melanoma. neoadjuvant immunotherapy resulting in pathologic CR demonstrates an impressive survival benefit compared to neoadjuvant targeted therapy resulting in pathologic CR. these results are intriguing and need further investigation as to the mechanism of pathological CR durability, or lack thereof, with various neoadjuvant approaches.

international neoadjuvant melanoma consortium [INMC] - in a pooled analysis, neoadjuvant immunotherapy and targeted therapy regimens were active in patients with resectable stage III melanoma and were associated with high pathological CR rates. this correlated with improved relapse free survival. although the field has moved onto adjuvant anti–PD-1 therapy, adjuvant ipilimumab with 3 mg/kg may represent an option for local recurrences after adjuvant anti-PD-1 failure.

## COMBI-i

investigational PD-1 inhibitor spartalizumab demonstrated a high rate of complete responses [CR] in combination with dabrafenib and trametinib in patients with previously untreated advanced BRAF V600 mutant melanoma. patients pooled from 2 parts of the 3-part COMBI-i study demonstrated a CR rate of more than 40%. first line treatment with the triplet was associated with an overall response rate [ORR] of 78% by investigator assessment and a CR in 42% at a median follow-up of 19.9 months.

treatment with targeted therapy has improved outcomes in patients with BRAF-mutant, unresectable or metastatic melanoma; however, many patients experience disease progression, and new treatment strategies are needed to further improve their outcomes. combining anti–PD-1 antibodies with BRAF and MEK inhibitors may be able to delay progression in patients with BRAF V600 mutant melanoma, owing to potential synergistic activity between BRAF inhibition and anti–PD-1 therapy.

previous clinical trials have demonstrated improved response rates by adding spartalizumab to dabrafenib and trametinib compared with the doublet without spartalizumab.

### pivotal EMPOWER-CSCC-1 phase II

emiplimab demonstrated substantial antitumour activity and induced durable responses in patients with locally advanced cutaneous squamous cell carcinoma

[CSCC]. objective response rate [ORR] was 43.6%. progression free probability at 12 months was 58.1% and the estimated probability of survival at 12 months was 93.2%. results of the study led to FDA approval of cemiplimab for patients with metastatic CSCC, or those with locally advanced disease who are not candidates for curative surgery or radiation.

## paediatric

### NCT02637687 and NCT02576431

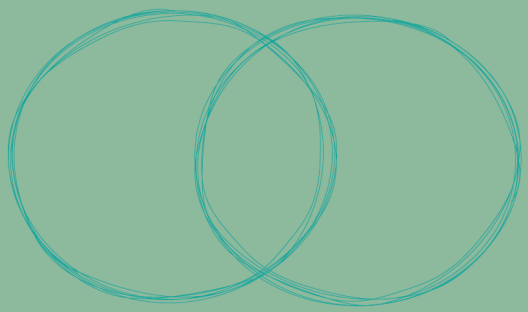
larotrectinib demonstrated efficacy across analyses for both pediatric patients and those with brain metastases or primary central nervous system [CNS] tumours, whether paediatric or adult, with TRK fusions. treatment with larotrectinib at either 100 mg or 150 mg twice daily resulted in an overall response rate [ORR] of 94% in paediatric patients with TRK fusion cancers, and responses were durable. in addition, larotrectinib was well tolerated in the paediatric cancer population.

larotrectinib is FDA approved for the treatment of patients with solid tumours harbuoring NTRK fusions, and exhibits high potency against TRKA, TRKB, and TRKC. TRK fusions are oncogenic drivers.

35% experienced a complete response [CR] to larotrectinib, 59% had a partial response [PR], and [6%] had stable disease. median time to response was about 1.8 months. thirty three patients [87%] remained on treatment or underwent surgery with curative intent.

the study findings expand on those from an earlier dataset of 17 paediatric patients, which showed encouraging anti-tumour activity with larotrectinib, a first-in-class and selective TRK inhibitor.

*based on the recent findings, routing testing for NTRK fusions in paediatric patients is warranted.*



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