CRISPR/CAS9-based DNA damage response screens reveal gene-drug interactions.

Related Articles

CRISPR/CAS9-based DNA damage response screens reveal gene-drug interactions.

DNA Repair (Amst). 2020 Jan 16;87:102803

Abstract
DNA damage response (DDR) is critically important for cell survival, genome maintenance, and its defect has been exploited therapeutically in cancer treatment. Many DDR-targeting agents have been generated and have entered the clinic and/or clinical trials. In order to provide a global and unbiased view of DDR network, we designed a focused CRISPR library targeting 365 DDR genes and performed CRISPR screens on the responses to several DDR inhibitors and DNA-damaging agents in 293A cells. With these screens, we determined responsive pathways enriched under treatment with different types of small-molecule agents. Additionally, we showed that POLE3/4-deficient cells displayed enhanced sensitivity to an ATR inhibitor, a PARP inhibitor, and camptothecin. Moreover, by performing DDR screens in isogenic TP53 wild-type and TP53 knock-out cell lines, our results suggest that the performance of our CRISPR DDR dropout screens is independent of TP53 status. Collectively, our findings indicate that CRISPR DDR screens can be used to identify potential targets of small-molecule drugs and reveal that TP53 status does not affect the outcome of these screens.

PMID: 31991288 [PubMed — as supplied by publisher]

Hidden in plain sight: umbilical melanoma.

Related Articles

Hidden in plain sight: umbilical melanoma.

Med J Aust. 2020 Jan 28;;
Authors: Kovitwanichkanont T, Joseph S, Yip L
PMID: 31990979 [PubMed — as supplied by publisher]

Gut microbial species and metabolic pathways associated with response to treatment with immune checkpoint inhibitors in metastatic melanoma.

Related Articles

Gut microbial species and metabolic pathways associated with response to treatment with immune checkpoint inhibitors in metastatic melanoma.

Melanoma Res. 2020 Jan 27;;
Authors: Wind TT, Gacesa R, Vich Vila A, de Haan JJ, Jalving M, Weersma RK, Hospers GAP

Abstract
In patients with metastatic cancer, gut microbiome composition differs between responder and non-responders to immune checkpoint inhibitors. However, there is little consensus on the microbiome taxa associated with response or lack of response. Additionally, recognized confounders of gut microbiome composition have generally not been taken into account. In this study, metagenomic shotgun sequencing was performed on freshly frozen pre-treatment stool samples from 25 patients (12 responders and 13 non-responders) with unresectable metastatic melanoma treated with immune checkpoint inhibitors. We observed no significant differences in alpha-diversity and bacterial prevalence between responders and non-responders (P > 0.05). In a zero-inflated multivariate analysis, correcting for important confounders such as age, BMI and use of antibiotics, 68 taxa showed differential abundance between responders and non-responders (false-discovery rate
PMID: 31990790 [PubMed — as supplied by publisher]

Related Articles


Authors: Chang M, Dalvin LA, Mazloumi M, Martin A, Yaghy A, Yang X, Bakhtiari S, Li L, Jennings E, Mashayekhi A, Shields CL

Abstract

PURPOSE: The aim of this study was to determine the impact of age on radiation complications after plaque radiotherapy and prophylactic intravitreal bevacizumab for uveal melanoma.

DESIGN: Retrospective cohort study.

METHODS: Retrospective single-center study of plaque-irradiated uveal melanoma with prophylactic intravitreal bevacizumab at 4-month intervals from July 2000 to January 2018.

RESULTS: Of 1131 eyes in 1131 patients, age was 70 years (n = 243). Comparison by age category (70 years) revealed the oldest group presenting with greatest tumor basal diameter (11.3 vs 11.3 vs 12.1 mm, P = 0.03) and worst visual acuity (20÷40 vs 20/40 vs 20/50, P = 0.02). After plaque (mean follow-up 40 vs 42 vs 32 months, P

CONCLUSIONS: After plaque radiotherapy for uveal melanoma and prophylactic intravitreal bevacizumab at 4-month intervals, patients younger than 50 years old have an increased 48-month risk of radiation maculopathy.

PMID: 31990743 [PubMed — in process]

Cumulative Incidence and Predictors of CNS Metastasis for Patients With American Joint Committee on Cancer 8th Edition Stage III Melanoma.

Related Articles

Cumulative Incidence and Predictors of CNS Metastasis for Patients With American Joint Committee on Cancer 8th Edition Stage III Melanoma.

J Clin Oncol. 2020 Jan 28;JCO1901508

Authors: Haydu LE, Lo SN, McQuade JL, Amaria RN, Wargo J.


Abstract

PURPOSE: Improved understanding of the incidence, risk factors, and timing of CNS metastasis is needed to inform surveillance strategies for patients with melanoma.

METHODS AND PATIENTS: Clinical data were extracted from the databases of 2 major melanoma centers in the United States and Australia for 1,918 patients with American Joint Committee on Cancer (AJCC) 8th edition stage III melanoma, diagnosed from 1998-2014, who had (negative) baseline CNS imaging within 4 months of diagnosis. The cumulative incidence of CNS metastasis was calculated in the presence of the competing risk of death, from stage III presentation and at benchmark time points 1, 2, and 5 years postdiagnosis.

RESULTS: At a median follow-up of 70.2 months, distant recurrence occurred in 711 patients (37.1%). The first site of distant metastasis was CNS only for 3.9% of patients, CNS and extracranial (EC) for 1.8%, and EC only for 31.4%. Overall, 16.7% of patients were diagnosed with CNS metastasis during follow-up. The cumulative incidence of CNS metastasis was 3.6% (95% CI, 2.9% to 4.6%) at 1 year, 9.6% (95% CI, 8.3% to 11.0%) at 2 years, and 15.8% (95% CI, 14.1% to 17.6%) at 5 years. The risk of CNS metastasis was significantly influenced by patient sex, age, AJCC stage, primary tumor site, and primary tumor mitotic rate in multivariable and conditional analyses. High primary tumor mitotic rate was significantly associated with increased risk of CNS metastasis at diagnosis and all subsequent time points examined.

CONCLUSION: Similar rates of CNS metastasis were observed in 2 large, geographically distinct cohorts of patients with stage III melanoma. The results highlight the importance of primary tumor mitotic rate. Furthermore, they provide a framework for developing evidence-based surveillance strategies and evaluating the impact of contemporary adjuvant therapies on the risk of CNS metastasis development.

PMID: 31990608 [PubMed — as supplied by publisher]

Codelivery of Anti-PD-1 Antibody and Paclitaxel with Matrix Metalloproteinase and pH Dual-Sensitive Micelles for Enhanced Tumor Chemoimmunotherapy.

Related Articles

Codelivery of Anti-PD-1 Antibody and Paclitaxel with Matrix Metalloproteinase and pH Dual-Sensitive Micelles for Enhanced Tumor Chemoimmunotherapy.

Small. 2020 Jan 28;e1906832

Abstract

Immune checkpoint blockade (ICB) is demonstrating great potential in cancer immunotherapy nowadays. Yet, the low response rate to ICB remains an urgent challenge for tumor immunotherapy. A pH and matrix metalloproteinase dual-sensitive micellar nanocarrier showing spatio-temporally controlled release of anti-PD-1 antibody (aPD-1) and paclitaxel (PTX) in solid tumors is prepared to realize synergistic cancer chemoimmunotherapy. Antitumor immunity can be activated by PTX-induced immunogenic cell death (ICD), while aPD-1 blocks the PD-1/PD-L1 axis to suppress the immune escape due to PTX-induced PD-L1 up-regulation, thus resulting in a synergistic antitumor chemoimmunotherapy. Through decoration with a sheddable polyethylene glycol (PEG) shell, the nanodrug may better accumulate in tumors to boost the synergistic antitumor treatment in a mouse melanoma model. The present study demonstrates a potent antitumor chemoimmunotherapy utilizing tumor microenvironment-sensitive micelles bearing a sheddable PEG layer to mediate site-specific sequential release of aPD-1 and PTX.

PMID: 31990457 [PubMed — as supplied by publisher]

Sonidegib and vismodegib in the treatment of patients with locally advanced basal cell carcinoma: a joint expert opinion.

Sonidegib and vismodegib in the treatment of patients with locally advanced basal cell carcinoma: a joint expert opinion.

J Eur Acad Dermatol Venereol. 2020 Jan 28.;


Abstract

Sonidegib and vismodegib are hedgehog pathway inhibitors (HhIs) approved for the treatment of advanced basal cell carcinoma (BCC). Until recently, vismodegib was the only targeted treatment available for patients with locally advanced BCC (laBCC) in cases where surgery and radiotherapy are inappropriate. Sonidegib has recently been approved and now presents an alternative treatment option. The clinical differences between the two HhIs in patients with laBCC are unclear, as no head-to-head randomized controlled trials are or will be initiated. Moreover, there were important differences in the designs of their pivotal studies, BOLT (sonidegib) and ERIVANCE (vismodegib), and these differences complicate evidence-based analysis of their relative efficacy and safety profiles. In this paper, a group of clinical experts in the management of laBCC summarizes the clinical and pharmacological profiles of sonidegib and vismodegib based on published data and their own clinical experience. One key difference between the two pivotal studies was the criteria used to assess BCC severity. ERIVANCE (a single-arm phase II trial) used the conventional Response Evaluation Criteria in Solid Tumors (RECIST), while the more recent double-blind randomized BOLT trial used the stringent modified RECIST (mRECIST). A pre-planned analysis adjusted the outcomes from BOLT with RECIST-like criteria and this enabled the experts to discuss relative efficacy outcomes for the two treatments. Centrally reviewed objective response rate (ORR) for vismodegib was 47.6% (95% CI 35.5−60.6) at 21-month follow-up using RECIST. After adjusting with RECIST-like criteria, the ORR for sonidegib according to central review at 18-month follow-up was 60.6% (95% CI 47.8−72.4). Both treatments were associated with similar patterns of adverse events. Sonidegib and vismodegib share the same efficacy and tolerability profiles, but their pharmacokinetic profiles show several differences, such as volume of distribution and half-life. Further studies are needed to understand how these differences may impact clinical practice.

PMID: 31990414 [PubMed — as supplied by publisher]

Melanoma Skin Cancer Detection based on Image Processing.

Related Articles

Melanoma Skin Cancer Detection based on Image Processing.

Curr Med Imaging Rev. 2020;16(1):50–58

Authors: Zghal NS, Derbel N

Abstract

BACKGROUND: Skin cancer is one of the most common forms of cancers among humans. It can be classified as non-melanoma and melanoma. Although melanomas are less common than non-melanomas, the former is the most common cause of mortality. Therefore, it becomes necessary to develop a Computer-aided Diagnosis (CAD) aiming to detect this kind of lesion and enable the diagnosis of the disease at an early stage in order to augment the patient’s survival likelihood.

AIMS: This paper aims to develop a simple method capable of detecting and classifying skin lesions using dermoscopy images based on ABCD rules.

METHODS: The proposed approach follows four steps. 1) The preprocessing stage consists of filtering and contrast enhancing algorithms. 2) The segmentation stage aims at detecting the lesion. 3) The feature extraction stage based on the calculation of the four parameters which are asymmetry, border irregularity, color and diameter. 4) The classification stage based on the summation of the four extracted parameters multiplied by their weights yields the total dermoscopy value (TDV); hence, the lesion is classified into benign, suspicious or malignant. The proposed approach is implemented in the MATLAB environment and the experiment is based on PH2 database containing suspicious melanoma skin cancer.

RESULTS AND CONCLUSION: Based on the experiment, the accuracy of the developed approach is 90%, which reflects its reliability.

PMID: 31989893 [PubMed — in process]
The Clinical Significance of Incidental Parotid Uptake in a PET/CT Study: A Diagnostic Algorithm.

Related Articles

The Clinical Significance of Incidental Parotid Uptake in a PET/CT Study: A Diagnostic Algorithm.
Authors: Üstün F, Taştekin E, Taş A, Altun GD

Abstract

BACKGROUND: Patients diagnosed with cancer do not have sufficient clinical data for the management of incidental parotid lesions. We aimed to reveal the importance of randomized parotid lesions encountered during oncologic F-18 fluorodeoxyglucose positron emission tomography (FDG PET/CT) imaging in our clinical practice and the diagnostic algorithm of such lesions.

METHODS: We performed a database search of PET/CT records generated from 2009 to 2015 for "parotid" in reports of patients who underwent PET/CT examination for a known malignancy elsewhere, or cancer screening.

RESULTS: Incidental parotid FDG uptake on PET/CT had a prevalence of 1.1%. The incidence of parotid metastasis in our series was 36.4%, and 75% of them had malign melanoma metastasis. Of the 11 cases, 5 were of Warthin tumours, and Warthin tumours showed stronger GLUT1 expression than metastatic parotid lesions.

CONCLUSION: In patients with malignancy elsewhere, focal involvement of FDG by the parotid gland, especially if malignant melanoma or SCC is absent, should not be considered a metastatic disease without histopathologic confirmation. If parotid disease would change the patient’s treatment plan and disease stage, the parotid lesion should be evaluated by additional methods, such as fine needle aspiration biopsy.

PMID: 31989884 [PubMed — in process]


Related Articles

J Cell Physiol. 2020 Jan 28;;
Authors: Mohammadalipour Z, Rahmati M, Khataee A, Moosavi MA

Abstract

The manipulation of autophagy provides a new opportunity for highly effective anticancer therapies. Recently, we showed that photodynamic therapy (PDT) with nitrogen-doped titanium dioxide (N-TiO2) nanoparticles (NPs) could promote the reactive oxygen species (ROS)-dependent autophagy in leukemia cells. However, the differential autophagic effects of N-TiO2 NPs in the dark and light conditions and the potential of N-TiO2-based PDT for the treatment of melanoma cells remain unknown. Here we show that depending on the visible-light condition, the autophagic response of human melanoma A375 cells to N-TiO2 NPs switches between two different statuses (ie., flux or blockade) with the opposite uncommon in the Caucasian population and has remained unreported in East-Central Europe.

OBJECTIVES: Our aim was to collect data from East-Central Europe by analyzing the demographic and clinicopathologic features of patients with ALM and comparing data with the reports in literature.

METHODS: We conducted a single-center, retrospective review between 1976 and 2016 at one of the largest melanoma referral centers in Hungary.

RESULTS: We identified 176 patients with ALM (3.83%) from 4593 patients with melanoma (mean age: 66.2 years). The tumors were mainly located on the lower extremities (88.63%). The mean Breslow tumor thickness was 3.861 mm, 37.50% of the tumors were thicker than 4.00 mm, and 71.6% exhibited microscopic ulceration. Nearly one-third of the patients underwent sentinel lymph node (SLN) biopsy, and 60.3% of the biopsies were positive for metastasis. The positive SLN status was associated with significantly thick tumors and reduced survival. Patients with ALM had 5- and 10-year overall survival rates of 60.5% and 41.6%, respectively. The mean delay in diagnosis was 18 months after the discovery of skin tumors. In multivariate analyses, age, tumor thickness, and distant metastasis were independent risk factors for poor survival (p

CONCLUSIONS: Our study, which is the first single-center report in East-Central Europe focusing on ALM, confirms that patient and tumor characteristics and prognostic factors are similar with previous literature data involving Caucasians; however, tumor thickness and survival suggest even worse prognosis.

PMID: 31989672 [PubMed — as supplied by publisher]
Mechanisms of checkpoint inhibition induced adverse events.

Related Articles

Mechanisms of checkpoint inhibition induced adverse events.

Clin Exp Immunol. 2020 Jan 28;


Abstract

Immune checkpoint inhibition has revolutionized the treatment of several solid cancers, most notably melanoma and non-small cell lung cancer (NSCLC). Drugs targeting CTLA-4 and PD-1 have made their way into routine clinical use, however this has not been without difficulties. Stimulation of the immune system to target cancer has been found to result in a reduction of self-tolerance, leading to the development of adverse effects that resemble autoimmunity. These adverse effects are erratic in their onset and severity and can theoretically affect any organ type. Several mechanisms for immune-related toxicity have been investigated over recent years, however no consensus on the cause or prediction of toxicity has been reached. This review seeks to examine reported evidence for possible mechanisms of toxicity, methods for prediction of those at risk, and a discussion of future prospects within the field.

PMID: 31989585 [PubMed — as supplied by publisher]

HSP27 Expression as a Novel Predictive Biomarker for Bevacizumab: is it Cost Effective?

Related Articles

HSP27 Expression as a Novel Predictive Biomarker for Bevacizumab: is it Cost Effective?

Pharmacoecon Open. 2020 Jan 27;

Authors: Seo MK, Straume O, Akslen LA, Cairns J

Abstract

BACKGROUND: Despite the extensive use of bevacizumab in a range of oncology indications, the US FDA revoked its approval for breast cancers, and multiple negative trials in several solid malignancies have been reported, so the need for predictive biomarkers has increased. The development of predictive biomarkers for anti-angiogenic bevacizumab therapy has long been pursued but without success.

INTRODUCTION: Heat shock protein (HSP)-27 expression has recently been identified as a predictive biomarker for bevacizumab in treating metastatic melanoma. This study aimed to evaluate the cost effectiveness of HSP27 biomarker testing before administration of bevacizumab.

METHODS: A partitioned survival analysis model with three mutually exclusive health states (progression-free survival, progressed disease, and death) was developed using a Norwegian health system perspective. The proportion of patients in each state was calculated using the area under the Kaplan-Meier curve for progression-free and overall survival derived from trials of bevacizumab and dacarbazine. Three strategies were compared: (1) test-treat with HSP27 biomarker and bevacizumab, (2) treat-all with dacarbazine without HSP27 testing, (3) treat-all with bevacizumab without HSP27 testing. Quality-adjusted life-years (QALYs) and costs were calculated for each strategy and discounted at 4%. A lifetime horizon was applied. Uncertainty analyses were performed. Expected value of perfect information (EVPI) was estimated to assess the potential value of further research to generate more evidence.

RESULTS: Although the test-treat strategy was cost effective compared with treat-all with dacarbazine, it was not cost effective compared with treat-all with bevacizumab without HSP27 testing. However, EVPI results showed very minimal or no value in conducting further research efforts to reduce uncertainties around current information.

CONCLUSION: The results of this study suggested that testing for HSP27 expression before administering bevacizumab is not cost effective compared with treat-all with bevacizumab without testing. It indicates that HSP27 expression is not cost effective as a potential predictive biomarker for bevacizumab. This may not necessarily mean that HSP27 is a bad biomarker for bevacizumab, but it may mean that bevacizumab is much better than dacarbazine regardless of HSP27 expression, so patient stratification according to HSP27 status is meaningless. Or, indeed, it may imply that HSP27 is not sufficiently good at identifying the right patients for bevacizumab.

PMID: 31989465 [PubMed — as supplied by publisher]

Tissue-resident memory T cells in the skin.

Related Articles

Tissue-resident memory T cells in the skin.

Inflamm Res. 2020 Jan 27;

Authors: Khalil S, Bardawil T, Kurban M, Abbas O

Abstract

PURPOSE: Tissue-resident memory T (TRM) cells are a newly described subset of memory T cells. The best characterized TRM cells are CD8+ and express CD103 and CD69. These cells are non-recirculating and persist long term in tissues, providing
immediate protection against invading pathogens. However, their inappropriate activation might contribute to the pathogenesis of autoimmune and inflammatory disorders. In the skin, these cells have been described in psoriasis, vitiligo, and melanoma among other diseases.

METHODS: Literature review was done to highlight what is currently known on the phenotype and function of TRM cells and summarizes the available data describing their role in various cutaneous conditions.

RESULTS: Resolved psoriatic skin and disease-naïve non-lesional skin contain a population of IL-17-producing TRM cells with shared receptor sequences that recognize common antigens and likely contribute to disease recurrence after cessation of therapy. In vitiligo, TRM cells produce perforin, granzyme B, and interferon-γ following stimulation by interleukin-15 and collaborate with recirculating memory T cells to maintain disease. In melanoma, increased accumulation of TRM cells was recently shown to correlate with improved survival in patients undergoing therapy with immune checkpoint inhibitors.

PMID: 31989191 [PubMed — as supplied by publisher]

Remodeling the fibrotic tumor microenvironment of desmoplastic melanoma to facilitate vaccine immunotherapy.

Related Articles
Remodeling the fibrotic tumor microenvironment of desmoplastic melanoma to facilitate vaccine immunotherapy.
Nanoscale. 2020 Jan 28.;
Authors: Zhu H, Liu Q, Miao L, Musetti S, Huo M, Huang L

Abstract
Highly fibrotic and collagen-rich properties in desmoplastic melanoma (DM) result in an immune-suppressive fibrotic tumor microenvironment (TME) that resists clinical therapies. The different clinical and pathological properties, as compared to conventional melanoma, lead to delayed diagnosis and it is difficult to deliver drugs effectively due to fibrosis. Herein, we designed a chemo-immuno strategy focused on combining vaccination immunotherapy with multi-targeting sunitinib (SUN) nano-therapy to remodel TME and generate a robust immune response and a stronger synergistic anti-cancer effect. This strategy was evaluated side-by-side with non-desmoplastic melanoma and achieved significant improvement in therapeutic efficacy. The combination treatment was also synergistically assessed with the desmoplastic melanoma model. This strategy can remodel the fibrotic immunosuppressive TME and result in a robust cytotoxic T-cell response by reducing the collagen content, normalizing blood vessels, inhibiting tumor-associated fibroblasts and reducing high levels of suppressor immune cells. The modification of fibrotic immunosuppressive TME may serve as a good approach to further enhance immunotherapy for desmoplastic tumors.

PMID: 31989142 [PubMed — as supplied by publisher]

Surface Mould Brachytherapy for Skin Cancers: The British Columbia Cancer Experience.

Related Articles
Surface Mould Brachytherapy for Skin Cancers: The British Columbia Cancer Experience.
Cureus. 2019 Dec 18;11(12):e6412
Authors: Casey S, Awotwi-Pratt J, Bahl G

Abstract
Purpose To report on skin tumor treatment with surface mould brachytherapy at our institution. Methods This was a retrospective review for all patients with skin tumors treated using Ir-192 high dose rate (HDR) surface mould brachytherapy from January 1, 2010 to December 31, 2017 in British Columbia. We identified 65 lesions (59 patients). Median age at diagnosis was 83 (range = 45–97). The majority were basal cell (54%, n = 35) or squamous cell carcinomas (31%, n = 20). Most lesions were located in the head and neck region. The most commonly used RT dose was 40 Gy/10 fractions; all patients had individualized CT-based planning. Results The two-year overall survival (OS) was 77.6% and two-year progression-free survival (PFS) was 71.5%. Most deaths were from unrelated causes. Response was assessed in clinic 2–4 months post-treatment. Our complete response (CR) rate was 96.8%, with partial response in two patients; two patients could not be assessed for response. We report a two-year local control (LC) rate of 84.9%, and local recurrence in five patients. The procedure was well tolerated, with no grade 3–5 acute or late toxicities. There was one case of grade 2 radionecrosis (Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03). The 100% isodose line median depth was 0.5 cm, and median surface dose = 126.5%. The median V90 = 92.3%. Conclusion Surface mould brachytherapy for skin tumors is a safe and effective modality, with excellent response rates. It is well-tolerated and a non-invasive option for elderly patients with comorbidities.

PMID: 31988814 [PubMed]

B4GALNT1 induces angiogenesis, anchorage independence growth and motility, and promotes tumorigenesis in melanoma by induction of ganglioside GM2/GD2.

Related Articles
B4GALNT1 induces angiogenesis, anchorage independence
growth and motility, and promotes tumorigenesis in melanoma by induction of ganglioside GM2/GD2.

Authors: Yoshida H, Koodie L, Jacobsen K, Hanzawa K, Miyamoto Y, Yamamoto M

Abstract
β-1,4-N-Acetyl-Galactosaminyltransferase 1 (B4GALNT1) encodes the key enzyme B4GALNT1 to generate gangliosides GM2/GD2. GM2/GD2 gangliosides are surface glycolipids mainly found on brain neurons as well as peripheral nerves and skin melanocytes and are reported to exacerbate the malignant potential of melanomas. In order to elucidate the mechanism, we performed functional analyses of B4GALNT1-overexpressing cells. We analyzed ganglioside pattern on four melanoma and two neuroblastoma cell lines by high performance liquid chromatography (HPLC). We overexpressed B4GALNT1 in GM2/GD2-negative human melanoma cell line (SH4) and confirmed production of GM2/GD2 by HPLC. They showed higher anchorage independence growth (AIG) in colony formation assay, and exhibited augmented motility. In vitro, cell proliferation was not affected by GM2/GD2 expression. In vivo, GM2/GD2-positive SH4 clones showed significantly higher tumorigenesis in NOD/Scid/IL2rγ-null mice, and immunostaining of mouse CD31 revealed that GM2/GD2 induced remarkable angiogenesis. No differences were seen in melanoma stem cell and Epithelial-Mesenchymal Transition markers between GM2/GD2-positive and -negative SH4 cells. We therefore concluded that B4GALNT1, and consequently GM2/GD2, enhanced tumorigenesis via induction of angiogenesis, AIG, and cell motility. RNA-Seq suggested periostin as a potential key factor for angiogenesis and AIG. These findings may lead to development of novel therapy for refractory melanoma.

PMID: 31988291 [PubMed — in process]

Association of anti-TNF with decreased survival in steroid refractory ipilimumab and anti-PD1 treated patients in the Dutch Melanoma Treatment Registry.

Related Articles
Association of anti-TNF with decreased survival in steroid refractory ipilimumab and anti-PD1 treated patients in the Dutch Melanoma Treatment Registry.

Clin Cancer Res. 2020 Jan 27;:

Abstract
Background Unleashing the immune system by PD-1 and/or CTLA-4 blockade can cause severe immune-related toxicity necessitating immunosuppressive treatment. Whether immunosuppression for toxicity impacts survival is largely unknown. Patients and methods Using data from the prospective nationwide Dutch Melanoma Treatment Registry (DMTR), we analysed the association between severe toxicity and overall survival (OS) in 1250 patients with advanced melanoma who were treated with immune checkpoint inhibitors (ICI) in first line between 2012 and 2017. Furthermore, we analysed whether

A nicotinamide phosphoribosyltransferase-GAPDH interaction sustains the stress-induced NMN/NAD+ salvage pathway in the nucleus.

Related Articles
A nicotinamide phosphoribosyltransferase-GAPDH interaction sustains the stress-induced NMN/NAD+ salvage pathway in the nucleus.

J Biol Chem. 2020 Jan 27;:

Abstract
All cells require sustained intracellular energy flux, which is driven by redox chemistry at the subcellular level. Nicotinamide adenine dinucleotide (NAD+), its phosphorylated variant NAD[+]+, and its reduced forms NAD/[NADH] are all redox cofactors with key roles in energy metabolism and are substrates for several NAD-consuming enzymes (e.g. poly-ADP ribose polymerases [PARPs], sirtuins, and others). The nicotinamide salvage pathway, constituted by nicotinamide mononucleotide adenylyltransferase (NMNAT) and nicotinamide phosphoribosyltransferase (NAMPT), mainly replenishes NAD+ in eukaryotes. Yet, unlike NMNAT1, NAMPT is not known to be a nuclear protein, prompting the question how the nuclear NAD+ pool is maintained and how it is replenished upon NAD+ consumption. In the present work, using human and murine cells; immunoprecipitation, pulldown, and surface plasmon resonance assays; and immunofluorescence, small-angle X-ray scattering (SAXS), and MS-based analyses, we report that GAPDH and NAMPT form a stable complex that is essential for nuclear translocation of NAMPT. This translocation furnishes NMN to replenish NAD+ in order to compensate for the activation of NAD-consuming enzymes by stressful stimuli induced by exposure to H2O2 or S-nitrosoglutathione and DNA damage inducers. These results indicate that by forming a complex with GAPDH, NAMPT can translocate to the nucleus and thereby sustain the stress-induced NMN/NAD+ salvage pathway.

PMID: 31988240 [PubMed — as supplied by publisher]
toxicity management affected survival in these patients. Results 1250 patients were included, of whom 589 received anti-PD1 monotherapy, 576 ipilimumab and 85 combination therapy. 312 patients (25%) developed severe (grade ≥3) toxicity. Patients experiencing severe ICI toxicity had a significantly prolonged survival with a median OS of 23 months compared to 15 months for patients without severe toxicity (HRadj 0.77; 95%CI 0.63−0.93). Among patients experiencing severe toxicity, survival was significantly decreased in patients who received anti-TNF +/-steroids for steroid-refractory toxicity compared to patients who were managed with steroids only (HRadj 1.61; 95%CI 1.03−2.51), with a median OS of 17 months and 27 months, respectively. Conclusion Patients experiencing severe ICI toxicity have a prolonged overall survival. However, this survival advantage is abrogated when anti-TNF is administered for steroid-refractory toxicity. Further prospective studies are needed to assess the effect of different immunosuppressive regimens on checkpoint inhibitor efficacy.

PMID: 31988197 [PubMed — as supplied by publisher]

Multiple pigmented lesions of the breast following ipsilateral breast carcinoma.

Related Articles

Multiple pigmented lesions of the breast following ipsilateral breast carcinoma.

Am J Med. 2020 Jan 24;:
Authors: Limmer A, Swali R, Robare S
PMID: 31987804 [PubMed — as supplied by publisher]

Detecting copy number alterations of oncogenes in cell-free DNA to monitor treatment response in acral and mucosal melanoma.

Related Articles

Detecting copy number alterations of oncogenes in cell-free DNA to monitor treatment response in acral and mucosal melanoma.

J Dermatol Sci. 2020 Jan 15;:
Authors: Mikoshiba A, Ashida A, Sakaizawa K, Kiniwa Y, Okuyama R

Abstract
BACKGROUND: Reliable biomarkers are necessary for assessment of treatment responses. Acral and mucosal melanomas are commonly associated with copy number (CN) alterations rather than specific point mutations, with CN alterations inKIT, CDK4, and CCND1 occurring frequently. Cell-free DNA is released to peripheral blood by both normal and tumor cells, and therefore contains the same genetic alterations present in the source tumor.

OBJECTIVE: To investigate the usefulness of detecting CN alterations in oncogenes in cell-free DNA for monitoring treatment response in acral and mucosal melanomas.

METHODS: We isolated cell-free DNA from peripheral blood and assessed the CN alterations in the cell-free DNA. Using droplet digital PCR, we examined CN alterations ofKIT, CDK4, and CCND1 in tumors from 37 melanoma patients (acral, n = 27; mucosal, n = 10) and peripheral blood from 24 melanoma patients (acral, n = 17; mucosal, n = 7).

RESULTS: CN gain was detected in at least one of the genes examined in 62.9% (17÷27) of acral melanomas and 70% (7÷10) of mucosal melanomas. CN gains were also detected in the plasma of some patients. Furthermore, plasma CN ratio was correlated with clinical condition. This correlation was especially clear in patients with high CN ratios in tumors and high tumor burdens.

CONCLUSION: Plasma CN ratios may be useful for evaluating treatment responses in patients with acral and mucosal melanoma.

PMID: 31987696 [PubMed — as supplied by publisher]

Reply to the letter to the Editor “Reply to ‘Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists’ by H. A. Haenssle et al. ” by L. Oakden-Rayner.

Related Articles

Reply to the letter to the Editor "Reply to ‘Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists’ by H. A. Haenssle et al. ” by L. Oakden-Rayner.

Authors: Haenssle HA, Fink C, Uhlmann L
PMID: 31987435 [PubMed — in process]
Paclitaxel with or without trametinib or pazopanib in advanced wild-type BRAF melanoma (PACMEL): a multicentre, open-label, randomised, controlled phase II trial.

Related Articles
Paclitaxel with or without trametinib or pazopanib in advanced wild-type BRAF melanoma (PACMEL): a multicentre, open-label, randomised, controlled phase II trial.


Abstract
BACKGROUND: Advanced melanoma treatments often rely on immunotherapy or targeting mutations, with few treatment options for wild-type BRAF (BRAF-wt) melanoma. However, the mitogen-activated protein kinase pathway is activated in most melanoma, including BRAF-wt. We assessed whether inhibiting this pathway by adding kinase inhibitors trametinib or pazopanib to paclitaxel chemotherapy improved outcomes in patients with advanced BRAF-wt melanoma in a phase II, randomised and open-label trial.

PATIENTS AND METHODS: Patients were randomised (1 : 1 : 1) to paclitaxel alone or with trametinib or pazopanib. Paclitaxel was given for a maximum of six cycles, while 2 mg trametinib and 800 mg pazopanib were administered orally once daily until disease progression or unacceptable toxicity. Participants and investigators were unblinded. The primary end point was progression-free survival (PFS). Key secondary end points included overall survival (OS) and objective response rate (ORR).

RESULTS: Participants were randomised to paclitaxel alone (n = 38), paclitaxel and trametinib (n = 36), or paclitaxel and pazopanib (n = 37). Adding trametinib significantly improved 6-month PFS [time ratio (TR), 1.47; 90% confidence interval (CI) 1.08–2.01, P = 0.04] and ORR (42% versus 13%; P = 0.01) but had no effect on OS (P = 0.25). Adding pazopanib did not benefit 6-month PFS; (TR 1.36; 90% CI 0.96–1.93; P = 0.14), ORR, or OS. Toxicity increased in both combination arms.

CONCLUSION: In this phase II trial, adding trametinib to paclitaxel chemotherapy for BRAF-wt melanoma improved PFS and substantially increased ORR but did not impact OS. This study was registered with the EU Clinical Trials Register, EudraCT number 2011–002545–35, and with the ISRCTN registry, number 43327231.

PMID: 31987431 [PubMed — in process]

Immunotherapy in organ-transplanted cancer patients: efficacy and risk of organ rejection.

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Immunotherapy in organ-transplanted cancer patients: efficacy and risk of organ rejection.

Authors: Ros J, Matos I, Martin-Liberal J

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Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma.

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Discontinuation of anti-PD-1 antibody therapy in the absence of disease progression or treatment limiting toxicity: clinical outcomes in advanced melanoma.

Ann Oncol. 2019 Jul;30(7):1154–1161

Abstract
BACKGROUND: Programmed cell death protein 1 (PD-1) blocking monoclonal antibodies improve the overall survival of patients with advanced melanoma but the optimal duration of treatment has not been established.

PATIENTS AND METHODS: This academic real-world cohort study investigated the outcome of 185 advanced melanoma patients who electively discontinued anti-PD-1 therapy with pembrolizumab (N=167) or nivolumab (N=18) in the absence of disease progression (PD) or treatment limiting toxicity (TLT) at 14 medical centres across Europe and Australia.

RESULTS: Median time on treatment was 12 months (range 0.7−43). The best objective tumour response at the time of treatment discontinuation was complete response (CR) in 117 (63%) patients, partial response (PR) in 44 (24%) patients and stable disease (SD) in 16 (9%) patients; 8 (4%) patients had no evaluable disease (NE). After a median follow-up of 18 months (range 0.7–48) after treatment discontinuation, 78% of patients
remained free of progression. Median time to progression was 12 months (range 2–23). PD was less frequent in patients with CR (14%) compared with patients with PR (32%) and SD (50%). Six out of 19 (32%) patients who were retreated with an anti-PD-1 at the time of PD obtained a new antitumour response.

CONCLUSIONS: In this real-world cohort of advanced melanoma patients discontinuing anti-PD-1 therapy in the absence of TLT or PD, the duration of anti-PD-1 therapy was shorter when compared with clinical trials. In patients obtaining a CR, and being treated for >6 months, the risk of relapse after treatment discontinuation was low. Patients achieving a PR or SD as best tumour response were at higher risk for progression after discontinuing therapy, and defining optimal treatment duration in such patients deserves further study. Retreatment with an anti-PD-1 at the time of progression may lead to renewed antitumour activity in some patients.


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Phase Ib study of atezolizumab combined with cobimetinib in patients with solid tumors.

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Phase Ib study of atezolizumab combined with cobimetinib in patients with solid tumors.


Abstract

BACKGROUND: Preclinical evidence suggests that MEK inhibition promotes accumulation and survival of intratumoral tumor-specific T cells and can synergize with immune checkpoint inhibition. We investigated the safety and clinical activity of combining a MEK inhibitor, cobimetinib, and a programmed cell death 1 ligand 1 (PD-L1) inhibitor, atezolizumab, in patients with solid tumors.

PATIENTS AND METHODS: This phase I/ Ib study treated PD-L1/PD-1-naïve patients with solid tumors in a dose-escalation stage and then in multiple, indication-specific dose-expansion cohorts. In most patients, cobimetinib was dosed once daily orally for 21 days on, 7 days off. Atezolizumab was dosed at 800 mg intravenously every 2 weeks. The primary objectives were safety and tolerability. Secondary end points included objective response rate, progression-free survival, and overall survival.

RESULTS: Between 27 December 2013 and 9 May 2016, 152 patients were enrolled. As of 4 September 2017, 150 patients received ≥1 dose of atezolizumab, including 14 in the dose-escalation cohorts and 136 in the dose-expansion cohorts. Patients had metastatic colorectal cancer (mCRC; n=84), melanoma (n=22), non-small-cell lung cancer (NSCLC; n=28), and other solid tumors (n=16). The most common all-grade treatment-related adverse events (AEs) were diarrhea (67%), rash (48%), and fatigue (40%), similar to those with single-agent cobimetinib and atezolizumab. One (