PRIORITY BRIEFS

563 Molecular Drivers of the Non–T-cell-Inflamed Tumor Microenvironment in Urothelial Bladder Cancer
Randy F. Sweis, Stefani Spranger, Riyue Bao, Gladell P. Paner, Walter M. Stadler, Gary Steinberg, and Thomas F. Gajewski

Immunotherapy resistance is a reality for many cancer patients. Three tumor-intrinsic molecular pathways, β-catenin, PPARγ, and FGFR3, were identified and linked to the exclusion of T cells from urothelial tumors. Targeting these pathways may enhance immune checkpoint efficacy.

569 Prolonged Benefit from Ipilimumab Correlates with Improved Outcomes from Subsequent Pembrolizumab
Amanda Shreders, Richard Joseph, Chengwei Peng, Fei Ye, Shilin Zhao, Igor Puzanov, Jeffrey A. Sosman, and Douglas B. Johnson

Anti–PD-1 therapies are becoming first-line treatments for metastatic melanoma, but how prior immune therapy affects anti–PD-1 efficacy is unknown. Prior ipilimumab was found to predict response to anti–PD-1, which could help select patients for therapy.

RESEARCH ARTICLES

574 Expanded and Activated Natural Killer Cells for Immunotherapy of Hepatocellular Carcinoma
Takahiro Kamiya, Yu-Hsiang Chang, and Dario Campana

Hepatocellular carcinoma (HCC) is often incurable. Human NK cells with enhanced cytotoxicity against HCC were expanded in vitro, generating efficient killers of HCC in culture and in mice, supporting the infusion of such cells for treatment of HCC.

582 Immune-Derived PD-L1 Gene Expression Defines a Subgroup of Stage II/III Colorectal Cancer Patients with Favorable Prognosis Who May Be Harmed by Adjuvant Chemotherapy

A subgroup of patients with colorectal cancer was defined by high PD-L1 gene expression on their tumor-infiltrating immune cells. These patients may be harmed by standard chemotherapy and may benefit from immunotherapy that targets the PD-1 immune checkpoint.

592 Pretreatment Immune Status Correlates with Progression-Free Survival in Chemotherapy-Treated Metastatic Colorectal Cancer Patients
Kohei Tada, Shigehisa Kitano, Hirokazu Shoji, Takashi Nishimura, Yasuhiro Shimada, Kengo Nagashima, Kazunori Aoki, Nobuyoshi Hiraoka, Yoshitaka Homma, Satoru Iwasa, Natsuko Okita, Atsuu Takashima, Ken Kato, Yasuhide Yamada, Naoyuki Katayama, Narikazu Bolai, Yuji Heike, and Tetsuya Hamaguchi

It was not clear whether immune cell subsets in peripheral blood have prognostic value for patients about to undergo first-line chemotherapy. This prospective study reveals an immune signature that correlates with significantly longer progression-free survival.

599 Immune-Derived PD-L1 Gene Expression Defines a Subgroup of Stage II/III Colorectal Cancer Patients with Favorable Prognosis Who May Be Harmed by Adjuvant Chemotherapy

A subgroup of patients with colorectal cancer was defined by high PD-L1 gene expression on their tumor-infiltrating immune cells. These patients may be harmed by standard chemotherapy and may benefit from immunotherapy that targets the PD-1 immune checkpoint.

600 Immunogenic Subtypes of Breast Cancer Delineated by Gene Classifiers of Immune Responsiveness
Lance D. Miller, Jeff A. Chou, Michael A. Black, Cristin Print, Julia Chifman, Angela Alistar, Thomas Putti, Xiaobo Zhou, Davide Bedognetti, Wouter Hendrickx, Ashok Pullikuth, Jonathan Rennhack, Eran R. Andrechek, Sandra Demaria, Ena Wang, and Francesco M. Marincola

Assessment of expression profiles and clinical data from many breast tumors enabled classifications having prognostic value. Tumors comprising molecularly distinct subtypes differed in potential for metastasis-protective immune responsiveness, perhaps reflecting a differential activation of immunomodulatory pathways.

611 Enhanced Tumor Control with Combination mTOR and PD-L1 Inhibition in Syngeneic Oral Cavity Cancers
Ellen C. Moore, Harrison A. Cash, Andria M. Caruso, Ravindra Uppaluri, James W. Hodge, Carter Van Waes, and Clint T. Allen

Inhibition of mTOR is felt to be systemically immunosuppressive. However, the antitumor immunity induced by checkpoint inhibition in an immunogenic model of oral cavity cancer was enhanced by the mTOR inhibitor rapamycin via a T cell–dependent mechanism.

621 Antitumor Efficacy of Radiation plus Immunotherapy Depends upon Dendritic Cell Activation of Effector CD8+ T Cells
Simon J. Dovedi, Grazyna Lipowska-Bhalla, Stephen A. Beers, Eleanor J. Cheadle, Lijun Mu, Martin J. Glennie, Timothy M. Illidge, and Jamie Honeychurch

Radiotherapy plus CD40 or TLR7 stimulation leads to long-term clearance of B- and T-cell lymphomas. These curative responses after combining radiotherapy with an immunomodulatory agent depended upon the priming of tumor-specific CD8+ T cells by dendritic cells.
Antitumor Efficacy of Anti-GD2 IgG1 Is Enhanced by Fc Glyco-Engineering
Hong Xu, Hongfen Guo, Irene Y. Cheung, and Nai-Kong V. Cheung

Most effective antibody immunotherapy relies on ADCC. A potent ADCC-enhanced antibody is described that, in comparison with Abs with altered affinities for Fc receptors, significantly improved the growth control of tumors expressing cancer-antigen GD2.

ADDENDUM

ADDENDUM: T Cells Expressing CD19/CD20 Bispecific Chimeric Antigen Receptors Prevent Antigen Escape by Malignant B Cells
Eugenia Zah, Meng-Yin Lin, Anne Silva-Benedict, Michael C. Jensen, and Yvonne Y. Chen

ABOUT THE COVER

Patients with advanced hepatocellular carcinoma (liver cancer) have a median life expectancy of 8 to 11 months. These tumors are frequently associated with viral hepatitis. Natural killer (NK) cells recognize virally infected cells and malignant cells, so to develop an immunotherapy, the authors expanded and activated NK cells ex vivo. These cells, when reinfused into immunodeficient mice hosting human tumors, enabled many mice to survive and efficiently killed tumor cells. The cover is based on a fluorescence confocal image (far right) of PLC/PRF/5 hepatocarcinoma cells (green) surrounded by expanded, activated human NK cells (red). Cover by Lewis Long; image captured by T. Kamiya.
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