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Hyperprogression following immunotherapy in an advanced colon cancer patient harboring the PIK3CA H1047R mutation

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INTRODUCTION

- The **PIK3CA H1047R mutation** has been postulated as a biomarker for **poor response to immunotherapy**.
- We present here a case report of colon adenocarcinoma with the PIK3CA H1047R mutation who developed **hypeprogressive disease** after receiving immunotherapy.

CLINICAL CASE

Present history:

- A **47-year-old female** patient was performed an urgent **total colectomy** due to intestinal obstruction.
- Diagnosis: Left-sided pT3pN2a **colon adenocarcinoma**. IHC: Proficient mismatch repair (**pMMR**) proteins. NGS: **PIK3CA (H1047R) and KRAS (G12A) mutations**. CT scan: hepatic and lung metastasis**. Stage IV**.
- First line treatment with **FOLFOX6 and bevacizumab** for 6 cycles. However, oxaliplatin was resumed due to grade 2 neurotoxicity. After 3 cycles, the next CT scan showed progressive disease. Retreatment with FOLFOX6 and bevacizumab - neurotoxicity had disappeared. However, a new progression was evident after 5 additional cycles
- **FOLFIRI- aflibercept** was chosen as the second line treatment. After 6 cycles, a CT scan showed a new progression in January 2022.

FOLFOX + Bevacizumab → 5FU + Bevacizumab → Progression → FOLFOX + Bevacizumab → FOLFIRI + Aflibercept → Progression

Physical exam: Unremarkable. Performance status 1.

Complementary tests: Increasing serum carcinoembryonic antigen. Basal hepatic and pulmonary target lesions on CT scan are shown on **image 1**

Diagnosis: *PIK3CA (H1047R) and KRAS (G12A) mutated, pMMR stable stage IV left-sided colon adenocarcinoma* *progressing to oxaliplatin, irinotecan, fluoropyrimidines and antiangiogenics.*

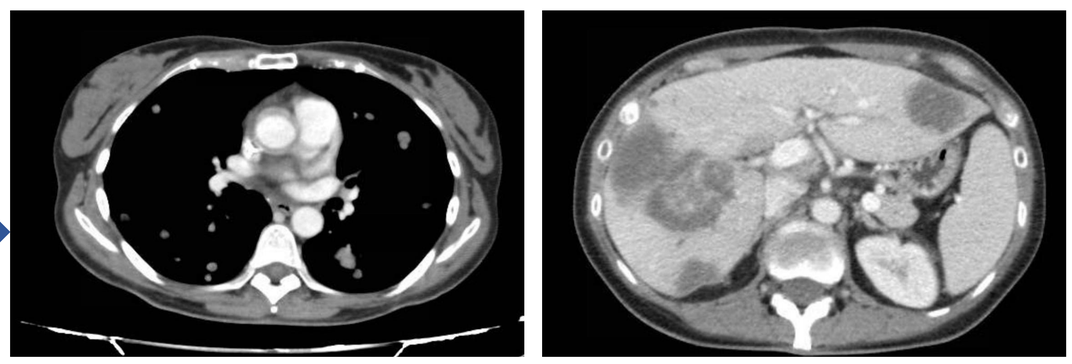

Image 1. ***Basal CT scan*** *showing pulmonary and hepatic lesions the present case - a PIK3CA H1047R mutated MMR stable stage IV left-sided adenocarcinoma of the colon - prior to nivolumab, ipilimumab and trametinib start.*

Treatment:

- The patient participated on the phase II clinical trial called CA209-9N9 which randomized eligible patients to receive nivolumab +- ipilimumab + trametinib versus regorafenib.
- She received a complete cycle of treatment with **nivolumab** 6 mg /kg Q 4W + **ipilimumab** 1 mg / kg Q 8 W + **trametinib** 1.5 mg QD continuous.

CA209-9N9 phase II clinical trial : **NIVOLUMAB + IPILIMUMAB + TRAMETINIB**

Follow-up:

- **Clinical deterioration** was fast due to abdominal distension, pain and fatigue.
- A **hyperprogression** was presented on the first CT scan evaluation showing ascites, pleural effusion and gross hepatic progression. I**mage 2.**
- The patient was referred to the **Palliative Care** Team and two weeks later she died at home with her family.

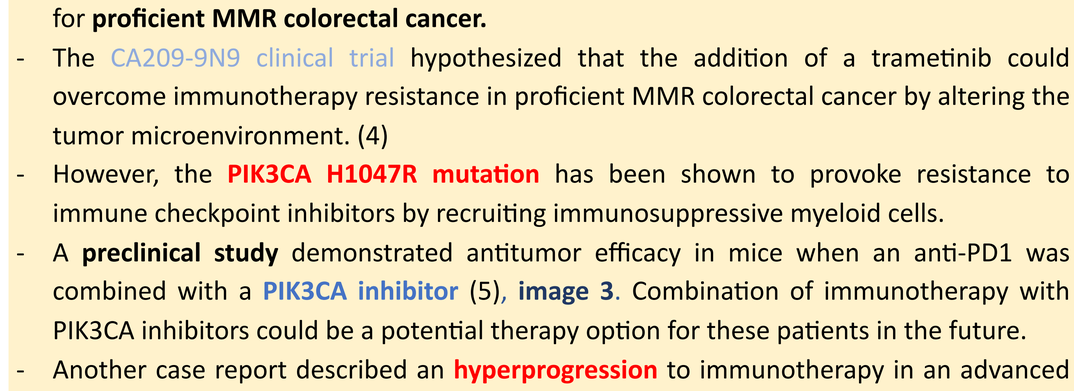

Image 2. ***Evaluation CT scan*** *after the first cycle of nivolumab, ipilimumab and trametinib showing pleural, pulmonary, hepatic and ascitic hyperprogressive disease. Although the definition is controversial, the majority of authors coincide that a hyperprogression implies RECIST progression in less than 2 months from the initiation of therapy, a ≥50 % increase in tumor burden and a ≥ 2-fold increase in tumor growth rate or kinetics.(7). The present case fulfilled all of these criteria.*

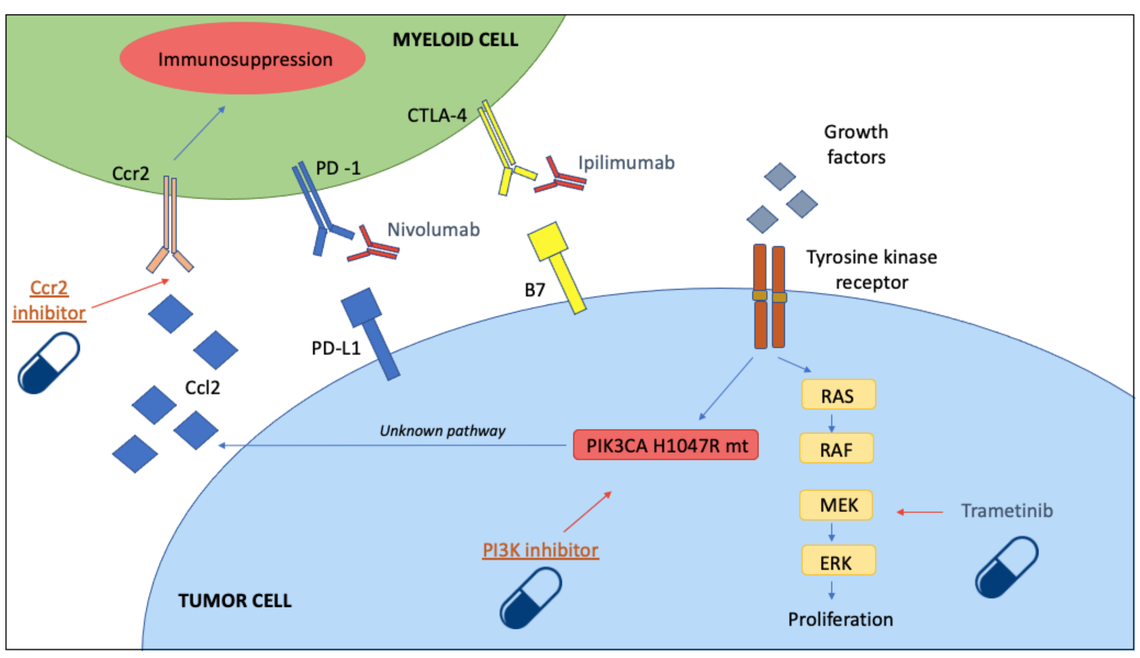

Image 3. ***Molecular pathways and target therapies.*** *PIK3CA H1047R mutation in tumor cells provokes Ccl2 chemokine secretion that ultimately binds to Ccr2 receptor in myeloid cells and induces immunosuppression. Potential target therapies that have already been tested in PI3K H1047R mice in combination with immunotherapy are BAY80-6946 (a pan-PI3K inhibitor) and BMS 687681 (a Ccr2 and Ccr5 inhibitor)(5).*

DISCUSSION

- Immunotherapy has revolutionized the treatment of deficient MMR colorectal cancer. (1–3). However, there is not yet any consistent clinical results in favor of immunotherapy for **proficient MMR colorectal cancer.**
- The CA209-9N9 clinical trial hypothesized that the addition of a trametinib could overcome immunotherapy resistance in proficient MMR colorectal cancer by altering the tumor microenvironment. (4)
- However, the **PIK3CA H1047R mutation** has been shown to provoke resistance to immune checkpoint inhibitors by recruiting immunosuppressive myeloid cells.
- A **preclinical study** demonstrated antitumor efficacy in mice when an anti-PD1 was combined with a **PIK3CA inhibitor** (5), **image 3**. Combination of immunotherapy with PIK3CA inhibitors could be a potential therapy option for these patients in the future.
- Another case report described an **hyperprogression** to immunotherapy in an advanced esophageal squamous cell carcinoma with the PIK3CA H1047R mutation. (6)
- We advocate for using with caution or **avoiding immunotherapy** in patients with the **PIK3CA H1047R mutation** due to its deleterious effects.

REFERENCES

1. André T, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, et al. Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer. New England Journal of Medicine. 2020 Dec 3;383(23):2207–18.
2. Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, et al. PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer. New England Journal of Medicine. 2022 Jun 23;386(25):2363–76.
3. Zhang X, Wu T, Cai X, Dong J, Xia C, Zhou Y, et al. Neoadjuvant Immunotherapy for MSI- H/dMMR Locally Advanced Colorectal Cancer: New Strategies and Unveiled Opportunities. Vol. 13, Frontiers in Immunology. Frontiers Media S.A.; 2022.
4. Baskin-Bey E, SK. Clinical Protocol CA2099N9. A Study Of Nivolumab In Combination With Trametinib With Or Without Ipilimumab In Participants With Previously Treated Metastatic Colorectal Cancers (CheckMate 9N9: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 9N9) Protocol Amendment: 03. Bristol-Myers Squibb. 2021.
5. Collins NB, al Abosy R, Miller BC, Bi K, Zhao Q, Quigley M, et al. PI3K activation allows immune evasion by promoting an inhibitory myeloid tumor microenvironment. J Immunother Cancer. 2022 Mar 9;10(3).
6. Sun D, Liu D, Liu Q, Hou H. Nivolumab induced hyperprogressive disease in advanced esophageal squamous cell carcinoma. Cancer Biol Ther. 2020;21(12):1097–104.
7. Frelaut M, le Tourneau C, Borcoman E. Hyperprogression under immunotherapy. Int J Mol Sci. 2019 Jun 1;20(11).