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ATR Mutation in Endometrioid Endometrial Cancer Is Associated With Poor Clinical Outcomes . . . Israel Zigelboim, Amy P. Schmidt, Feng Gao, et al pp 3091-3096

Purpose: Mutations in the DNA damage response gene *ATR* (exon 10 A10 mononucleotide repeat) have been previously described in endometrial and other cancers with defective DNA mismatch repair. In vitro studies showed that endometrial cancer cell lines with A10 repeat tract truncating mutations have a failure in the ATR-dependent DNA damage response. Cell lines carrying A10 mutations fail to trigger Chk1 activation in response to ionizing radiation and topoisomerase inhibitors. We sought to determine the frequency and clinicopathologic significance of *ATR* mutations in patients with endometrioid endometrial cancer.

Patients and Methods: The *ATR* exon 10 A10 repeat was analyzed by direct sequencing in 141 tumors with microsatellite instability (MSI-positive) and 107 microsatellite stable (MSI-negative) tumors. The relationships between mutations and clinicopathologic variables, including overall and disease-free survival, were assessed using contingency table tests and Cox proportional hazard models.

Results: *ATR* mutations were identified in 12 cases (4.8%; three cases with insertions and nine cases with deletions). Mutations occurred exclusively in MSI-positive tumors ($P = .02$), with an overall mutation rate of 8.5%. Mutation was not associated with age, race, surgical stage, International Federation of Gynecology and Obstetrics grade, or adjuvant treatment. Multivariate analyses revealed a significant association with reduced overall survival (hazard ratio [HR] = 3.88; 95% CI, 1.64 to 9.18; $P = .002$) and disease-free survival (HR = 4.29; 95% CI, 1.48 to 12.45; $P = .007$).

Conclusion: Truncating *ATR* mutations in endometrial cancers are associated with biologic aggressiveness as evidenced by reduced disease-free and overall survival. Knowledge of *ATR* mutation status may hold promise for individualized treatment and targeted therapies in patients with endometrial cancer.

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Safety and Efficacy of Patupilone in Patients With Advanced Ovarian, Primary Fallopian, or Primary Peritoneal Cancer: A Phase I, Open-Label, Dose-Escalation Study . . . Wim W. ten Bokkel Huinink, Jozef Sufliarsky, Willem M. Smit, et al pp 3097-3103

Purpose: To evaluate the safety, maximum tolerated dose (MTD), and pharmacokinetics of patupilone administered once every 3 weeks with proactive standardized diarrhea management in patients with resistant or refractory ovarian, fallopian, or peritoneal cancer.

Patients and Methods: Patients received patupilone (6.5 to 11.0 mg/m²) every 3 weeks via 20-minute infusion. Adverse events, dose-limiting toxicities (DLT), MTD, and tumor response were determined. The tumor response was measured by Response Evaluation Criteria in Solid Tumors (RECIST) and cancer antigen 125 levels.

Results: Forty-five patients were enrolled. Adverse events were mild to moderate in intensity, and grade 3 diarrhea (13%) was the most commonly reported serious adverse event. Grade 3 peripheral neuropathy was noted in two patients (4%). Diarrhea, peripheral neuropathy, and fatigue were the most common DLTs; however, these were uncommon in the first cycle and the MTD was therefore not reached in this study. Overall response (OR; complete and partial responses; median cycles, 8) per RECIST in patients with measurable disease ($n = 36$) was 19.5%. Median duration of disease stabilization (complete and partial responses and stable disease) was 15.8 months. These results appear improved from a previous study in a similar patient population using a weekly schedule (2.5 mg/m²/week; $N = 53$; OR, 5.7%).

Conclusion: Patupilone once every 3 weeks was well-tolerated at doses up to 11.0 mg/m². Patupilone demonstrated promising antitumor activity in patients with drug-resistant/refractory disease. An ongoing phase III study in this patient population is testing the 10.0 mg/m² dose.

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Phase II Trial of Ixabepilone As Second-Line Treatment in Advanced Endometrial Cancer: Gynecologic Oncology Group Trial 129-P . . . Don S. Dizon, John A. Blessing, D. Scott McMeekin, et al pp 3104-3108

Purpose: A phase II study was conducted to determine the response rate of ixabepilone (BMS-247550, National Cancer Institute (NCI)-supplied agent investigational new drug No. 59,699) in patients with persistent or recurrent endometrial cancer who have progressed despite standard therapy.

Patients and Methods: Eligible patients had recurrent or persistent endometrial cancer and measurable disease. One prior chemotherapeutic regimen, which could have included either paclitaxel or docetaxel, was allowed. Patients received ixabepilone 40 mg/m² as a 3-hour infusion on day 1 of a 21-day cycle. Treatment was continued until disease progression or until unacceptable toxicity occurred.

Results: Fifty-two patients were entered on the study, and 50 of these were eligible. The median age was 64 years (range, 40 to 83 years). Prior treatment included radiation in 21 patients (42%) and hormonal therapy in eight patients (16%). All patients had prior chemotherapy, and 47 (94%) received prior paclitaxel therapy. The overall response rate was 12%; one patient achieved a complete remission (2%), and five achieved partial remission (10%). Stable disease for at least 8 weeks was noted in 30 patients (60%). The median progression-free survival (PFS) was 2.9 months, and the 6-month PFS was 20%. Major grade 3 toxicities were neutropenia (52%), leukopenia (48%), gastrointestinal (24%), neurologic (18%), constitutional (20%), infection (16%), and anemia (14%).

Conclusion: In a cohort of women with advanced or recurrent endometrial cancer who were previously treated with paclitaxel, ixabepilone showed modest activity of limited duration as a second-line agent.

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Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial . . . *Thierry André, Corrado Boni, Matilde Navarro, et al* pp 3109-3116

Purpose: Three-year disease-free survival (DFS) was significantly improved in patients who had undergone resection with curative intent for stage II or III colon cancer who received bolus plus continuous-infusion fluorouracil plus leucovorin (LV5FU2) with the addition of oxaliplatin (FOLFOX4). Final results of the study, including 6-year overall survival (OS) and 5-year updated DFS, are reported.

Patients and Methods: A total of 2,246 patients were randomly assigned to receive LV5FU2 or FOLFOX4 for 6 months. The primary end point was DFS. Secondary end points were OS and safety.

Results: Five-year DFS rates were 73.3% and 67.4% in the FOLFOX4 and LV5FU2 groups, respectively (hazard ratio [HR] = 0.80; 95% CI, 0.68 to 0.93; $P = .003$). Six-year OS rates were 78.5% and 76.0% in the FOLFOX4 and LV5FU2 groups, respectively (HR = 0.84; 95% CI, 0.71 to 1.00; $P = .046$); corresponding 6-year OS rates for patients with stage III disease were 72.9% and 68.7%, respectively (HR = 0.80; 95% CI, 0.65 to 0.97; $P = .023$). No difference in OS was seen in the stage II population. The incidence of second noncolorectal cancers was 5.5% and 6.1% in the FOLFOX4 and LV5FU2 groups, respectively. Among patients receiving oxaliplatin, the frequency of grade 3 peripheral sensory neuropathy was 1.3% 12 months after treatment and 0.7% at 48 months.

Conclusion: Adding oxaliplatin to LV5FU2 significantly improved 5-year DFS and 6-year OS in the adjuvant treatment of stage II or III colon cancer and should be considered after surgery for patients with stage III disease.

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Randomized Phase III Trial Comparing Biweekly Infusional Fluorouracil/Leucovorin Alone or With Irinotecan in the Adjuvant Treatment of Stage III Colon Cancer: PETACC-3 . . . *Eric Van Cutsem, Roberto Labianca, György Bodoky, et al* pp 3117-3125

Purpose: The primary objective of this randomized, multicenter, phase III trial was to investigate whether the addition of irinotecan to the de Gramont infusional fluorouracil (FU)/leucovorin (LV) adjuvant regimen (LV5FU2) would improve disease-free survival (DFS) in patients with stage III colon cancer.

Patients and Methods: After curatively intentioned surgery, patients with stage II and III colon cancer were randomly allocated surgery to receive LV5FU2 (LV 200 mg/m² as a 2-hour infusion, followed by FU; as a 400 mg/m² bolus and then a 600 mg/m² continuous infusion over 22 hours, days 1 and 2, every 2 weeks for 12 cycles: de Gramont regimen) with or without irinotecan (180 mg/m² as a 30- to 90-minute infusion, day 1, every 2 weeks). In total, 260 (7.9%) of 3,278 patients received an alternative high-dose infusional FU/LV regimen (Arbeitsgemeinschaft Internische Onkologie regimen) with or without irinotecan.

Results: The principal efficacy analysis was based on 2,094 treated patients with stage III disease, randomly allocated in the LV5FU2 strata. After a median follow-up of 66.3 months, the 5-year DFS rate was 56.7% with irinotecan/LV5FU2 and 54.3% with LV5FU2 alone (primary end point: log-rank $P = .106$). Combining irinotecan with LV5FU2 did not significantly improve overall survival in this patient group compared with LV5FU2 alone (5-year rate 73.6% v 71.3%, respectively; log-rank $P = .094$). The addition of irinotecan to LV5FU2 was associated with an increased incidence of grade 3 to 4 GI events and neutropenia.

Conclusion: Irinotecan added to LV5FU2 as adjuvant therapy did not confer a statistically significant improvement in DFS or overall survival in patients with stage III colon cancer compared with LV5FU2 alone.

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Pazopanib, a Multikinase Angiogenesis Inhibitor, in Patients With Relapsed or Refractory Advanced Soft Tissue Sarcoma: A Phase II Study From the European Organisation for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group (EORTC Study 62043) . . . *Stefan Sleijfer, Isabelle Ray-Coquard, Zsuzsa Papp, et al* pp 3126-3132

Purpose: Given the importance of angiogenesis in soft tissue sarcoma (STS), pazopanib, an oral angiogenesis inhibitor that targets vascular endothelial growth factor receptor and platelet-derived growth factor receptor, was explored in patients with advanced STS.

Patients and Methods: Patients with intermediate- or high-grade advanced STS who were ineligible for chemotherapy or who had received no more than two prior cytotoxic agents for advanced disease, who had documented progression, who had adequate performance status, and who had good organ function were eligible. Pazopanib 800 mg was given daily. The primary end point was progression-free rate at 12 weeks (PFR_{12 weeks}). Secondary end points were response, safety, and overall survival. Four different strata were studied: adipocytic STS, leiomyosarcomas, synovial sarcomas, and other STS types. A Simon two-stage design was applied (P1 = 40%; P0 = 20%; $\alpha = \beta = .1$) for each stratum.

Results: One hundred forty-two patients were enrolled. The adipocytic STS stratum was closed after the first stage, given insufficient activity (PFR_{12 weeks} five [26%] of 19). PFR_{12 weeks} was 18 (44%) of 41 patients in the leiomyosarcoma cohort, 18 (49%) of 37 in the synovial sarcomas, and 16 (39%) of 41 in the other STS types. Compared with historical controls who were treated with second-line chemotherapy, progression-free and overall survivals were prolonged in the three cohorts in which the primary end point was reached. The most frequent drug-related toxicities were hypertension, fatigue, hypopigmentation, and nausea. Other toxicities included liver enzyme elevations, myelosuppression, and proteinuria, all of which were mostly grades 1 to 2. The most frequent grades 3 to 4 toxicities were hyperbilirubinemia (6.3%), hypertension (7.7%), and fatigue (7.7%).

Conclusion: Pazopanib is well tolerated in patients with relapsed, advanced STS and demonstrates interesting activity that warrants additional study in patients with leiomyosarcomas, synovial sarcomas, and other STS types.

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Phase II Study of Sorafenib in Patients With Metastatic or Recurrent Sarcomas . . . Robert G. Maki, David R. D'Adamo, Mary L. Keohan, et al pp 3133-3140

Purpose: Since activity of sorafenib was observed in sarcoma patients in a phase I study, we performed a multicenter phase II study of daily oral sorafenib in patients with recurrent or metastatic sarcoma.

Patients and Methods: We employed a multiarm study design, each representing a sarcoma subtype with its own Simon optimal two-stage design. In each arm, 12 patients who received 0 to 1 prior lines of therapy were treated (0 to 3 for angiosarcoma and malignant peripheral-nerve sheath tumor). If at least one Response Evaluation Criteria in Solid Tumors (RECIST) was observed, 25 further patients with that sarcoma subtype were accrued.

Results: Between October 2005 and November 2007, 145 patients were treated; 144 were eligible for toxicity and 122 for response. Median age was 55 years; female-male ratio was 1.8:1. The median number of cycles was 3. Five of 37 patients with angiosarcoma had a partial response (response rate, 14%). This was the only arm to meet the RECIST response rate primary end point. Median progression-free survival was 3.2 months; median overall survival was 14.3 months. Adverse events (typically dermatological) necessitated dose reduction for 61% of patients. Statistical modeling in this limited patient cohort indicated sorafenib toxicity was correlated inversely to patient height. There was no correlation between phosphorylated extracellular signal regulated kinase expression and response in six patients with angiosarcoma with paired pre- and post-therapy biopsies.

Conclusion: As a single agent, sorafenib has activity against angiosarcoma and minimal activity against other sarcomas. Further evaluation of sorafenib in these and possibly other sarcoma subtypes appears warranted, presumably in combination with cytotoxic or kinase-specific agents. *J Clin Oncol* 27:3133-3140. © 2009 by American Society of Clinical Oncology

Imatinib Plasma Levels Are Correlated With Clinical Benefit in Patients With Unresectable/Metastatic Gastrointestinal Stromal Tumors . . . George D. Demetri, Yanfeng Wang, Elisabeth Wehrle, et al pp 3141-3147

Purpose: To study the pharmacokinetics (PK) of imatinib (IM) in patients with advanced GI stromal tumors (GISTs) treated in a randomized phase II study and to explore the potential relationship between IM plasma levels and long-term clinical outcomes.

Patients and Methods: Patients were randomly assigned to receive IM at 400 mg versus 600 mg daily. IM plasma levels were analyzed in a subset of patients (n = 73) for whom PK data on day 1 and at steady-state (SS, day 29) were available. IM PK was evaluated using a population PK approach. The relationship between IM plasma exposure and clinical outcome was explored by grouping patients into quartiles according to IM trough concentration (C_{min}). The clinical outcome parameters evaluated include overall objective benefit rate (OOBR; complete response plus partial response plus stable disease) time to progression (TTP), and *KIT* genotyping.

Results: IM PK exposure showed a high inter-patient variability, and clinical outcomes were correlated with IM trough levels at SS. The median TTP was 11.3 months for patients in the lowest C_{min} quartile (Q1, < 1,110 ng/mL) compared with more than 30 months for Q2 to Q4 ($P = .0029$). OOBR was also inferior in Q1 patients. In patients with GIST with *KIT* exon 11 mutations (n = 39), the OOBR was 67% for Q1 patients versus 100% for all others ($P = .001$).

Conclusion: In patients with advanced GIST, IM trough levels at SS were associated with clinical benefit. Patients with IM C_{min} below 1,100 ng/mL showed a shorter TTP and lower rate of clinical benefit (OOBR). Further studies are justified to test whether monitoring IM plasma levels might optimize clinical outcomes for patients with GIST.

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Phase II Multicenter Trial of Imatinib in 10 Histologic Subtypes of Sarcoma Using a Bayesian Hierarchical Statistical Model . . . Rashmi Chugh, J. Kyle Wathen, Robert G. Maki, et al pp 3148-3153

Purpose: The purpose of this trial was to assess the efficacy of imatinib in patients with one of 10 different subtypes of advanced sarcoma.

Patients and Methods: Eligible patients were treated daily with imatinib dosed at 300 mg twice a day (for body-surface area ≥ 1.5 m²). The primary end point was response (clinical benefit response [CBR]), defined as complete (CR) or partial response (PR) at 2 months, or stable disease, CR, or PR at 4 months. Rules for early termination within each disease type were based on a Bayesian hierarchical probability model (BHM) accounting for correlation of the responses of the 10 subtypes. Available tissue samples were analyzed for molecules within the KIT/platelet-derived growth factor receptor (PDGFR) signal transduction pathway.

Results: One hundred eighty-five assessable patients with one of 10 subtypes of sarcoma were treated. One CR and three PRs were achieved. A CBR was achieved in 28 patients treated overall and by subtype: two angiosarcomas (n = 16), 0 Ewing (n = 13), one fibrosarcoma (n = 12), six leiomyosarcomas (n = 29), seven liposarcomas (n = 31), three malignant fibrous histiocytomas (n = 30), five osteosarcomas (n = 27), one malignant peripheral-nerve sheath tumor (n = 7), 0 rhabdomyosarcoma (n = 2), and three synovial sarcomas (n = 22). Variable expression and mutations within the KIT/PDGFR pathway were observed.

Conclusion: This is the first phase II study of a new agent in sarcoma to include sufficient patients with each of the common histologic subtypes to permit generalizable conclusions. The BHM is an effective method for studying rare diseases and their subtypes, when it is reasonable to assume that their response rates are exchangeable. Although rare dramatic responses were seen, imatinib is not an active agent in advanced sarcoma in these subtypes.

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MDM2 and Ki-67 Predict for Distant Metastasis and Mortality in Men Treated With Radiotherapy and Androgen Deprivation for Prostate Cancer: RTOG 92-02 . . . Li-Yan Khor, Kyoung-hwa Bae, Rebecca Paulus, et al pp 3177-3184

Purpose: MDM2 regulates p53, which controls cell cycle arrest and apoptosis. Both proteins, along with Ki-67, which is an established strong determinant of metastasis, have shown promise in predicting the outcome of men treated with radiation therapy (RT) with or without short-term androgen deprivation (STAD). This report compares the utility of abnormal expression of these biomarkers in estimating progression in a cohort of men treated on RTOG 92-02.

Patients and Methods: Adequate tissue for immunohistochemistry was available for p53, Ki-67, and MDM2 analyses in 478 patient cases. The percentage of tumor nuclei staining positive (PSP) was quantified manually or by image analysis, and the per-sample mean intensity score (MIS) was quantified by image analysis. Cox regression models were used to estimate overall mortality (OM), and Fine and Gray's regressions were applied to the end points of distant metastasis (DM) and cause-specific mortality (CSM).

Results: In multivariate analyses that adjusted for all markers and treatment covariates, MDM2 overexpression was significantly related to DM ($P = .02$) and OM ($P = .003$), and Ki-67 overexpression was significantly related to DM ($P < .0001$), CSM ($P = .0007$), and OM ($P = .01$). P53 overexpression was significantly related to OM ($P = .02$). When considered in combination, the overexpression of both Ki-67 and MDM2 at high levels was associated with significantly increased failure rates for all end points ($P < .001$ for DM, CSM, and OM).

Conclusion: Combined MDM2 and Ki-67 expression levels were independently related to distant metastasis and mortality and, if validated, could be considered for risk stratification of patients with prostate cancer in clinical trials.

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Genomic Grade Index Is Associated With Response to Chemotherapy in Patients With Breast Cancer . . . Cornelia Liedtke, Christos Hatzis, William Fraser Symmans, et al pp 3185-3191

Purpose: The genomic grade index (GGI) is a 97-gene measure of histological tumor grade. High GGI is associated with decreased relapse-free survival in patients receiving either endocrine or no systemic adjuvant therapy. Herein we examined whether GGI predicts pathologic response to neoadjuvant chemotherapy in patients with HER-2-normal breast cancer.

Methods: Gene expression data (gene chips) was generated from fine-needle aspiration biopsies ($n = 229$) prospectively collected before neoadjuvant paclitaxel, fluorouracil, doxorubicin, and cyclophosphamide chemotherapy. Pathologic response was quantified using the residual cancer burden (RCB) method. The association between the GGI and pathologic response was assessed in univariate and multivariate analyses. The performance of a response predictor combining clinical variables and GGI was evaluated under cross-validation.

Results: Eighty-five percent of grade 1 tumors had low GGI, 89% of grade 3 tumors had high GGI, and 63% of grade 2 tumors had low GGI. Among both estrogen receptor (ER)-positive and -negative cancers, high GGI score was associated with pathologic complete response (RCB-0) or minimal residual disease (RCB-1). A multivariate model combining GGI and clinical parameters had an overall accuracy of 71%, compared with 58% for the GGI alone, for prediction of pathologic response. However, high GGI score was also associated with significantly worse distant relapse-free survival in patients with ER-positive cancer ($P = .005$), and was not associated with survival in patients with ER-negative cancer.

Conclusion: High GGI is associated with increased sensitivity to neoadjuvant paclitaxel plus fluorouracil, adriamycin, and cyclophosphamide chemotherapy in both ER-negative and ER-positive patients, but it remains a predictor of worse survival in ER-positive patients.

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Endocrine Effects of Adjuvant Letrozole Compared With Tamoxifen in Hormone-Responsive Postmenopausal Patients With Early Breast Cancer: The HOBEO Trial . . . Emanuela Rossi, Alessandro Morabito, Francesca Di Rella, et al pp 3192-3197

Purpose: We compared the endocrine effects of 6 and 12 months of adjuvant letrozole versus tamoxifen in postmenopausal patients with hormone-responsive early breast cancer within an ongoing phase III trial.

Patients and Methods: Patients were randomly assigned to receive tamoxifen, letrozole, or letrozole plus zoledronic acid. Serum values of estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, dehydroepiandrosterone-sulphate (DHEA-S), progesterone, and cortisol were measured at baseline and after 6 and 12 months of treatment. For each hormone, changes from baseline at 6 and 12 months were compared between treatment groups, and differences over time for each group were analyzed.

Results: Hormonal data were available for 139 postmenopausal patients with a median age of 62 years, with 43 patients assigned to tamoxifen and 96 patients assigned to letrozole alone or combined with zoledronic acid. Baseline values were similar between the two groups for all hormones. Many significant changes were observed between drugs and for each drug over time. Namely, three hormones seemed significantly affected by one drug only: estradiol that decreased and progesterone that increased with letrozole and cortisol that increased with tamoxifen. Both drugs affected FSH (decreasing with tamoxifen and slightly increasing with letrozole), LH (decreasing more with tamoxifen than with letrozole), testosterone (slightly increasing with letrozole but not enough to differ from tamoxifen), and DHEA-S (increasing with both drugs but not differently between them). Zoledronic acid did not have significant impact on hormonal levels.

Conclusion: Adjuvant letrozole and tamoxifen result in significantly distinct endocrine effects. Such differences can explain the higher efficacy of letrozole as compared with tamoxifen.

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Prognostic Importance of *MN1* Transcript Levels, and Biologic Insights From *MN1*-Associated Gene and MicroRNA Expression Signatures in Cytogenetically Normal Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study

Christian Langer, Guido Marcucci, Kelsi B. Holland, et al pp 3198-3204

Purpose: To determine the prognostic importance of the meninoma 1 (*MN1*) gene expression levels in the context of other predictive molecular markers, and to derive *MN1* associated gene- and microRNA-expression profiles in cytogenetically normal acute myeloid leukemia (CN-AML).

Patients and Methods: *MN1* expression was measured in 119 untreated primary CN-AML adults younger than 60 years by real-time reverse-transcriptase polymerase chain reaction. Patients were also tested for *FLT3*, *NPM1*, *CEBPA*, and *WT1* mutations, *MLL* partial tandem duplications, and *BAALC* and *ERG* expression. Gene- and microRNA-expression profiles were attained by performing genome-wide microarray assays. Patients were intensively treated on two first-line Cancer and Leukemia Group B clinical trials.

Results: Higher *MN1* expression associated with *NPM1* wild-type ($P < .001$), increased *BAALC* expression ($P = .004$), and less extramedullary involvement ($P = .01$). In multivariable analyses, higher *MN1* expression associated with a lower complete remission rate ($P = .005$) after adjustment for WBC; shorter disease-free survival ($P = .01$) after adjustment for *WT1* mutations, *FLT3* internal tandem duplications (*FLT3*-ITD), and high *ERG* expression; and shorter survival ($P = .04$) after adjustment for *WT1* and *NPM1* mutations, *FLT3*-ITD, and WBC. Gene- and microRNA-expression profiles suggested that high *MN1* expressers share features with high *BAALC* expressers and patients with wild-type *NPM1*. Higher *MN1* expression also appears to be associated with genes and microRNAs that are active in aberrant macrophage/monocytoid function and differentiation.

Conclusion: *MN1* expression independently predicts outcome in CN-AML patients. The *MN1* gene- and microRNA-expression signatures suggest biologic features that could be exploited as therapeutic targets.

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Evaluation of the Optimal Number of Lesions Needed for Tumor Evaluation Using the Response Evaluation Criteria in Solid Tumors: A North Central Cancer Treatment Group Investigation . . . Shauna L. Hillman, Ming-Wen An,

Michael J. O'Connell, et al pp 3205-3210

Purpose: In February 2000, the criteria for measuring tumor shrinkage as an indicator of antitumor activity were redefined by the Response Evaluation Criteria in Solid Tumors (RECIST). This resulted in simplifying bidimensional to unidimensional measurement of lesions. Under RECIST, all lesions, up to 10, must be measured. Scanning and measuring multiple lesions is costly, time-consuming, and a disincentive to participation in clinical trials. We investigated whether fewer than 10 lesions can be measured without compromising the accuracy of assessing a regimen's activity.

Patients and Methods: Thirty-two North Central Cancer Treatment Group trials including 2,374 patients were analyzed. Twelve studies were conducted before RECIST; 20 were conducted post-RECIST. Agreement between objective status by cycle, confirmed response, overall response rate, and time to progression (TTP) was evaluated based on all 10 versus the largest one through five lesions.

Results: The median number of lesions reported on RECIST trials did not differ from pre-RECIST trials (median = 2.0). One lesion at baseline was reported in 49% of patients, two lesions in 28% of patients, three lesions in 12% of patients, four lesions in 6% of patients, and five lesions in 5% of patients in post-RECIST trials. Utilizing the largest two lesions produced excellent concordance with that using all lesions for all end points. In no trial did the overall response rate differ by more than 3% when two versus all lesions were considered. Evaluating more than two lesions did not significantly improve agreement.

Conclusion: Based on these trials, the assessment of more than two lesions did not alter the conclusions regarding a treatment's efficacy as judged by response rate or TTP.

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Adherence to Long-Term Surveillance Mammography Among Women With Ductal Carcinoma In Situ Treated With Breast-Conserving Surgery . . . Larissa Nekhlyudov, Laurel A. Habel, Ninah S. Achacoso, et al pp 3211-3216

Purpose: Breast-conserving surgery (BCS) is an effective treatment for ductal carcinoma in situ (DCIS) but women who undergo BCS remain at risk for recurrences. Whether mammographic surveillance after BCS occurs and by whom is not known.

Methods: We reviewed medical records of women diagnosed with DCIS between 1990 and 2001 and treated with BCS. Using descriptive statistics, generalized estimating, and logistic regression modeling, we examined the rates and predictors of surveillance mammography over a 10-year period after BCS.

Results: The cohort included 3,037 women observed for a median of 4.8 years (range, 0.5 to 15.7). Of the 2,676 women observed for at least 1 year after BCS, most (79%) had at least one surveillance mammogram during the first year of follow-up; 69% in year 5 and 61% in year 10. Among those observed for 5 years, surveillance mammograms were more likely among women age 60 to 69 years (odds ratio [OR], 1.72; 95% CI, 1.26 to 2.34), users of menopausal hormone therapy at diagnosis (OR, 1.26; 95% CI, 1.01 to 1.57) as well as those treated with adjuvant radiation (OR, 1.28; 95% CI, 1.08 to 1.53) and adjuvant radiation with tamoxifen (OR, 1.61; 95% CI, 1.13 to 2.30). Surveillance mammograms were less likely among obese women (OR, 0.70; 95% CI, 0.56 to 0.86). The findings were similar among women observed for 10 years. Only 34% and 15% of women observed for 5 and 10 years, respectively, had a surveillance mammogram during each year of follow-up.

Conclusion: Surveillance mammography after BCS among insured women with DCIS often did not occur yearly and declined over time after treatment. Patients and providers must remain vigilant about surveillance after BCS.

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Phase III Study by the Norwegian Lung Cancer Study Group: Pemetrexed Plus Carboplatin Compared With Gemcitabine Plus Carboplatin As First-Line Chemotherapy in Advanced Non-Small-Cell Lung Cancer. . . Bjørn H. Grønberg, Roy M. Bremnes, Øystein Flotten, et al pp 3217-3224

Purpose: To compare pemetrexed/carboplatin with a standard regimen as first-line therapy in advanced non-small-cell lung cancer NSCLC.

Patients and Methods: Patients with stage IIIB or IV NSCLC and performance status of 0 to 2 were randomly assigned to receive pemetrexed 500 mg/m² plus carboplatin area under the curve (AUC) = 5 (Calvert's formula) on day 1 or gemcitabine 1,000 mg/m² on days 1 and 8 plus carboplatin AUC = 5 on day 1 every 3 weeks for up to four cycles. The primary end point was health-related quality of life (HRQoL) defined as global quality of life, nausea/vomiting, dyspnea, and fatigue reported on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and the lung cancer-specific module LC13 during the first 20 weeks. Secondary end points were overall survival and toxicity.

Results: Four hundred thirty-six eligible patients were enrolled from April 2005 to July 2006. Patients who completed the baseline questionnaire were analyzed for HRQoL (n = 427), and those who received ≥ one cycle of chemotherapy were analyzed for toxicity (n = 423). Compliance of HRQoL questionnaires was 87%. There were no significant differences for the primary HRQoL end points or in overall survival between the two treatment arms (pemetrexed/carboplatin, 7.3 months; gemcitabine/carboplatin, 7.0 months; *P* = .63). The patients who received gemcitabine/carboplatin had more grade 3 to 4 hematologic toxicity than patients who received pemetrexed/carboplatin, including leukopenia (46% v 23%, respectively; *P* < .001), neutropenia (51% v 40%, respectively; *P* = .024), and thrombocytopenia (56% v 24%, respectively; *P* < .001). More patients on the gemcitabine/carboplatin arm received transfusions of RBCs and platelets, whereas the frequencies of neutropenic infections and thrombocytopenic bleedings were similar on both arms.

Conclusion: Pemetrexed/carboplatin provides similar HRQoL and survival when compared with gemcitabine/carboplatin with less hematologic toxicity and less need for supportive care.

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Metastatic Renal Cell Carcinoma: Many Treatment Options, One Patient . . . Brian I. Rini pp 3225-3234

There has been a recent expansion of therapeutic options in metastatic renal cell carcinoma (RCC) targeted at the vascular endothelial growth factor and mammalian target of rapamycin pathways, which are fundamental to the biology of RCC. These treatment options have similarities in antitumor effect but also important differences in regards to clinical effects, toxicity and patient populations in which they have been investigated. Further, issues regarding the role of debulking nephrectomy, timing of therapy, and appropriate sequencing of agents have emerged as clinically relevant. There are thus potentially many different treatment approaches to each metastatic RCC patient. This review discusses how to integrate the available data regarding targeted therapy in metastatic RCC into personalized cancer care.

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American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction . . . Kala Visvanathan,

Rowan T. Chlebowski, Patricia Hurley, et al pp 3235-3258

Purpose: To update the 2002 American Society of Clinical Oncology guideline on pharmacologic interventions for breast cancer (BC) risk reduction.

Methods: A literature search identified relevant randomized trials published since 2002. Primary outcome of interest was BC incidence (invasive and noninvasive). Secondary outcomes included BC mortality, adverse events, and net health benefits. An expert panel reviewed the literature and developed updated consensus guidelines.

Results: Seventeen articles met inclusion criteria. In premenopausal women, tamoxifen for 5 years reduces the risk of BC for at least 10 years, particularly estrogen receptor (ER) –positive invasive tumors. Women ≤ 50 years of age experience fewer serious side effects. Vascular and vasomotor events do not persist post-treatment across all ages. In postmenopausal women, raloxifene and tamoxifen reduce the risk of ER-positive invasive BC with equal efficacy. Raloxifene is associated with a lower risk of thromboembolic disease, benign uterine conditions, and cataracts than tamoxifen in postmenopausal women. No evidence exists establishing whether a reduction in BC risk from either agent translates into reduced BC mortality.

Recommendations: In women at increased risk for BC, tamoxifen (20 mg/d for 5 years) may be offered to reduce the risk of invasive ER-positive BC, with benefits for at least 10 years. In postmenopausal women, raloxifene (60 mg/d for 5 years) may also be considered. Use of aromatase inhibitors, fenretinide, or other selective estrogen receptor modulators to lower BC risk is not recommended outside of a clinical trial. Discussion of risks and benefits of preventive agents by health providers is critical to patient decision making.

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