MY CANCER GENOME™

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In This Issue

New Articles of Interest

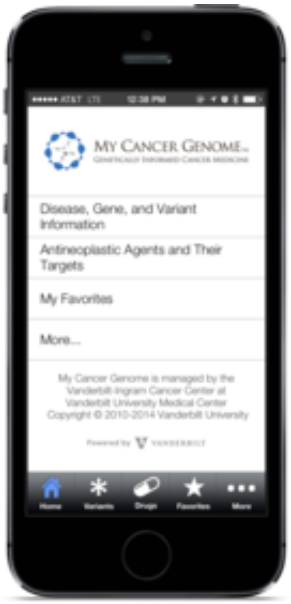
Ignatius Ou, et al. Next-generation sequencing reveals a novel NSCLC ALK F1174V mutation and confirms ALK G1202R mutation confers high-level resistance to alectinib (CH5424802/RO5424802) in ALK-rearranged NSCLC patients who progressed on crizotinib. J Thorac Oncol 2014 Apr;9(4):549-53

Imielinski M, et al. Oncogenic and sorafenib-sensitive ARAF mutations in lung adenocarcinoma. J. Clin. Invest. 2014 Apr 1;124(4):1582-6

Newsletter-Related Content on MCG.org

ESR1 in Breast Cancer

My Cancer Genome Launches Expanded Mobile App



My Cancer Genome has released an expanded mobile app with searchable, regularly updated information from the My Cancer Genome website about genetically informed cancer medicine. The content includes information about cancer types, cancer-related genes, and specific cancer-related genetic mutations. This app expands the information about anticancer agents and targeted therapies available in the MCG Drug List app that was released in June 2013. Content in the My Cancer Genome website and mobile application is provided and updated by physicians and physician–scientists from 22 institutions in 10 countries, and covers several hundred mutations in 19 cancer types. Features of the mobile app include saving favorite searches and pages of interest to keep up to date when the pages are updated. The app also allows the user to search for content related to cancer mutations that may be relevent to several different cancer types. Read more in the Vanderbilt Reporter.

The My Cancer Genome Mobile App is free and available for iPhone and iPad through the iTunes mobile app store.

Content Update Highlight: ESR1 Mutations in Breast Cancer

Expression of the estrogen receptor is predictive for response to therapy and prognostic for survival outcomes in breast cancer patients. However, until recently, *ESR1* mutations were not known to be important in breast cancer because they were not detected in large studies of primary (untreated) breast cancer. In the past year, several different point mutations in the ligand-binding domain of *ESR1* have been identified in retrospective studies in tumor samples

Anticancer Agents

ALK in Non-Small Cell Lung Cancer (NSCLC)

Clinical Trial Search

ALK-Associated Lung Cancer Clinical Trials

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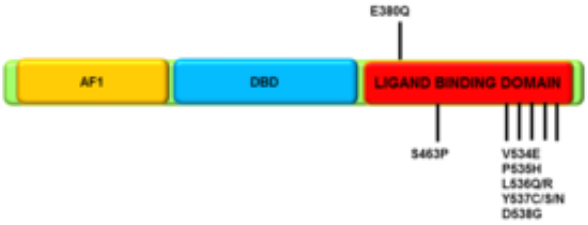
from patients with ER-positive metastatic breast cancer resistant to treatment with antiestrogen therapy.



Thirty-six patient cases with ER-positive breast cancer and one or two *ESR1* mutations have now been described in six studies, with rates in ER-positive treatment-resistant patient case sets ranging from 12-55%. Preclinical studies have supported that the *ESR1* mutations confer constitutive ligand-independent activation of ER transcription and ERα. The breast cancer section of My Cancer Genome has been updated with a new page "ESR1 mutations associated with acquired resistance to antiestrogen therapy."

Content Update Highlight: Recent FDA Approvals

The FDA has recently approved three anticancer agents. Zykadia (ceritinib) is the first second-generation ALK-inhibitor, Cyramza (ramucirumab) is the first targeted therapy approved for stomach cancer, and Sylvant (siltuximab) is the first drug approved for the rare disorder multicentric Castleman's disease. The Overview of targeted therapies page, the Anticancer agents table, and the iOS mobile app have been updated with this information.

Anticancer agent: **Ceritinib** is an orally administered kinase inhibitor targeting ALK.

- **Trade Name**: Zykadia
- **Type of Approval**: Breakthrough designation, expedited priority review, orphan status
- **Indication**: ALK-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Anticancer agent: **Ramucirumab** is an orally administered therapeutic antibody targeting angiogenesis via the vascular endothelial growth factor receptor 2 (VEGFR-2/KDR) receptor.

- **Trade Name**: Cyramza
- **Type of Approval**: Expedited priority review, orphan status
- **Indication**: Advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single agent after prior fluoropyrimidine- or platinum-containing chemotherapy

Anticancer agent: **Siltuximab** is an IV-administered immunotherapy targeting interleukin 6 (IL-6).

- **Trade Name**: Sylvant
- **Type of Approval**: Expedited priority review, orphan status
- **Indication**: Multicentric Castleman's disease

Article of Interest Highlight

Ceritinib in ALK-rearranged non-small-cell lung cancer

Authors: Shaw AT, Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR, Vansteenkiste J, Sharma S, De Pas T, Riely GJ, Solomon BJ, Wolf J, Thomas M, Schuler M, Liu G, Santoro A, Lau YY, Goldwasser M, Boral AL, Engelman JA

Study Type: Large prospective phase I trial with a dose-escalation phase evaluating 10 doses of ceritinib, and a three-arm expansion phase with efficacy endpoints

Study Treatment: Ceritinib (Zykadia, LDK378), an oral tyrosine kinase inhibitor of ALK. In the phase I dose escalation portion, ceritinib was administered orally once with a three-day PK evaluation period, and subsequently daily oral dosing for 21-day cycle. In the expansion portion, ceritinib was administered once orally daily at the MTD for each 21-day cycle, with treatment until progression, unacceptable toxicity, or withdrawal.

Eligibility: NSCLC patients with an ALK rearrangement or patients with other cancers with genetic aberrations in ALK were eligible. Patients with asymptomatic central nervous system metastases were eligible. Patients who had received prior treatment with ALK inhibitors were eligible.

Outcome Measures: In the phase I dose-escalation portion, the safety outcome endpoints were the maximum tolerated dose and dose-limiting toxicities. In the phase I expansion portion, the efficacy outcome endpoints included overall response rate and progression-free survival.

Results: 130 patients were treated as of October 2012. 59 patients were treated in the dose-escalation portion and 71 were treated in the expansion phase, with 114 NSCLC patients treated at at least the 400mg ceritinib dose level. The MTD was 750mg and dose-limiting toxicities included diarrhea, vomiting, nausea, dehydration, elevated aminotransferase level and hypophosphatemia. The response rate in 114 patients treated with 400mg ceritinib or higher was 58% and median progression free survival was 7 months. One patient with anaplastic large-cell lymphoma and one patient with inflammatory myofibroblastic tumor also demonstrated a response to ceritinib therapy.

Acquired resistance subgroup: 19 patients with crizotinib-resistant ALK-rearranged NSCLC had a repeat biopsy before treatment with ceritinib. Five patients had NSCLC harboring the resistance mutations ALK L1196M (3 patients), S1206Y (1 patient) and G1269A+1151Tins (1 patient). Two patients had NSCLC with ALK amplification. The response rate in the crizotinib-resistant

NSCLC patients treated with ceritinib was 68%.

Related papers:

- Friboulet L., et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discov. Epub 2014 Mar 27.
- Ignatius O., et al. Next-generation sequencing reveals a novel NSCLC ALK F1174V mutation and confirms ALK G1202R mutation confers high-level resistance to alectinib (CH5424802/RO5424802) in ALK-rearranged NSCLC patients who progressed on crizotinib. J Thorac Oncol. 2014 Apr;9(4):549-53