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**Immunosurveillance and Regression in the Context of Squamous Pulmonary Premalignancy** ..... 1442

K. Krysan, L.M. Tran, and S.M. Dubinett

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**Therapy Response and Outcome Explained by Leukemia Cell of Origin** ..... 1445

Z. Gu, K.E. Dickerson, and J. Xu

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**Environment Influences Tumor Progression and Transcriptional Subtype in a New Model of Pancreatic Cancer** ..... 1448

K.A. Pickering and J.P. Morton

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## Science in Society

**The Race toward Equity: Increasing Racial Diversity in Cancer Research and Cancer Care** .. 1451

D.C. Brady and A.T. Weeraratna

**MINI REVIEW** **Cancer in the Fourth Dimension: What Is the Impact of Circadian Disruption?** ..... 1455  
M. Pariollaud and K.A. Lamia

**RESEARCH BRIEFS** **Clinical Portrait of the SARS-CoV-2 Epidemic in European Patients with Cancer** ..... 1465

D.J. Pinato, A. Zambelli, J. Aguilar-Company, M. Bower, C.C.T. Sng, R. Salazar, A. Bertuzzi, J. Brunet, R. Mesia, E. Seguí, F. Biello, D. Generali, S. Grisanti, G. Rizzo, M. Libertini, A. Maconi, N. Harbeck, B. Vincenzi, R. Bertulli, D. Ottaviani, A. Carbó, R. Bruna, S. Benafif, A. Marrari, R. Wuerstlein, M.C. Carmona-García, N. Chopra, C. Tondini, O. Mirallas, V. Tovazzi, M. Betti, S. Provenzano, V. Fotia, C.A. Cruz, A. Dalla Pria, F. D'Avanzo, J.S. Evans, N. Saoudi-Gonzalez, E. Felip, M. Galazi, I. Garcia-Fructuoso, A.J.X. Lee, T. Newsom-Davis, A. Patriarca, D. García-Illescas, R. Reyes, P. Dileo, R. Sharkey, Y.N.S. Wong, D. Ferrante, J. Marco-Hernández, A. Sureda, C. Maluquer, I. Ruiz-Camps, G. Gaidano, L. Rimassa, L. Chiudinelli, M. Izuzquiza, A. Cabirta, M. Franchi, A. Santoro, A. Prat, J. Tabernero, and A. Gennari

**Précis:** Higher risk of death from COVID-19 among patients with cancer was correlated with male sex, greater age, presence of multiple comorbidities, advanced-stage disease, and active disease; there was no association between risk and anticancer treatment.

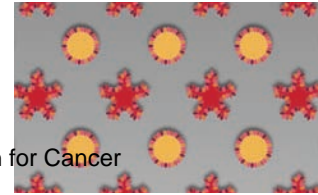
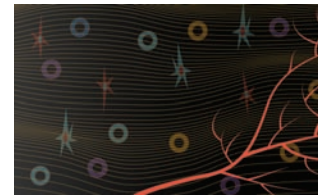
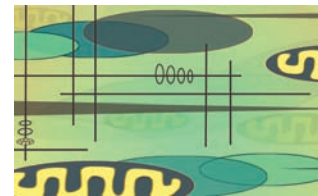
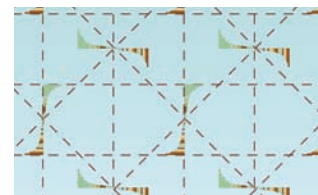
**Clinical BRCA1/2 Reversion Analysis Identifies Hotspot Mutations and Predicted Neoantigens Associated with Therapy Resistance** ..... 1475

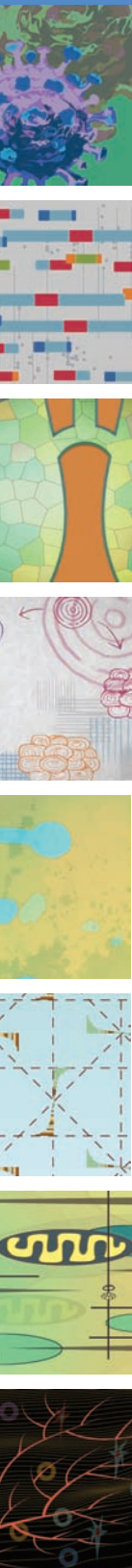
S.J. Pettitt, J.R. Frankum, M. Punta, S. Lise, J. Alexander, Y. Chen, T.A. Yap, S. Haider, A.N.J. Tutt, and C.J. Lord

**Précis:** Reversion mutations that cause resistance of initially homologous recombination-deficient tumors to PARP inhibitors and platinum-based chemotherapies often affect *BRCA1/2* and may lead to susceptibility to immunotherapy.

**Immune Surveillance in Clinical Regression of Preinvasive Squamous Cell Lung Cancer** .. 1489

A. Pennycuik, V.H. Teixeira, K. AbdulJabbar, S.E.A. Raza, T. Lund, A.U. Akarca, R. Rosenthal,





L. Kalinke, D.P. Chandrasekharan, C.P. Pipinikas, H. Lee-Six, R.E. Hynds, K.H.C. Gowers, J.Y. Henry, F.R. Millar, Y.B. Hagos, C. Denais, M. Falzon, D.A. Moore, S. Antoniou, P.F. Durrenberger, A.J. Furness, B. Carroll, C. Marceaux, M.-L. Asselin-Labat, W. Larson, C. Betts, L.M. Coussens, R.M. Thakrar, J. George, C. Swanton, C. Thirlwell, P.J. Campbell, T. Marafioti, Y. Yuan, S.A. Quezada, N. McGranahan, and S.M. Janes

**Précis:** Poor CD8<sup>+</sup> T-cell infiltration, defective antigen presentation, and aberrant upregulation of *CCL27* and *CCR10* and downregulation of *TNFSF9* (all immune system genes) were associated with progression of preinvasive lung carcinoma *in situ*.

See commentary, p. 1442

### Leukemia Cell of Origin Influences Apoptotic Priming and Sensitivity to LSD1 Inhibition . . . . . 1500

S.F. Cai, S.H. Chu, A.D. Goldberg, S. Parvin, R.P. Koche, J.L. Glass, E.M. Stein, M.S. Tallman, F. Sen, C.A. Famulare, M. Cusan, C.-H. Huang, C.-W. Chen, L. Zou, K.B. Cordner, N.L. DelGaudio, V. Durani, M. Kini, M. Rex, H.S. Tian, J. Zuber, T. Baslan, S.W. Lowe, H.Y. Rienhoff Jr, A. Letai, R.L. Levine, and S.A. Armstrong

**Précis:** Compared with granulocyte-monocyte progenitor cell-derived acute myeloid leukemia, hematopoietic stem cell-derived leukemia was more resistant to LSD1 inhibition and apoptosis, but resistance was reversed by venetoclax.

See commentary, p. 1445

## RESEARCH ARTICLES

### Utilization of COVID-19 Treatments and Clinical Outcomes among Patients with Cancer: A COVID-19 and Cancer Consortium (CCC19) Cohort Study . . . 1514



D.R. Rivera, S. Peters, O.A. Panagiotou, D.P. Shah, N.M. Kuderer, C.-Y. Hsu, S.M. Rubinstein, B.J. Lee, T.K. Choueiri, G. de Lima Lopes Jr., P. Grivas, C.A. Painter, B.I. Rini, M.A. Thompson, J. Arcobello, Z. Bakouny, D.B. Doroshow, P.C. Egan, D. Farmakiotis, L.A. Fecher, C.R. Friese, M.D. Galsky, S. Goel, S. Gupta, T.R. Halfdanarson, B. Halmos, J.E. Hawley, A.R. Khaki, C.A. Lemmon, S. Mishra, A.J. Olszewski, N.A. Pennell, M.M. Puc, S.G. Revankar, L. Schapira, A. Schmidt, G.K. Schwartz, S.A. Shah, J.T. Wu, Z. Xie, A.C. Yeh, H. Zhu, Y. Shyr, G.H. Lyman, and J.L. Warner on behalf of the COVID-19 and Cancer Consortium

**Précis:** In a large observational study in patients with COVID-19 and cancer, survival was not significantly influenced by receipt of COVID-19 treatments, except hydroxychloroquine plus any other treatment, which was associated with reduced survival.

### Phase I Trial of the PARP Inhibitor Olaparib and AKT Inhibitor Capivasertib in Patients with BRCA1/2- and Non-BRCA1/2-Mutant Cancers . . . . . 1528



T.A. Yap, R. Kristeleit, V. Michalarea, S.J. Pettitt, J.S.J. Lim, S. Carreira, D. Roda, R. Miller, R. Riisnaes, S. Miranda, I. Figueiredo, D. Nava Rodrigues, S. Ward, R. Matthews, M. Parmar, A. Turner, N. Tunariu, N. Chopra, H. Gevensleben, N.C. Turner, R. Ruddle, F.I. Raynaud, S. Decordova, K.E. Swales, L. Finneran, E. Hall, P. Rugman, J.P.O. Lindemann, A. Foxley, C.J. Lord, U. Banerji, R. Plummer, B. Basu, J.S. Lopez, Y. Drew, and J.S. de Bono

**Précis:** In a phase I trial of patients with advanced solid tumors, combination treatment with the PARP inhibitor olaparib and the AKT inhibitor capivasertib showed early signs of efficacy, supporting preclinical observations of synergy.

### Extracellular ATP and CD39 Activate cAMP-Mediated Mitochondrial Stress Response to Promote Cytarabine Resistance in Acute Myeloid Leukemia . . . . . 1544

N. Aroua, E. Boet, M. Ghisi, M.-L. Nicolau-Travers, E. Saland, R. Gwilliam, F. de Toni, M. Hosseini, P.-L. Mouchel, T. Farge, C. Bosc, L. Stuani, M. Sabatier, F. Mazed, C. Larrue, L. Jarrou, S. Gandarillas, M. Bardotti, M. Picard, C. Syrykh, C. Laurent, M. Gotanègre, N. Bonnefoy, F. Bellvert, J.-C. Portais, N. Nicot, F. Azuaje, T. Kaoma, C. Joffre, J. Tamburini, C. Récher, F. Vergez, and J.-E. Sarry

**Précis:** CD39-expressing acute myeloid leukemia cells expanded after cytarabine treatment and activated the cell survival-promoting mitochondrial stress response, leading to relapse with chemotherapy-resistant disease.

### Intraductal Transplantation Models of Human Pancreatic Ductal Adenocarcinoma Reveal Progressive Transition of Molecular Subtypes . . . 1566



K. Miyabayashi, L.A. Baker, A. Deschênes, B. Traub, G. Caligiuri, D. Plenker, B. Alagesan, P. Belleau, S. Li, J. Kendall, G.H. Jang, R.K. Kawaguchi, T.D.D. Somerville, H. Tiriach, C.-I. Hwang, R.A. Burkhart, N.J. Roberts, L.D. Wood, R.H. Hruban, J. Gillis, A. Krasnitz, C.R. Vakoc, M. Wigler, F. Notta, S. Gallinger, Y. Park, and D.A. Tuveson

**Précis:** A new mouse model enabled ascertainment of molecular details of the two pancreatic ductal adenocarcinoma subtypes, revealing that the transition from a slow-growing to a fast-growing tumor is marked by activation of KRAS signaling genes.

See commentary, p. 1448

## Lineage Reversion Drives WNT Independence in Intestinal Cancer ..... 1590

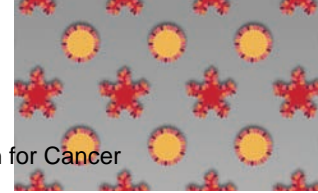
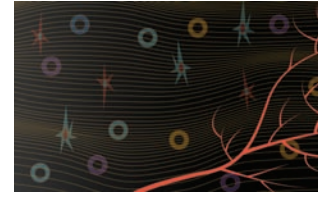
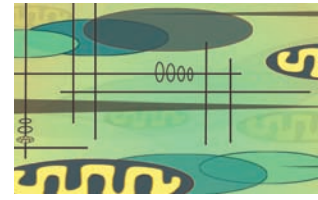
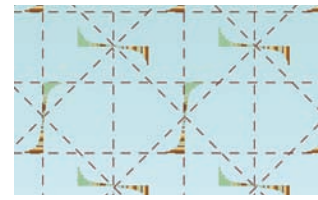
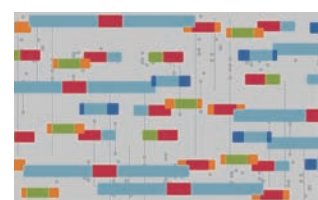
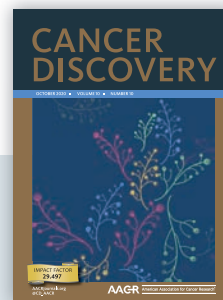
T. Han, S. Goswami, Y. Hu, F. Tang, M.P. Zafra, C. Murphy, Z. Cao, J.T. Poirier, E. Khurana, O. Elemento, J.F. Hechtman, K. Ganesh, R. Yaeger, and L.E. Dow

**Précis:** Colorectal cancer organoids escaped dependence on WNT signaling via a combination of cancer-associated mutations and priming by TGF $\beta$ , abundant in the tumor microenvironment, indicating a possible mechanism of resistance to PORCN inhibitors.

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**ON THE COVER** Pancreatic ductal adenocarcinoma (PDAC) comes in two subtypes, one referred to as basal-like (or squamous) and the other denoted classic (or progenitor). The two types have markedly different gene-expression profiles and carry different prognoses, with basal-like PDAC being more aggressive. Miyabayashi and colleagues developed a novel mouse model in which PDAC organoids are engrafted into the pancreatic ducts, where PDACs develop in humans, and PDACs grown in this way recapitulated the two subtypes observed in patients. Analyses of these tumors revealed that cell plasticity-mediated switching between the subtypes could occur, and the transition from a classic-like to a basal-like subtype was associated with activation of genes in the KRAS pathway. For more information, see the article by Miyabayashi and colleagues on page 1566.



# CANCER DISCOVERY

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