patients) or 230 (20% of 1159 MSI-h CRC patients). The number of possible LS patients reaches as many as 653 if we exclude the 506 patients with MSI-h and the \( \text{BRAF} \) V600 mutation, which is associated with MSI-h in non-hereditary CRC patients \[2, 3\]. This figure may include a subset of non-hereditary CRC patients with \( \text{MLH1} \) promoter hypermethylation, which the authors did not investigate. Interestingly, the subgroup with the best prognosis was the 427 CRC patients with MSI-h and \( \text{KRAS/BRAF} \) wt tumors, who may well be affected by LS. The issue of diagnosis and prognosis of LS patients has been partially addressed by Sinicrope et al. \[4\] in their study on 3503 stage III CRC patients. They showed that familial CRC patients had a better prognosis compared with sporadic CRC patients. However, they only inferred familiality from MMR deficiency, \( \text{BRAF} \) wt status and/or \( \text{MLH1} \) promoter hypermethylation in CRC tissue, and did not seek confirmation through germline GT.

It would be interesting to learn whether Dienstmann et al. referred MSI-h and \( \text{BRAF} \) wt CRC patients for genetic counseling (GC) and possibly testing (GT), in order to:

1. estimate more precisely the proportion of patients with stage II–III MSI-h and \( \text{BRAF} \) wt CRCs who are affected by LS, and to assess their prognosis;
2. establish the proportion of suspected LS patients who are referred to GC and GT by their oncologists, in order to identify at-risk relatives and reduce their cancer mortality through surveillance;
3. suggest different follow-up to radically resected stage II–III CRC patients affected by LS, when compared with those with sporadic disease.

These goals are not negligible: MSI is increasingly viewed as the pathway toward universal screening for LS (NICE 2017) \[2\], but referral to GC and GT is necessary for such screening to be clinically useful (ASCO-ESMO guidelines 2015) \[3\].

Oncologists from 212 practices in the US who participated in a pilot test within the ASCO Quality Oncology Practice Initiative in 2011 were reported to refer only 26% of CRC patients at risk of being LS for GC and GT \[5\]. Therefore, we believe it is necessary to emphasize the importance of actively identifying these patients in clinical practice. As Dienstmann et al. point out, we are now in an era of precision medicine: individualized approaches to prognostication and follow-up in MSI-h and \( \text{BRAF} \) wt CRC patients should include GC and GT, if patients consent, to identify those who are affected by LS.

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References


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An unknown reaction to pembrolizumab: giant cell arteritis

An 88-year-old female with a past medical history of a hypertension, atrial fibrillation, and stage IV non-small-cell lung cancer (NSCLC) presented to the emergency department with sudden onset left eye blindness and abdominal pain. She was noted to have worsening anemia and heme-occult positive stools; however, abdominal imaging did not indicate any acute pathology. Given her baseline poor functional status, the patient was not a candidate for aggressive interventions. One week before presentation, the patient had received a first dose of pembrolizumab, 200 mg intravenous (i.v.) infusion, which was to be administered once every 3 weeks. Upon consultation with an ophthalmologist, she was found to have biopsy confirmed giant cell arteritis (GCA). For her GCA, she was treated with high-dose oral prednisone with close clinical monitoring. She endured a prolonged hospital course with constipation, anemia and atrial fibrillation with rapid ventricular rate. The patient was cardioverted twice, and her anemia was treated with two separate transfusion of packed red blood cells.

After discharge, the patient received another dose of 200 mg of i.v. pembrolizumab, on schedule. Subsequently, she returned to the emergency department 5 days later with worsening...
abdominal pain and three episodes of watery diarrhea. An infectious work-up was negative, and a CT scan of her abdomen demonstrated focal areas of sigmoid colitis. It was believed that the pathology from both her GCA and colitis were induced by pembrolizumab.

Although colitis is a known and observed phenomena of immunologic therapy [1], GCA has yet to be associated with pembrolizumab. The patient was treated with high-dose i.v. steroids. Unlike oral steroids, the patient stated that her eyesight subjectively improved with i.v. steroids. However, due to her poor functional status from prolonged hospitalizations, and concern for worsening gastrointestinal bleeding, the patient decided to switch to oral prednisone, in hope of a gradual taper.

Although the current standard of care for NSCLC with appropriate PD-L1 status are immunologicos [2], the possibility of inducing autoimmune effects should be carefully considered in regards to a patient’s quality of life. The current literature correlates PD-1 to several classes of immune-related adverse effects [3, 4]. However, GCA has not been attributed to pembrolizumab in the current literature.

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**Combination therapy of erlotinib/crizotinib in a lung adenocarcinoma patient with primary EGFR mutation plus secondary MET amplification and a novel acquired crizotinib-resistant mutation MET G1108C**

A 36-year-old non-smoking Chinese woman was diagnosed as stage IV lung adenocarcinoma and pneumonia by chest computed tomography (CT) scan (Figure 1A) and biopsy in June 2016. CT scan and brain enhanced magnetic resonance imaging (MRI) showed left pleural effusion and multiple metastases in lymph nodes, liver and brain. The patient adopted chest drainage and was given pemetrexed and nedaplatin for treatment. The patient maintained stable disease for about 6 months. However, metastasis in right adrenal occurred in November 2016. Clinical symptoms and chest CT revealed disease progression a month later together with multiple bone metastases. Apart from the continually present EGFR L858R mutation (AF 74.94%) and amplification (LR 2.68), the secondary ctDNA analysis revealed copy number amplification of MET (LR 2.77), considered responsible for erlotinib resistance [1].

Subsequently, the patient was treated with erlotinib (150 mg/day) and crizotinib (250 mg/day) in January 2017, based on the confirmed safe use by a phase I clinical trial [2]. Four weeks after the combination therapy, cough was significantly relieved and a dramatic response was observed in lung (Figure 1A). Yet the combination therapy resulted in severe side-effects including vomiting and rash. Nine weeks post-combination therapy, nevertheless, the patient again showed progressed symptoms. The following ctDNA analysis demonstrated three novel mutations: NRAS G12D (AF 0.64%), EGFR L858R mutation (AF 33.91%) and amplification (LR 1.68), indicating a great benefit of erlotinib for brain metastases.

The patient has shown free brain lesions since October 2016, indicating a great benefit of erlotinib for brain metastases. However, high levels of EGFR mutation and amplification were detected throughout the therapy, implying other TKIs could be considered for the continued treatment when patient’s brain metastases disappeared. Upon detecting EGFR mutations with concurrent MET amplification, we observed dramatic response post to the combination therapy of erlotinib/crizotinib. Yet due to paucity of the drugs targeting the upcoming MET-resistant...