Targeting galectin-1 by aflibercept strongly enhances its antitumor effect in neuroendocrine carcinomas.

Related Articles

Targeting galectin-1 by aflibercept strongly enhances its antitumor effect in neuroendocrine carcinomas.

Neuroendocrinology. 2020 Jan 28;
Authors: Rodríguez-Remirez M, Del Puerto-Nevado L, Fernández Aceñero MJ, Cruz-Ramos M, García-García L, Solanes S, Molina-Roldán E, García-Foncillas J, Cebrián A

Abstract

BACKGROUND: Galectin-1 (Gal-1) plays major roles in cancer by modulating different processes leading to tumor development and progression. In the last years, it has been suggested as a promising target for anticancer therapy. Recently, aflibercept has shown high affinity for Gal-1. Here, we investigated how aflibercept could exert its antitumor activity via Gal-1-driven pathways in neuroendocrine carcinomas (NEC).

METHODS AND RESULTS: NEC tumor xenograft were used to assess the effect of aflibercept on Gal-1 functions. Aflibercept induced a significant reduction of Gal-1 at epithelial, stromal and extracellular localizations in lung NEC, whereas this was not observed in colon NECs which displayer low expression of Gal-1. Additionally, aflibercept significantly reduced p-VEGFR2 protein, extracellular matrix remodeling, epithelial-mesenchymal transition and activation of cancer-associated fibroblast hampering cell invasion in lung NEC but not in colon NEC. Gal-1 screening in human NECs confirmed that pulmonary and pancreatic tumors displayed higher levels of Gal-1 than colon NECs, becoming good candidates to benefit from aflibercept treatment.

CONCLUSIONS: The lack of validated predictive markers of aflibercept is a weakness for guaranteeing the best treatment management with this drug. This work provides new mechanistic insight of aflibercept depending on Gal-1. Thus, in tumors overexpressing Gal-1 aflibercept has not only an antiangiogenic effect but also prevents Gal-1-mediated tumor-stroma crosstalk. The stronger aflibercept effect in tumors with high levels of Gal-1 points out this protein as a molecular marker to predict the efficacy of this agent not only for NECs but also for other tumors with high levels of this protein.

PMID: 31991407 [PubMed — as supplied by publisher]

Protective effect of diallyl disulfide against cerulein-induced acute pancreatitis and associated lung injury in mice.

Related Articles

Protective effect of diallyl disulfide against cerulein-induced acute pancreatitis and associated lung injury in mice.

Int Immunopharmacol. 2020 Jan 25;80:106136
Authors: Mathan Kumar M, Tamizhselvi R

Abstract

Garlic (Allium sativum) — derived organosulfur compound diallyl disulfide (DADS) possesses antioxidant, anti-inflammatory and anti-cancer effects. This study was aimed to investigate the anti-inflammatory role and the underlying molecular mechanisms of DADS in cerulein-induced acute pancreatitis (AP) and associated lung injury. Administration of DADS significantly attenuated the severity of pancreatic and pulmonary inflammation by inhibiting cerulein induced serum amylase, myeloperoxidase activity (MPO) and histological changes in pancreas and lung. Furthermore, the anti-inflammatory effect of DADS was associated with the decrease in tumor necrosis factor (TNF)-α,cystathionine-γ-lyase (CSE), preprotachykinin A (PPTA), neurokinin-1-receptor (NK1R) expression and hydrogen sulfide (H2S) production in both pancreas and lung. In addition, DADS reduced caerulein-induced I-κB degradation and subsequent translocation of NF-κB in the pancreas and lung. These results show for the first time that in AP, DADS exhibits an anti-inflammatory effect by inhibiting CSE/H2S and SP/NK1R signaling and NF-κB pathway.

PMID: 31991372 [PubMed — as supplied by publisher]
Immune Modulation by Telomerase-Specific Oncolytic Adenovirus Synergistically Enhances Antitumor Efficacy with Anti-PD1 Antibody.

Related Articles

Immune Modulation by Telomerase-Specific Oncolytic Adenovirus Synergistically Enhances Antitumor Efficacy with Anti-PD1 Antibody.

Mol Ther. 2020 Jan 10;


Abstract
The clinical benefit of monotherapy involving immune checkpoint inhibitors (ICIs) such as anti-programmed death-1 antibody (PD-1 Ab) is limited to small populations. We previously developed a telomerase-specific oncolytic adenovirus, Telomelysin (OBP-301), the safety of which was confirmed in a phase I clinical study. Here, we examined the potential of OBP-502, an OBP-301 variant, as an agent for inducing immunogenic cell death (ICD) and synergistically enhancing the efficacy of OBP-502 with PD-1 Ab using CT26 murine colon cancer and PAN02 murine pancreatic cancer cell lines. OBP-502 induced the release of ICD molecules such as adenosine triphosphate (ATP) and high-mobility group box protein 1 (HMGB1) from CT26 and PAN02 cells, leading to recruitment of CD8-positive lymphocytes and inhibition of Foxp3-positive lymphocyte infiltration into tumors. Combination therapy involving OBP-502 intratumoral administration and PD-1 Ab systemic administration significantly suppressed the growth of both OBP-502-treated tumors and not treated with OBP-502 (so-called abscopal effect) in CT26 and PAN02 bilateral subcutaneous tumor models, in which active recruitment of CD8-positive lymphocytes was observed even in tumors not treated with OBP-502. This combined efficacy was similar to that observed in a CT26 rectal orthotopic tumor model involving liver metastases. In conclusion, telomerase-specific oncolytic adenoviruses are promising candidates for combined therapies with ICIs.

PMID: 31991110 [PubMed — as supplied by publisher]

Identify potential clinical significance of long noncoding RNA forkhead box P4 antisense RNA 1 in patients with early stage pancreatic ductal adenocarcinoma.

Related Articles

Identify potential clinical significance of long noncoding RNA forkhead box P4 antisense RNA 1 in patients with early stage pancreatic ductal adenocarcinoma.

Cancer Med. 2020 Jan 28;

Authors: Liu XG, Xu H, Chen M, Tan XY, Chen XF, Yang YG, Lin MZ, Liu GH, Liang XL, Qian YB, Yuan GJ, Chen MQ, Li WT, Miao HL, Li MY, Liao XW, Dai W, Chen NP

Abstract
Previous studies have shown that forkhead box P4 antisense RNA 1 (FOXP4-AS1) is dysregulated in tumor tissues and can serve as a prognostic indicator for multiple cancers. However, the clinical significance of FOXP4-AS1 in pancreatic ductal adenocarcinoma (PDAC) remains unclear. The goal of this study is to recognize the possible clinical significance of long noncoding RNA FOXP4-AS1 in patients with early stage PDAC. A total of 112 patients from The Cancer Genome Atlas (TCGA) PDAC cohort, receiving RNA sequencing, were involved in the study. Survival analysis, functional mechanism, and potential small molecule drugs of target therapy of FOXP4-AS1 were performed in this study. Survival analysis in TCGA PDAC cohort suggested that patients with high FOXP4-AS1 expression had significantly augmented possibility of death than in PDAC patients with lower FOXP4-AS1 expression (adjusted P = .008; adjusted HR = 2.143, 95% CI = 1.221−3.760). In this study, a genome-wide RNA sequencing dataset was used to identify 927 genes co-expressing with FOXP4-AS1 in PDAC tumor tissues. A total of 676 differentially expressed genes were identified between different FOXP4-AS1 expression groups. Functional enrichment analysis of these genes and gene set enrichment analysis for PDAC genome-wide RNA sequencing dataset was done. We have found that FOXP4-AS1 may function in PDAC by participating in biological processes and pathways including oxidative phosphorylation, tricarboxylic acid cycle, classical tumor-related pathways such as NF-kappaB as well as Janus kinase/signal transducers in addition to activators of transcription, cell proliferation, and adhesion. In addition, we also screened two potential targeted therapeutic small molecule drugs (dimenhydrinate and metanephrine) for FOXP4-AS1 in PDAC. In conclusion, our present study demonstrated that higher expression of FOXP4-AS1 in PDAC tumor tissues were related with an inferior medical outcome. Through multiple genome-wide approaches, we identified the potential molecular mechanisms of FOXP4-AS1 in PDAC and two targeted therapeutic drugs for it.

PMID: 31991068 [PubMed — as supplied by publisher]
Endocytosis of ATB0,+(SLC6A14)-targeted liposomes for drug delivery and its therapeutic application for pancreatic cancer.

Related Articles

Endocytosis of ATB0,+(SLC6A14)-targeted liposomes for drug delivery and its therapeutic application for pancreatic cancer.

Expert Opin Drug Deliv. 2020 Jan 28;:

Abstract
Background: SLC6A14 (ATB0,+), a Na+/Cl-coupled transporter for neutral/cationic amino acids, is overexpressed in many cancers; it has been investigated as a target for improved liposomal drug delivery to treat liver cancer. Research design and methods: Here we explored the mechanism of ATB0,+–mediated entry of such liposomes. As ATB0,+ is highly expressed in pancreatic cancer, we also examined the therapeutic utility of ATB0,+–targeted liposomal drug delivery to treat this cancer. Results: The uptake of lysine-conjugated liposomes (LYS-LPs) was greater in ATB0,+–positive MCF7 cells. The uptake process consisted of two steps: binding and internalization. The binding of LYS-LPs to MCF7 cells was higher than that of bare liposomes, and the process was dependent on Na+ and Cl–, and inhibitable by ATB0,+ substrates or blocker. In contrast, the internalization step was independent of lysine. The cellular entry of LYS-LPs facilitated by ATB0,+ occurred via endocytosis with transient endosomal degradation of ATB0,+ protein with subsequent recovery. Moreover, LYS-LPs also enhanced the uptake and cytotoxicity of gemcitabine in these cells in an ATB0,+–dependent manner. Conclusions: We conclude that ATB0,+ could be exploited for targeted drug delivery in the form of lysine-conjugated liposomes and that the approach represents a novel strategy for enhanced pancreatic cancer therapy.

PMID: 31990587 [PubMed — as supplied by publisher]

Solid pseudopapillary neoplasm of the pancreas: a report of 10 cases and literature review.

Related Articles

Solid pseudopapillary neoplasm of the pancreas: a report of 10 cases and literature review.

ANZ J Surg. 2020 Jan 28;:

Abstract
Background: Solid pseudopapillary tumour of the pancreas (SPTP) is a rare pancreatic tumour characterized by a non-specific clinical presentations and vague radiologic features. The aim of this study is to identify these tumours from other pancreatic neoplasms because complete resection is curative in most cases and provides long-term survival. Methods: A retrospective analysis of patients operated for SPTP between January 2000 and December 2018 was conducted. The collected data included age, gender, clinical findings, laboratory tests, radiological findings, anatomicopathological examination, immunohistochemistry results, surgical treatment, mortality, morbidity and recurrence. Results: Ten cases of SPTP have been diagnosed between January 2000 and December 2018 representing 5.1% of all pancreatic tumours operated during this period (male/female: 2/8; median age 41.2 years; range 19–78 years). The most common symptom was abdominal pain and physical examination was normal in four of 10 cases. The most common tumour localization was the tail of the pancreas. The main tumour size was 7.2 cm (range 2–15 cm). One patient had abdominal disseminated disease. Surgical interventions were distal pancreatectomy in five cases, enucleation in one case, cephalic duodeno-pancreatectomy in two cases, central pancreatectomy in one case and pancreatic biopsy in one case. Only one patient received adjuvant chemotherapy. During follow-up, one patient died after 12 months and another developed unique hepatic metastasis that was resected. Conclusion: Although it is delayed in diagnosis, the overall prognosis of these tumours remains good even with local recurrence and metastasis. Complete surgical resection is the treatment of choice even in cases of recurrence.

PMID: 31989788 [PubMed — as supplied by publisher]

PTBP3 promotes malignancy and hypoxia-induced chemoresistance in pancreatic cancer cells by ATG12 up-regulation.

Related Articles

PTBP3 promotes malignancy and hypoxia-induced chemoresistance in pancreatic cancer cells by ATG12 up-regulation.

J Cell Mol Med. 2020 Jan 27;:

Abstract
Pancreatic ductal adenocarcinoma (PDAC) tumours exhibit a high level of heterogeneity which is associated with hypoxia and strong resistance to chemotherapy. The RNA splicing protein polyuridine tract-binding protein 3 (PTBP3) regulates hypoxic gene expression by selectively binding to hypoxia-regulated
transcripts. We have investigated the role of PTBP3 in tumour development and chemotherapeutic resistance in human PDAC tissues and pancreatic cancer cells. In addition, we determined the sensitivity of cancer cells to gemcitabine with differential levels of PTBP3 and whether autophagy and hypoxia affect gemcitabine resistance in vitro. PTBP3 expression was higher in human pancreatic cancer than in paired adjacent tissues. PTBP3 overexpression promoted PDAC proliferation in vitro and tumour growth in vivo, whereas PTBP3 depletion had opposing effects. Hypoxia significantly increased the expression of PTBP3 in pancreatic cancer cells in vitro. Under hypoxic conditions, cells were more resistance to gemcitabine. Knockdown of PTBP3 results in decreased resistance to gemcitabine, which was attributed to attenuated autophagy. We propose that PTBP3 binds to multiple sites in the 3′-UTR of ATG12 resulting in overexpression. PTBP3 increases cancer cell proliferation and autophagic flux in response to hypoxic stress, which contributes to gemcitabine resistance.

PMID: 31989778 [PubMed — as supplied by publisher]

**Detection and Characterization of Oncogene Mutations in Preneoplastic and Early Neoplastic Lesions.**

Related Articles

**Detection and Characterization of Oncogene Mutations in Preneoplastic and Early Neoplastic Lesions.**

Methods Mol Biol. 2020;2102:419–437

Authors: Minamoto T

Abstract

While it has been more than 30 years since its discovery, the ras family of genes has not yet lost its impact on basic and clinical oncology. These genes remain central to the field of molecular oncology as tools for investigating carcinogenesis and oncogenic signaling, as powerful biomarkers for the identification of those who have or are at high risk of developing cancer, and as oncogene targets for the design and development of new chemotherapeutic drugs. Mutational activation of the K-RAS proto-oncogene is an early event in the development and progression of the colorectal, pancreatic, and lung cancers that are the major causes of cancer death in the world. The presence of point mutational “hot spots” at sites necessary for the activation of this proto-oncogene has led to the development of a number of highly sensitive PCR-based methods that are feasible for the early detection of K-RAS oncogene mutations in the clinical setting. In light of these facts, mutation at the K-RAS oncogene has the potential to serve as a useful biomarker in the early diagnosis and risk assessment of cancers with oncogenic ras signaling. This chapter describes a highly sensitive method for detecting mutant K-RAS, enriched PCR, and its application to early detection of alterations in this oncogene in preneoplastic and early neoplastic lesions of the colon and rectum.

PMID: 31989570 [PubMed — in process]

**A novel peptide-based electrochemical biosensor for the determination of a metastasis-linked protease in pancreatic cancer cells.**

Related Articles

**A novel peptide-based electrochemical biosensor for the determination of a metastasis-linked protease in pancreatic cancer cells.**

Anal Bioanal Chem. 2020 Jan 27;
Authors: Muñoz-San Martín C, Pedrero M, Gamella M, Montero-Calle A, Barderas R, Campuzano S, Pingarrón JM

Abstract
Proteases are involved in cancer' taking part in immune (dis)regulation, malignant progression and tumour growth. Recently, it has been found that expression levels of one of the members of the serine protease family, trypsin, is upregulated in human cancer cells of several organs, being considered as a specific cancer biomarker. Considering the great attention that electrochemical peptide sensors have nowadays, in this work, we propose a novel electroanalytical strategy for the determination of this important biomolecule. It implies the immobilization of a short synthetic peptide sequence, dually labelled with fluorescein isothiocyanate (FITC) and biotin, onto neutravidin-modified magnetic beads (MBs), followed by the peptide digestion with trypsin. Upon peptide disruption, the modified MBs were incubated with a specific fluorescein Fab fragment antibody labelled with horseradish peroxidase (HRP-antiFITC) and magnetically captured on the surface of a screen-printed carbon electrode (SPCE), where amperometric detection was performed using the hydroquinone (HQ)/HRP/H2O2 system. The biosensor exhibited a good reproducibility of the measurements (RSD 3.4%, n = 10), and specificity against other proteins and proteases commonly found in biological samples. This work reports the first quantitative data so far on trypsin expression in human cell lysates. The developed bioplatform was used for the direct determination of this protease in lysates from pancreatic cancer, cervix carcinoma and kidney cells in only 3 h and 30 min using low amounts (~ 0.1 μg) of raw extracts. Graphical abstract.

PMID: 31989193 [PubMed — as supplied by publisher]

Familial Pancreatic Cancer at Elderly Siblings in Japan.

Related Articles
Familial Pancreatic Cancer at Elderly Siblings in Japan.

Euroasian J Hepatogastroenterol. 2019 Jan-Jun;9(1):52-54

Authors: Kashimoto Y, Onji M, Takeji S, Yamamoto S, Miyake T, Uehara T, Kawasaki K, Murakami T, Miyaike J, Oomoto M, Bando K, Horiike N, Abe M, Kumagi T

Abstract
Two female siblings aged 87 and 90 years were clinically diagnosed as pancreatic cancer by abdominal ultrasonography and abdominal contrast-enhanced CT. Pancreatic cancer of these patients was confirmed during the autopsy. Both patients shared risk factors of pancreatic cancer; old age, diabetes, and passive smoking. Strong family history of pancreatic cancer was found in these two patients as their father and younger brother were also suffering from this cancer. The present study seems to report two eldest cases of familial pancreatic cancer in siblings. How to cite this article: Kashimoto Y, Onji M, et al. Familial Pancreatic Cancer at Elderly Siblings in Japan. Euroasian J Hepatogastroenterol 2019;9(1):52-54.

PMID: 31988854 [PubMed]
Unexpected metastasis of intraductal papillary neoplasm of the bile duct without an invasive component to the brain and lungs: A case report.

Related Articles

Machine Learning and Network Analyses Reveal Disease Subtypes of Pancreatic Cancer and their Molecular Characteristics.

Controlled clustering enhances PDX1 and NKX6.1 expression in pancreatic endoderm cells derived from pluripotent stem cells.

PMID: 31988390 [PubMed — in process]
Authors: Tran R, Moraes C, Hoesli CA

Abstract
Pluripotent stem cell (PSC)-derived insulin-producing cells are a promising cell source for diabetes cellular therapy. However, the efficiency of the multi-step process required to differentiate PSCs towards pancreatic beta cells is variable between cell lines, batches and even within cultures. In adherent pancreatic differentiation protocols, we observed spontaneous local clustering of cells expressing elevated nuclear expression of pancreatic endocrine transcription factors, PDX1 and NKX6.1. Since aggregation has previously been shown to promote downstream differentiation, this local clustering may contribute to the variability in differentiation efficiencies observed within and between cultures. We therefore hypothesized that controlling and directing the spontaneous clustering process would lead to more efficient and consistent induction of pancreatic endocrine fate. Micropatterning cells in adherent microwells prompted clustering, local cell density increases, and increased nuclear accumulation of PDX1 and NKX6.1. Improved differentiation profiles were associated with distinct filamentous actin architectures, suggesting a previously overlooked role for cell-driven morphogenetic changes in supporting pancreatic differentiation. This work demonstrates that confined differentiation in cell-adhesive micropatterns may provide a facile, scalable, and more reproducible manufacturing route to drive morphogenesis and produce well-differentiated pancreatic cell clusters.

PMID: 31988329 [PubMed — in process]

FAM172A inhibits EMT in pancreatic cancer via ERK-MAPK signaling.

Related Articles
FAM172A inhibits EMT in pancreatic cancer via ERK-MAPK signaling.

Biol Open. 2020 Jan 27;:

Abstract
Background FAM172A, as a newly discovered gene, is little known in cancer development, especially in pancreatic cancer (PC). Methods We investigated the potential role and molecular mechanism of FAM172A in epithelial to mesenchymal transition (EMT) in both human clinical samples and PC cells. Results FAM172A was downregulated in human PC tissues compared with that in adjacent pancreas by IHC and qRT-PCR. FAM172A expression was negatively associated with tumor size (P=0.015), T stage (P=0.006), lymph nodes metastasis (P=0.028) and the worse prognosis of PC patients (P=0.004). Meanwhile, a positive relationship between FAM172A and E-cadherin (E-cad) (r=0.381, P=0.002) was observed in clinical samples which contributed to the better prognosis of PC patients (P=0.014). FAM172A silencing induced EMT in both AsPC-1 and BxPC-3 cells, including inducing the increase of Vimentin, MMP9 and pERK and the decrease of E-cad and β-catenin expression, stimulating EMT-like cell morphology and enhancing cell invasion and migration in PC cells. However, MEK1 inhibitor PD98059 reversed FAM172A silencing-enhanced EMT in PC cells. Conclusion FAM172A inhibits EMT of PC cells via ERK-MAPK signaling.

PMID: 31988076 [PubMed — as supplied by publisher]

The tumor suppressor BAP1 regulates the Hippo pathway in pancreatic ductal adenocarcinoma.

Related Articles
The tumor suppressor BAP1 regulates the Hippo pathway in pancreatic ductal adenocarcinoma.

Cancer Res. 2020 Jan 27;:
Authors: Lee HJ, Pham T, Chang MT, Barnes D, Cai AG, Noubade R, Totpal K, Chen X, Tran C, Hagenbeek T, Wu X, Eastham-Anderson J, Tao J, Lee W, Bastian BC, Carbone M, Webster JD, Dey A

Abstract
The deubiquitinating enzyme BAP1 is mutated in a hereditary cancer syndrome with a high risk for mesothelioma and melanocytic tumors. Here, we show that pancreatic intra-epithelial neoplasia driven by oncogenic mutant Kras G12D progressed to pancreatic adenocarcinoma in the absence of BAP1. The Hippo pathway was deregulated in BAP1− deficient pancreatic tumors, with the tumor suppressor LATS exhibiting enhanced ubiquitin-dependent proteasomal degradation. Therefore, BAP1 may limit tumor progression by stabilizing LATS and thereby promoting activity of the Hippo tumor suppressor pathway.

PMID: 31988076 [PubMed — as supplied by publisher]

Socioeconomic status in relation to risks of major gastrointestinal cancers in Chinese adults: a prospective study of 0.5 million people.

Related Articles
Socioeconomic status in relation to risks of major gastrointestinal cancers in Chinese adults: a prospective study of 0.5 million people.

Cancer Epidemiol Biomarkers Prev. 2020 Jan 27;:

Abstract
BACKGROUND: Low socioeconomic status (SES) is associated with higher risk of certain gastrointestinal (e.g. colorectal,
pancreatic, and liver) cancers in Western populations. Evidence is very limited in China where correlates and determinants of SES differ from those in the West.

METHODS: The prospective China Kadoorie Biobank recruited 512,715 adults (59% women, mean age 51 years) from 10 (5 urban, 5 rural) regions. During 10 years of follow-up, 27,940 incident cancers (including 3061 colorectal, 805 pancreatic, and 2904 liver) were recorded among 510,131 participants without prior cancer at baseline. Cox regression was used to estimate adjusted hazard ratios (HRs) for specific cancers associated with area-level (e.g. per capita gross domestic product, disposable income) and individual-level (e.g. education, household income) SES.

RESULTS: Area-level SES and household income showed positive associations with incident colorectal and pancreatic cancer and inverse associations with liver cancer (p for trend < 40IU/ml 111 months, p = 0.042), T stage (T1-2 163 vs. T3-4 98 months, p CONCLUSION: Adjuvant treatment seems indicated in pancreatobiliary or mixed type AMPAC.

PMID: 31987649 [PubMed — as supplied by publisher]

Circulating tumor DNA as a potential marker of adjuvant chemotherapy benefit following surgery for localized pancreatic cancer.

Related Articles

Circulating tumor DNA as a potential marker of adjuvant chemotherapy benefit following surgery for localized pancreatic cancer.

Ann Oncol. 2019 Sep;30(9):1472-1478


Abstract

BACKGROUND: In early-stage pancreatic cancer, there are currently no biomarkers to guide selection of therapeutic options. This prospective biomarker trial evaluated the feasibility and potential clinical utility of circulating tumor DNA (ctDNA) analysis to inform adjuvant therapy decision making.

MATERIALS AND METHODS: Patients considered by the multidisciplinary team to have resectable pancreatic adenocarcinoma were enrolled. Pre- and post-operative samples for ctDNA analysis were collected. PCR-based SafeSeqS assays were used to identify mutations at codon 12, 13 and 61 of KRAS in the primary pancreatic tumor and to detect ctDNA. Results of ctDNA analysis were correlated with CA19-9, recurrence-free and overall survival (OS). Patient management was per standard of care, blinded to ctDNA data.

RESULTS: Of 112 patients consented pre-operatively, 81 (72%) underwent resection. KRAS mutations were identified in 91% (38±42) of available tumor samples. Of available plasma samples (N = 42), KRAS mutated ctDNA was detected in 62% (23±37) pre-operative and 37% (13±35) post-operative cases. At a median follow-up of 38.4 months, ctDNA detection in the pre-operative setting was associated with inferior recurrence-free survival (RFS) [hazard ratio (HR) 4.1; P = 0.002] and OS (HR 4.1; P = 0.015). Detectable ctDNA following curative intent resection was associated with inferior RFS (HR 5.4; P CONCLUSION: ctDNA studies in localized pancreatic cancer are challenging, with a substantial number of patients not able to undergo resection, not having sufficient tumor tissue for analysis or not completing per protocol sample collection. ctDNA analysis, pre- and/or post-surgery, is a promising prognostic marker. Studies of ctDNA guided therapy are justified, including of treatment intensification strategies for patients with detectable ctDNA post-operatively who appear at very high risk of recurrence despite gemcitabine-based adjuvant therapy.

PMID: 31987402 [PubMed — in process]

A decade of clinical development of PARP inhibitors in perspective.

Related Articles

A decade of clinical development of PARP inhibitors in perspective.

Ann Oncol. 2019 Sep;30(9):1437-1447

Authors: Mateo J, Lord C, Serra V, Tutt A, Balmaña J, Castroviejo-Bermejo M, Cruz C, Oaknin A, Kaye SB, de Bono JS

Abstract

Genomic instability is a hallmark of cancer, and often is the result of altered DNA repair capacities in tumour cells. DNA damage repair defects are common in different cancer types; these alterations can also induce tumour-specific vulnerabilities that can be exploited therapeutically. In 2009, a first-in-man clinical trial of the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib clinically validated the synthetic lethal interaction between inhibition of PARP1, a key sensor of DNA damage, and BRCA1/BRCA2 deficiency. In this review, we summarize a decade of PARP inhibitor clinical development, a work that has resulted in the registration of several PARP inhibitors in breast (olaparib and talazoparib) and ovarian cancer (olaparib, niraparib and rucaparib, either alone or following platinum chemotherapy as maintenance therapy). Over the past 10 years, our knowledge on the mechanism of action of PARP inhibitor as well as how tumours become resistant has been extended, and we summarise this work here. We also discuss opportunities for expanding the precision medicine approach with PARP inhibitors, identifying a wider population who could benefit from this drug class. This includes developing and validating better predictive biomarkers for patient stratification, mainly based on homologous recombination defects beyond BRCA1/BRCA2 mutations, identifying DNA repair deficient tumours in other cancer types such as prostate or pancreatic cancer, or by designing combination therapies with PARP inhibitors.

PMID: 31987398 [PubMed — in process]
Different shades of pancreatic ductal adenocarcinoma, different paths towards precision therapeutic applications.

Related Articles

**Different shades of pancreatic ductal adenocarcinoma, different paths towards precision therapeutic applications.**

Ann Oncol. 2019 Sep;30(9):1428–1436


Abstract

**BACKGROUND:** Different histological and molecular subtypes of pancreatic ductal adenocarcinoma (PDAC), with different molecular composition and survival statistics, have recently been recognised.

**MATERIALS AND METHODS:** This review describes the currently available studies regarding molecular and histological subtypes in PDAC. Studies from major cohorts such as International Cancer Genome Consortium as well as smaller cohorts are reviewed. We discuss where the described subtypes overlap, where the discrepancies are and which paths forward could be taken regarding diagnosis, ontogeny and therapy.

**RESULTS:** Four molecular subtypes with strong overlap among the different studies can be found, next to a list of mixed findings. Two of the four subtypes (epithelial classical and mesenchymal basal-like) were represented in every study and were often discriminated in other solid tumours as well. These two subtypes differ substantially in prognosis. One biomarker has been discovered, only discriminating these two subtypes, and insights into subtype-specific therapeutic vulnerabilities are scarce.

**CONCLUSION:** Subtypes can be reproducibly detected in cohorts of PDAC patients and two of them directly relate with prognosis. A consensus on the subtypes is warranted. Further discovery and validation studies are needed to identify strong biomarkers, to comprehend subtype ontogeny and to define strategies for precision medicine.

PMID: 31987397 [PubMed — in process]

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European cancer mortality predictions for the year 2019 with focus on breast cancer.

Related Articles

**European cancer mortality predictions for the year 2019 with focus on breast cancer.**


Abstract

**BACKGROUND:** To overcome the lag with which cancer statistics become available, we predicted numbers of deaths and rates from all cancers and selected cancer sites for 2019 in the European Union (EU).

**MATERIALS AND METHODS:** We retrieved cancer death certifications and population data from the World Health Organization and Eurostat databases for 1970–2014. We obtained estimates for 2019 with a linear regression on number of deaths over the most recent trend period identified by a logarithmic Poisson joinpoint regression model. We calculated the number of avoided deaths over the period 1989–2019.

**RESULTS:** We estimated about 1 410 000 cancer deaths in the EU for 2019, corresponding to age-standardized rates of 130.9÷100 000 men (-5.9% since 2014) and 82.9 women (-3.6%). Lung cancer trends in women are predicted to increase 4.4% between 2014 and 2019, reaching a rate of 14.8. The projected rate for breast cancer was 13.4. Favourable trends for major neoplasms are predicted to continue, except for pancreatic cancer. Trends in breast cancer mortality were favourable in all six countries considered, except Poland. The falls were largest in women 50–69 (-16.4%), i.e. the age group covered by screening, but also seen at age 20–49 (-13.8%), while more modest at age 70–79 (-6.1%). As compared to the peak rate in 1988, over 5 million cancer deaths have been avoided in the EU over the 1989–2019 period. Of these, 440 000 were breast cancer deaths.

**CONCLUSION:** Between 2014 and 2019, cancer mortality will continue to fall in both sexes. Breast cancer rates will fall steadily, with about 35% decline in rates over the last three decades. This is likely due to reduced hormone replacement therapy use, improvements in screening, early diagnosis and treatment. Due to population ageing, however, the number of breast cancer deaths is not declining.

PMID: 31987345 [PubMed — in process]

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ctDNA to detect minimal residual disease in pancreatic cancer: moving into clinical trials.

Related Articles

**ctDNA to detect minimal residual disease in pancreatic cancer: moving into clinical trials.**

Ann Oncol. 2019 Sep;30(9):1410–1413

Authors: Montagut C, Vidal J

PMID: 31987393 [PubMed — in process]
Health-related quality of life in patients with a germline BRCA mutation and metastatic pancreatic cancer receiving maintenance olaparib.

Related Articles

Health-related quality of life in patients with a germline BRCA mutation and metastatic pancreatic cancer receiving maintenance olaparib.


Abstract

BACKGROUND: Patients with metastatic pancreatic cancer often have a detriment in health-related quality of life (HRQoL). In the randomized, double-blind, phase III POLO trial progression-free survival was significantly longer with maintenance olaparib, a poly(ADP-ribose) polymerase inhibitor, than placebo in patients with a germline BRCA1 and/or BRCA2 mutation (gBRCAm) and metastatic pancreatic cancer whose disease had not progressed during first-line platinum-based chemotherapy. The prespecified HRQoL evaluation is reported here.

PATIENTS AND METHODS: Patients were randomized to receive maintenance olaparib (300mg b.i.d.; tablets) or placebo. HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item module at baseline, every 4 weeks until disease progression, at discontinuation, and 30 days after last dose. Scores ranged from 0 to 100; a ≥10-point change or difference between arms was considered clinically meaningful. Adjusted mean change from baseline was analysed using a mixed model for repeated measures. Time to sustained clinically meaningful deterioration (TSCMD) was analysed using a log-rank test.

RESULTS: Of 154 randomized patients, 89 of 92 olaparib-arm and 58 of 62 placebo-arm patients were included in HRQoL analyses. The adjusted mean change in Global Health Status (GHS) score from baseline was