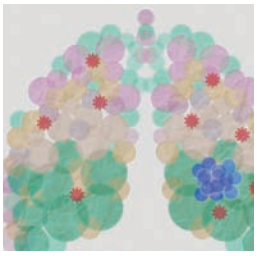
PD-1 Blockade Is Not Unsafe in Patients with Lung Cancer and COVID-19

- COVID-19 severity and mortality were not increased in patients with lung cancer who received prior PD-1 blockade.
- Although PD-1 blockade was not a risk factor in this population, severity and mortality in this group were high.
- This suggests that PD-1 blockade should be used when indicated in patients with lung cancer despite COVID-19.

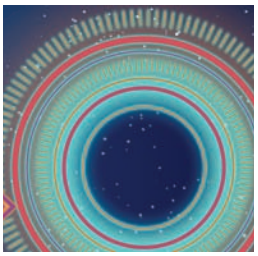


A key issue in oncology practice during the COVID-19 pandemic is whether PD-1 blockade affects the severity of COVID-19 in patients with cancer. PD-1 blockade may increase COVID-19 severity by contributing to hyperactive immune responses to SARS-CoV-2 infection—or, alternatively, may reduce severity by enhancing control of initial viral infection. To minimize lung cancer as a confounder, Luo and colleagues assessed the outcomes of concurrent COVID-19 and lung cancer in 69 consecutive patients at a single institution in New York City. They performed manual annotation, including collecting data from a detailed self-reported smoking survey. PD-1 blockade was not a notable risk factor for increased COVID-19 severity or death among these patients, regardless of whether patients received the immunotherapy recently or at any point prior to infection. There was a slight, statistically insignificant numeric increase in severity with PD-1 blockade, but controlling for smoking history—which is an expected imbalance in receipt of prior PD-1 blockade and a risk factor for severe COVID-19 outcomes—abolished this correlation. This work suggests that prior PD-1 blockade is not a clinically meaningful risk factor for worsened COVID-19 outcomes, implying that PD-1 blockade should be used when indicated despite the pandemic. Larger studies are needed to more fully examine this question. Finally, it should be noted that, in this study population, more than half of patients with lung cancer and COVID-19 were hospitalized and almost half of those hospitalized died, emphasizing the need for studies to better understand risk factors and the disease course in this group. ■

See article, p. 1121.

Anti-EGFR Overcomes KRAS^{G12C}-Inhibitor Resistance in Colorectal Cancer

- KRAS^{G12C} inhibition is effective in some *KRAS*^{G12C}-mutant cancers, but not *KRAS*^{G12C}-mutant colorectal cancer.
- *KRAS*^{G12C}-mutant colorectal cancer cells had higher basal activation of the upstream receptor tyrosine kinase EGFR.
- Inhibition of EGFR plus KRAS^{G12C} was effective in colorectal cancer cells and patient-derived organoids and xenografts.



Although KRAS^{G12C} inhibition has shown efficacy in patients with *KRAS*^{G12C}-mutant non–small cell lung cancer (NSCLC), results have been less promising in patients with *KRAS*^{G12C}-mutant colorectal cancer. To understand the mechanism underlying KRAS^{G12C}-inhibitor resistance in *KRAS*^{G12C}-mutant colorectal cancer, Amodio, Yaeger, Arcella, and colleagues started by testing the effects of the KRAS^{G12C} inhibitor AMG510 in *KRAS*^{G12C}-mutant NSCLC and colorectal cancer cell lines. This revealed that AMG510 treatment did not result in sustained inhibition of phosphorylation of the downstream kinase ERK in colorectal cancer cells—instead, phospho-ERK levels rebounded in colorectal cancer but not NSCLC cells after exposure to AMG510. Further investigation revealed that the colorectal cancer cells, unlike the NSCLC cells, had high basal activation of upstream receptor tyrosine kinases, including EGFR. Correspondingly, treatment of *KRAS*^{G12C}-mutant colorectal cancer cells with the EGFR inhibitor cetuximab sensitized the cells to AMG510, and cetuximab plus AMG510 treatment inhibited cell proliferation and was cytotoxic in a colorectal cancer cell line with acquired resistance (via *KRAS*^{G12C} mutation) to the EGFR antibody panitumumab. Extending these findings, combination treatment with cetuximab plus AMG510 exerted synergistic proliferation suppression in patient-derived organoids representing *KRAS*^{G12C}-mutant colorectal cancer, and patient-derived xenograft experiments using tumors from two patients with *KRAS*^{G12C}-mutant colorectal cancer demonstrated that cetuximab plus AMG510 led to marked or even complete tumor shrinkage. Together, these results provide insight into the reason behind the low efficacy of KRAS^{G12C} inhibition in *KRAS*^{G12C}-mutant colorectal cancer and suggest a therapeutic strategy that may be useful for overcoming this resistance. ■

See article, p. 1129.

Surmountable *JAK1/2* and *B2M* Mutations Confer Anti–PD-1 Resistance

- *JAK1*, *JAK2*, or *B2M* loss-of-function mutations caused resistance to anti–PD-1 therapy in colon cancer models.
- A TLR9 agonist or an IL2 agonist overcame resistance in *JAK1/2*- or *B2M*-mutant tumors, respectively.
- Mechanism-informed treatments based on TLR9 or IL2 may be of interest for cancers resistant to anti–PD-1.

Loss-of-function mutations in *JAK1/2* (encoding JAK1 and JAK2, tyrosine kinases involved in IFN signaling) and *B2M* (encoding β_2 microglobulin, a component of the MHC class I complex) are implicated in resistance of cancers to anti–PD-1 therapy. To better understand the mechanisms underlying resistance, Torrejon and colleagues first investigated the effects of *JAK1*, *JAK2*, or *B2M* knockout in human melanoma cell lines. *JAK1* or *JAK2* knockout caused insensitivity to IFN-mediated cytotoxicity via reduced IFN-induced transcription, whereas *B2M* knockout did not affect IFN sensitivity but prevented melanoma cells from being recognized by antigen-specific T cells due to loss of cell-surface expression of MHC class I. In a mouse model of colon adenocarcinoma with high mutational burden, *JAK1*, *JAK2*, or *B2M* knockout caused resistance to anti–PD-1 treatment, with *JAK1*- and *JAK2*-knockout tumors lacking IFNγ signal amplification, and *B2M*-knockout tumors losing surface MHC antigen expression and not being recognized by T cells. In this model, *JAK1/2* knockout–induced resistance could be overcome by combining intratumoral TLR9-agonist administration with anti–PD-1 via reactivation of IFN signaling. In the *B2M*-knockout model, resistance could be ameliorated by adding the IL2 agonist bempegaldesleukin to anti–PD-1 via natural killer–mediated responses. Importantly, the TLR9 agonist or bempegaldesleukin could also alleviate resistance in a mouse model of melanoma that exhibits primary resistance to anti–PD-1. Together, these results provide further evidence for the role of JAK1/2 and B2M in resistance to anti–PD-1 and support mechanism-informed therapies that are currently being investigated in clinical trials of patients with resistance to PD-1 blockade therapy. ■

See article, p. 1140.

Bempegaldesleukin plus Nivolumab Is Safe in Multiple Malignancies

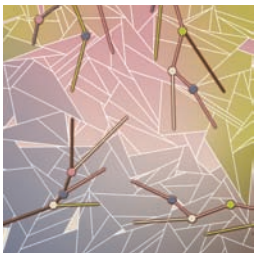
- The IL2 pathway agonist bempegaldesleukin plus anti–PD-1 therapy with nivolumab was tested in a phase I trial.
- In 38 patients with advanced melanoma, renal cell carcinoma, or non–small cell lung cancer, treatment was safe.
- Response correlated with higher T-cell infiltration and clonality, consistent with bempegaldesleukin's mechanism.

Although immune-checkpoint inhibitors produce favorable response rates in several cancers, these agents are not always effective, perhaps sometimes in part due to low levels of tumor-infiltrating lymphocytes. Based on evidence that the IL2 pathway agonist bempegaldesleukin can promote proliferation and activation of $CD4^+$ and $CD8^+$ T cells as well as natural killer cells in the tumor microenvironment, Diab, Tannir, Bentebibel, and colleagues conducted a phase I trial of bempegaldesleukin plus the PD-1 antibody nivolumab in 38 patients with immunotherapy-naïve advanced melanoma, renal cell carcinoma, or non–small cell lung cancer (11, 22, and 5 patients, respectively). Among the 37 patients for whom efficacy evaluation was conducted, 18.9% attained complete responses and 40.5% experienced partial responses, and the median duration of response was not reached after a median follow-up period of 18 months. Consistent with the proposed mechanism for bempegaldesleukin, T-cell infiltration and clonality were increased by week three of treatment in tumors that responded to the treatment, an observation that warrants further study in larger trials. With regard to safety and tolerability, all patients experienced at least one treatment-emergent adverse event, most commonly flu-like symptoms, rash, fatigue, pruritus, arthralgia, decreased appetite, or headache, and there were no treatment-related deaths. Based on the results of this study, the trial has been expanded to include patients with other tumor types; additionally, treatment with bempegaldesleukin plus nivolumab is now being evaluated in phase II and III trials including patients with various malignancies. ■

See article, p. 1158.

Targetable Mutations Occur in CDK4/6 Inhibitor–Resistant Breast Cancer

- Genomic alterations in *RB1*, *AURKA*, and others correlated with CDK4/6-inhibitor resistance in HR$^+$HER2$^-$ breast cancer.
- These alterations were found in patient tumors and many occurred with prolonged CDK4/6-inhibitor treatment *in vitro*.
- In a phase I trial of an AURKA inhibitor, a patient with CDK4/6 inhibitor–resistant disease had a response.

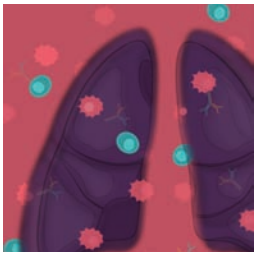


CDK4/6 inhibitors are useful for the treatment of hormone receptor–positive (HR$^+$), HER2$^-$ breast cancer, but primary resistance and acquired resistance are problematic, and the mechanisms that drive resistance are not fully understood. Wander, Cohen, Gong, and colleagues performed whole-exome sequencing on 59 biopsies from 58 patients with CDK4/6 inhibitor–treated, HR$^+$HER2$^-$ metastatic breast cancer, including 18 biopsies from tumors sensitive to CDK4/6 inhibition, 28 from tumors intrinsically resistant to CDK4/6 inhibition, and 13 from tumors with acquired resistance to CDK4/6 inhibition. This analysis identified several genomic alterations that may confer resistance, including loss of the tumor suppressor gene *RB1* and activating alterations in *AKT1*, *RAS*, *AURKA*, *CCNE2*, *ERBB2*, and *FGFR2*; further, immunohistochemistry showed that some resistant tumors had lost ER expression. *In vitro*, CRISPR–Cas9-mediated knockout of *RB1* or lentiviral overexpression of *AKT1*, *KRAS*^{G12D}, *AURKA*, or *CCNE2* rendered HR$^+$HER2$^-$ breast cancer cells resistant to CDK4/6 inhibition. Further, HR$^+$HER2$^-$ breast cancer cells cultured with CDK4/6 inhibitors until the development of resistance exhibited genetic alterations in *RB1*, *KRAS*, *AURKA*, or *CCNE2*. Highlighting the potential clinical relevance of these findings, one patient with metastatic HR$^+$HER2$^-$ breast cancer that recurred after more than three years of benefit from a CDK4/6 inhibitor and letrozole was enrolled in a phase I clinical trial of an AURKA inhibitor, which led to prolonged disease stabilization. In summary, this work elucidates several previously unknown mechanisms of resistance to CDK4/6 inhibition in breast cancer and provides evidence that many of these mechanisms may be clinically exploitable. ■

See article, p. 1174.

Amivantamab Inhibits Growth of *EGFR* Exon 20 Insertion–Driven NSCLC

- Amivantamab was active in *EGFR* exon 20 insertion–driven non–small cell lung cancer (NSCLC) *in vitro* and *in vivo*.
- This EGFR–MET-targeted bispecific antibody induced EGFR and MET downregulation and programmed cell death.
- Patients in a phase I trial with *EGFR* exon 20 insertion–driven NSCLC showed promising responses to amivantamab.



Although non–small cell lung cancers (NSCLC) harboring diverse EGFR-activating mutations often respond to EGFR-directed tyrosine kinase inhibitors (TKI), NSCLCs driven by *EGFR* exon 20 insertions generally do not respond to these targeted therapies. Yun and colleagues investigated the use of the EGFR–MET-targeted bispecific antibody amivantamab, which has shown early evidence of efficacy in some types of *EGFR*-mutant NSCLC, in *EGFR* exon 20 insertion–driven NSCLC. In cell lines bearing a diverse range of *EGFR* exon 20 insertions, amivantamab inhibited proliferation to a greater extent than TKIs by promoting apoptosis. Additionally, primary cell cultures and organoids grown from patient tumors with *EGFR* exon 20 insertions were also sensitive to amivantamab. Mechanistically, amivantamab treatment led to internalization and subsequent downregulation of EGFR and MET as well as induction of antibody-dependent cell-mediated cytotoxicity. *In vivo*, xenografts derived from *EGFR* exon 20 insertion–driven cell lines or patient-derived cells were also sensitive to amivantamab, displaying reduced tumor volume following amivantamab treatment. Finally, emphasizing the potential clinical relevance of these findings, early results from an ongoing phase I trial of amivantamab in patients with advanced NSCLC have shown that amivantamab may have antitumor activity in patients with *EGFR* exon 20 insertion–driven disease, with promising reductions in tumor volume observed. Collectively, this work demonstrates the potential value of amivantamab in patients with *EGFR* exon 20 insertion–driven NSCLC, a disease subtype with limited treatment options. ■

See article, p. 1194.

Differing Immune-Cell Subsets Underlie Sex Disparities in Glioblastoma

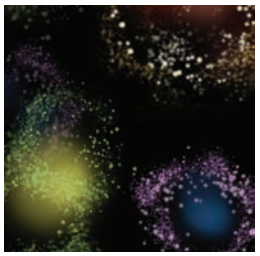
- Sex-based differences in populations of suppressive immune-cell subsets were seen in mouse glioblastoma models.
- Monocytic and granulocytic myeloid-derived suppressor cells were enriched in males and females, respectively.
- These differences were associated with treatment responses and observed in patients, implying clinical relevance.

Disparities in immune system functions between male and female patients may underlie some of the observed sex differences in cancer incidence, prognosis, and treatment response, but this subject has been scarcely explored in glioblastoma. Bayik and colleagues found that monocytic myeloid-derived suppressor cells (MDSC) were enriched in the tumors of male mice but not female mice following intracranial glioblastoma-cell injection. Additionally, granulocytic MDSCs were enriched in the peripheral blood of female mice but not male mice after the tumor implantation. Notably, depletion of granulocytic MDSCs with neutralizing antibodies provided a survival advantage in female but not male glioblastoma-bearing mice, and monocytic MDSCs could not be depleted using neutralizing antibodies in mice of either sex, an effect that appeared to be due to rapid proliferation of monocytic MDSCs. Gene-expression profiling of MDSC subsets from bone marrow of male and female mice followed by a network-medicine analysis identified potential susceptibilities of monocytic MDSCs to antiproliferative drugs and granulocytic MDSCs to IL1 pathway inhibitors. Consistent with these predictions, the antiproliferative agent fludarabine extended survival in male but not female glioblastoma-bearing mice, whereas anti-IL1β extended survival in female but not male glioblastoma-bearing mice. Supporting the clinical relevance of these findings, glioblastomas from male patients were enriched with proliferative monocytic MDSCs, and high expression of genes representing a granulocytic MDSC gene signature or *IL1B* (encoding IL1β) was associated with poor prognosis in female patients. Together, this work reveals a previously unknown explanation for sex differences in glioblastoma and demonstrates how this knowledge may be therapeutically exploitable. ■

See article, p. 1210.

INPP4B Loss Promotes Triple-Negative Breast Cancer via EGFR Signaling

- The lipid phosphatase INPP4B was a tumor suppressor in a mouse model of triple-negative breast cancer.
- *INPP4B* loss activated the PI3K–AKT and MEK–ERK pathways, causing sensitivity to PI3K and MEK inhibitors.
- Lack of *INPP4B* reduced EGFR trafficking to late endosomes, causing EGFR buildup and higher EGFR signaling.



Loss-of-function mutations in *INPP4B*, encoding a member of the PI3K–AKT pathway that dephosphorylates $PI(3,4)P_2$ to PI(3)P, have been observed in triple-negative breast cancer (TNBC); however, the role of these mutations is unclear. In a mouse model of TNBC, Liu and colleagues found that *INPP4B* knockout led to increased penetrance of the TNBC phenotype, providing evidence for *INPP4B*'s role as a tumor-suppressor gene in this malignancy. Although *INPP4B* deficiency can impair DNA repair and lead to chromosomal instability, this was not observed in this TNBC model. Instead, loss of *INPP4B* was associated with activation of the PI3K–AKT and MEK–ERK pathways. Consequently, *INPP4B* deficiency in tumors led to increased susceptibility to PI3K and MEK inhibitors. Consistent with INPP4B's established lipid phosphatase activity on $PI(3,4)P_2$, buildup of $PI(3,4)P_2$ as a constituent of intracellular endocytic vesicles, but not the plasma membrane, was observed in *INPP4B*-deficient cells. Notably, *INPP4B*-deficient cells also exhibited delayed degradation of the upstream receptor tyrosine kinases EGFR and MET, and *INPP4B* loss also caused increased EGFR levels in tumors. Mechanistically, this could be explained by an observed reduction in EGFR trafficking from early endosomes to late endosomes and then lysosomes in *INPP4B*-deficient cells, delaying EGFR degradation and leading to an increase in downstream signaling. In summary, this work provides support for the proposed role of *INPP4B* as a tumor-suppressor gene in TNBC and characterizes the mechanistic basis by which this occurs. ■

See article, p. 1226.

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