New strategies and designs in pancreatic cancer research: consensus guidelines report from a European expert panel†


1Gastrointestinal Cancer Unit, Hôpital Erasme, Université Libre de Bruxelles, Brussels; 2Department of Hepatology, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium; 3Institut National de la Santé et de la Recherche Médicale, Marseille, France; 4Department of Gastroenterology and Endocrinology, University of Marburg, Marburg, Germany; 5Nancy University and Department of Medical Oncology, Centre Alexis Vautrin, Nancy; 6Digestive Surgery Department, Institut Mutualiste Montsouris, Paris; 7Gastroenterology Department, Hôpital Beaujon, Clichy; 8Medical Oncology Department, Institut Curie, Hôpital René-Huguenin, Saint-Cloud; 9Digestive Oncology Department, Institut G. Roussy, Villejuif, France; 10Medical Oncology Department, Hospital Vall d’Hebron, Barcelona, Spain; 11Department of Surgery, St Josef-Hospital, Ruhr-University, Bochum, Germany; 12Department of Radiation Oncology, Academic Medical Centre, Amsterdam, The Netherlands; 13Department of Gastroenterology, Hôpital Pitié Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France; 14Department of Gastroenterology and Hepato-Pancreatology, Gastrointestinal Cancer Unit, Hôpital Universitaire Erasme, Brussels; 15Department of Gastroenterology, Institut J. Bordet, Brussels; 16Department of Medical Imaging, Hôpital Erasme, Brussels, Belgium; 17Department of General and Visceral Surgery, J. W. Goethe University Medical Center, Frankfurt; 18Institute of Pathology, University Hospital Carl Gustav Carus, Dresden; 19Canstattklinik St Theresia, Saarbrücken, Germany; 20Department of Oncology, Université Libre de Bruxelles, Brussels; 21Department of Surgery, Clinic for Visceral and Transplantation Surgery, Hôpital Universitaire de Genève, Geneva, Switzerland; 22Department of Surgery, University of Liverpool, Liverpool, UK

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Although the treatment of pancreatic ductal adenocarcinoma (PDAC) remains a huge challenge, it is entering a new era with the development of new strategies and trial designs. Because there is an increasing number of novel therapeutic agents and potential combinations available to test in patients with PDAC, the identification of robust prognostic and predictive markers and of new targets and relevant pathways is a top priority as well as the design of adequate trials incorporating molecular-driven hypothesis. We presently report a consensus strategy for research in pancreatic cancer that was developed by a multidisciplinary panel of experts from different European institutions and collaborative groups involved in pancreatic cancer. The expert panel embraces the concept of exploratory early proof of concept studies, based on the prediction of response to novel agents and combinations, and randomised phase II studies permitting the selection of the best therapeutic approach to go forward into phase III, where the recommended primary end point remains overall survival. Trials should contain as many translational components as possible, relying on standardised tissue and blood processing and robust biobanking, and including dynamic imaging. Attention should not only be paid to the pancreatic cancer cells but also to microenvironmental factors and stem/stellate cells.

**Key words:** chemoradiation, FOLFIRINOX, pancreatic cancer, preclinical, research strategy

**introduction**

Worldwide the incidence of pancreatic ductal adenocarcinoma (PDAC) continues to increase and ranks as the fourth commonest cause of cancer death [1]. For all stages, survival at 5 years is <5% [2]. At diagnosis, 50%–60% of patients have advanced disease with distant metastases and of the 10% or so of patients who undergo a curative resection, many will relapse with distant metastases and/or locoregionally [3].

In patients with resectable disease, adjuvant chemotherapy more than doubles the 5-year survival rate, from ~10% with surgery alone to ~25% with postoperative chemotherapy [4–6]. In contrast, level I evidence for adjuvant radiochemotherapy (RCT) is lacking and its role is still controversial, especially in Europe [7–10].

In locally advanced PDAC, many studies investigated the role of chemoradiation. In a qualitative systematic review including
two systematic reviews, 13 randomised trials and 6 nonrandomised studies, it was shown that RCT is better than best supportive care, better than radiotherapy alone, but not better, yet more toxic, than chemotherapy alone [11]. A major methodological drawback is the fact that the vast majority of published studies concerns either observational reports or single-arm prospective studies, with highly selected patient cohorts. Nevertheless, in a subgroup of patients with well-controlled localised disease, consolidation RCT may have a place after several months of upfront chemotherapy and may offer survival benefit [12]. This strategy is currently evaluated in an ongoing international phase III trial.

Chemotherapy alone remains the standard of care in this setting.

In metastatic PDAC, monotherapy with gemcitabine has remained the main therapeutic option for >10 years [13]. In phase III studies, many combinations of drugs and new targeted therapies have been tested with gemcitabine. Unfortunately, most of these studies are negative and fail to confer any significant added benefit on overall survival in comparison with gemcitabine alone. Combinations of gemcitabine with a fluoropyrimidine or a platinum derivative have only been associated with a significant improvement in overall survival in meta-analyses [13–15]. Only one study evaluating a targeted therapy reports an overall survival improvement with a combination of erlotinib and gemcitabine, but this effect is modest with a survival benefit of <2 weeks [16]. Recently, at the 2010 American Society of Clinical Oncology meeting, the FOLFIRINOX regimen, which combines the three cytotoxics 5-fluorouracil (5-FU), irinotecan and oxaliplatin, has shown to confer a significantly longer progression-free and also overall survival in comparison with gemcitabine alone [17].

Although the treatment of pancreatic cancer remains a huge challenge, it is entering a new era with the development of new strategies and trial designs. Because there is an increasing number of novel therapeutic agents and potential combinations available to test in patients with PDAC, the identification of robust prognostic and predictive markers and of new targets and relevant pathways is a top priority [18]. Effective biomarkers will permit stratification of patients for specific treatments based on molecular-driven hypotheses. Such strategies should aim to improve overall survival.

The integration of all these basic, clinical and methodological issues in the design of new clinical trials is highly desirable if we want to make substantial progress in pancreatic cancer research and treatment.

At the initiative of the European Organisation for Research and Treatment of Cancer Gastrointestinal Group, a consensus strategy for research in pancreatic cancer was developed by a multidisciplinary panel of experts from different European institutions and collaborative groups involved in pancreatic cancer research and included a 1-day meeting in Brussels.

The present report summarises the major topics, issues, challenges and directions addressed by the panel and the consensus recommendations for guiding research strategies in pancreatic cancer.

**objectives, scope, methods and issues**

The main objectives of the meeting were:

- to address critical questions, unmet needs and priorities in pancreatic cancer treatment and research;
- to discuss and identify consensus areas and collaborations within the European research network to develop new and complementary strategies and designs in pancreatic cancer for the next 3–5 years; and
- to establish and disseminate recommendations from the European experts panel to the oncology community.

Experts in oncology, surgery, radiotherapy, pathology, gastroenterology, statistics and basic and translational research were invited to participate in a 1-day workshop. Before the meeting, key issues were identified and series of presentations were prepared summarising the up-to-the-minute status quo of pancreatic cancer research. The main focus of the meeting was to integrate current clinical and basic knowledge into the future investigational strategies.

**preclinical models: identification and validation of new molecular targets/pathways**

The search for novel therapeutic approaches to pancreatic cancer over the past 60 years has been soberly disappointing. Most of the drugs directed against targets identified in preclinical studies have not been able to demonstrate a clinically relevant benefit for patients with pancreatic cancer. In contrast, many potential targets have yet to be evaluated in part due to the lack of appropriate *in vivo* models. Therefore, there is an urgent need to (i) develop and apply suitable high-throughput screening strategies to identify novel functionally relevant targets and (ii) use appropriate preclinical *in vivo* models recapitulating the human situation to validate putative drug targets *in vivo*.

For screening strategies aiming at identifying novel therapeutic targets, cancer cell lines and tissues traditionally represent the input material for DNA genomic studies (array comparative genomic hybridisation, single-nucleotide polymorphism, copy number variation, deep sequencing), RNA expression (complementary DNA microarray, microRNA arrays, alternative splicing) and epigenetic studies (decodification of the histone code, including acetylation, phosphorylation and methylation in PDAC) [19, 20]. More recently, both cancer tissues and serum samples have been exploited as a resource for proteomics (two-dimensional polyacrylamide gel electrophoresis, matrix-assisted laser desorption/ionisation-time-of-flight, surface-enhanced laser desorption/ionisation-time-of-flight). Identification of circulating predictive or prognostic markers in serum rather than tumour tissue may be very rewarding in a disease where obtaining tissue remains a challenge. The advent of several new technologies has opened up the possibility to functionally screen distinct groups of genes ranging from promising drug targets up to the whole genome. These loss-of-function screens use RNA interference libraries that are able to knock down the expression of multiple genes, the impact of which on cell viability, migration or drug resistance can be measured simultaneously in a high-throughput manner.
The therapeutic yield of the in vitro screening approaches for target identification has been limited by the fact that pancreatic cancer is characterised by an extremely high proportion of stromal cells surrounding the cancer cells. This might be one important explanation, why novel drugs, although effective in vitro, frequently fail to show a clinical benefit in vivo in subsequent trials. Therefore, preclinical in vivo models are essential that may recapitulate the cross talk between different tumour and stromal components that is able to enhance tumour cell survival, cancer progression and the resistance to most therapeutic strategies well known to the clinician [21, 22].

The close interaction between tumour cells and inflammatory and mesenchymal microenvironment is able to modulate the growth characteristics of the tumour leading to phenomena such as epithelial to mesenchymal transition of the tumour cells with increased invasiveness and resistance to apoptosis. Moreover, the cross talk between tumour and stromal cells also affects the vascularity of the stroma, frequently resulting in a hypovascular stroma that impairs the accessibility of the tumour cells by anticancer drugs [23]. Recent data also suggest that tumour–stroma interactions also affect the niche of multidrug-resistant cells, including cancer stem cells. An earlier attempt to overcome the limitations of in vitro assays was to use xenograft models with subcutaneous or orthotopic implantation of (human) tumour cells in immunocompromised mice [23, 24]. Although therapeutic approaches may work well in mouse xenografts, these frequently fail in patients, limiting the interpretation and transferability of xenograft data to human PDAC.

In recent years, genetically engineered mouse models have been developed that have been based on the predominant molecular alterations seen in the human disease and better recapitulate the morphological features of human pancreatic cancer [25–27]. Their marked stromal reaction resembles human disease quite strikingly. Hence, these genetic mouse models are more promising for the identification of new targets and validation of novel drugs. However, genetically engineered models also have limitations. Mouse tumours exhibit a different tumour biology and do not reflect the genetic heterogeneity of human tumours. Furthermore, correlative studies between human and murine tissues are often hampered by different antibody affinities.

Beyond the use of mouse models, preclinical validation must also focus on human pancreatic cancer tissues. Expression levels of potential drug targets have to be assessed and correlated to clinical parameters such as survival and response to different drugs. Validation with prospective and standardised human tissue sampling is therefore essential to improve the transfer of potential drug targets into the clinic. Ideally, tissue sampling should be carried out in the context of prospective studies accompanied by a translational programme that allows identification of predictive and prognostic markers as well as validation of potential drug targets in a standardised manner.

Evaluation of target expression levels in human tissues does not usually predict response to a given drug in vivo. To overcome this obstacle, ex vivo chemosensitivity testing has been developed to assess the efficacy of novel drugs with human material prospectively. Chemosensitivity assays are intended to predict the sensitivity of cells derived from pancreatic tumours at the time of surgery or biopsy to chemotherapeutic drugs or novel agents, with the intent of identifying more effective treatment protocols that would translate into improved clinical survival. A variety of sensitivity assays have been developed in other cancers and various attempts are ongoing to establish and prospectively validate these chemosensitivity assays in pancreatic cancer. The ultimate goal of these assays is to develop a chimiogram, similar to the concept of an antibiogram, using single or combined anticancer drugs to establish a profile of sensitivity or resistance for a particular patient. It needs to be determined whether the promising results obtained in other cancer entities can be translated to pancreatic cancer [28].

In parallel with the research on pancreatic cancer per se, attention should also be paid to the exploration of susceptibility genes for pancreatic cancer [29], which may enable the identification of more groups of individuals at increased risk of developing pancreatic cancer than are currently known. This may guide the development of preventive strategies as well as novel targets for drug development.

**collection of biospecimens, biobanking**

Emphasis should be made on the prospective collection of well-annotated tumour material and blood from patients, preferably within the context of clinical trials. To avoid variability in biospecimen collection, processing and storage, pathologists and basic researchers should harmonise these processes within the framework of internationally agreed guidelines and standard operating procedures [30].

**functional imaging**

Functional imaging by diffusion-weighted magnetic resonance imaging (MRI), perfusion MRI/computed tomography (CT) or positron emission tomography (PET) protocols represents an interesting tool avenue to elucidate the mechanism of action of drugs (cytotoxic, antiangiogenic and antistromal), to assess efficacy of drugs and to identify (non-)responders early on in the treatment process.

Dynamic contrast-enhanced MRI is a noninvasive imaging technique already used in the staging of pancreatic cancer. The intravenous administration of a gadolinium-based contrast agent is needed to carry out the study. The acquired data can be analysed using a pharmacokinetic model to obtain quantitative parameters: these are blood flow and contrast transfer coefficient ($K_{trans}$) related to tissue perfusion/permeability, $v_i$ representing the tissue volume fraction occupied by the extravascular extracellular space and $v_p$ representing the tissue volume fraction occupied by the intravascular space [31]. Previous publications have reported the technical feasibility and reproducibility of the technique and its utility in monitoring treatment response in nonresectable pancreatic ductal adenocarcinoma ([32, 33] and M. A. Bali, unpublished data).

So far, functional imaging is restricted to academic centres and is being increasingly adopted in early phase I/II clinical trials for correlative studies. Efforts should be made to standardise image acquisition, definition of target lesions and well-defined assessment of response. Validation (e.g. by pathological correlation) of functional imaging is considered
equally important. Offering technical and logistical platforms for central reviewing is a priority.

integrating surgery in multimodal therapy and research

There is still room for improving the outcome of patients with pancreatic cancer following R0 or R1 resection, in the era of adjuvant gemcitabine. Results may be improved by selecting the patients who are more likely to benefit from a particular drug regimen. Results are still awaited concerning the human equilibrative nucleoside transporter 1 (hENT1) testing to identify gemcitabine sensitivity in the context of the completed ESPAC-3 trial. Patients who are less likely to benefit from gemcitabine may be candidates for another drug regimen (5-FU based) [34]. The recent results of the (modified) FOLFIRINOX combination in the advanced setting asks questions about the potential advantages for using this regimen in the (neo)adjuvant setting but careful consideration is needed in the trial design to take this forward given the significantly increased toxicity [17, 35].

Level I evidence for the use of neoadjuvant chemo(radio)therapy in patients with resectable pancreatic cancer is lacking, as all of the attempted clinical trials in the past have failed to complete target recruitment. Continuing challenges in any trial design include biliary obstruction, the need for histological proof and psychological factors related to postponing surgery and the fear of progression. There are less problems for the conduct of neoadjuvant strategies in borderline resectable tumours, provided that consensus is reached upon definition of resectability on imaging and margin positivity by expert radiologists and surgeons. The planned ESPAC-5 study is a randomised phase II study that will explore three different strategies: upfront surgery, chemotherapy followed by surgery and chemoradiotherapy before resection. All patients will be offered postoperative chemotherapy. The primary end point of this trial will be resectability. In this trial, there are explicit criteria to judge resectability and central imaging review before randomisation.

In this setting, all experts agreed on the value of randomised phase II studies before embarking on large phase III trials with survival as primary end point. No consensus was reached on the most appropriate end point of neoadjuvant protocols for borderline resectable tumours, but the percentage of R0 resections or the pathologically documented response rate in case of preoperative therapy may be less subjective than resectability per se.

remaining challenges with radiation therapy

RCT has shown disappointing results in locally advanced pancreatic cancer (LAPC). Apart from pain palliation and a modest survival gain over best supportive care or radiation alone, response rates are low [11, 36, 37]. This may be partly due to an underestimation by radiological measurement. PDAC is in general a tumour with a large stromal component and therefore less likely to shrink radiologically, despite a possible response from cancer cells. Functional imaging may be more appropriate to measure response for LAPC. Response rates to RCT are best measured in studies carried out in the neoadjuvant setting; 53 of these studies were carried out in patients with borderline resectable PDAC and the mean response rate of RCT was 29%, with a great variation between individual studies [38]. In these preoperative RCT studies, an invariably high R0 resection rate is reported, as well as a variable but high resection rate. Some of these studies report a high survival rate compared with historical control groups of patients with primarily resectable tumours [39]. A major methodological flaw of these preoperative RCT studies is that none of them is randomised and they all report the results of the subset of patients who actually underwent a resection, rather then reporting by intention to treat [38, 39]. Hence, the potential benefit of increasing the resection rate is not taken into account. This also applies to the aforementioned systematic review [38]. Another methodological disadvantage of single-arm phase II studies in PDAC is that a small difference in selection of patients may have a relatively great impact on outcome, making comparison between studies hazardous. Future phase II or III clinical studies of preoperative RCT should at least report by intention to treat and preferably be randomised comparisons in well-defined patient cohorts.

Despite the aforementioned methodological shortcomings, literature appears to indicate that preoperative RCT in borderline resectable and presumably also primarily resectable PDAC may improve resection rate, R0 resection rate and possibly overall survival [38, 39]. This hypothesis is valid and should be tested in randomised prospective studies.

issues and future of systemic therapy

The FOLFIRINOX regimen is the first gemcitabine-free regimen that has shown to be more efficient than gemcitabine in patients with good performance status (PS = 0–1), metastatic pancreatic cancer mainly of the body of the pancreas and younger than 76 years. The FOLFIRINOX regimen significantly improved overall survival and progression-free survival in all prognostic subgroups. The combination delayed definitive degradation of quality of life for all dimensions (except diarrhoea). However, the regimen was associated with more grade 3/4 toxic effects than gemcitabine including diarrhoea (12.3; 1.6%), nausea (15.6; 6.3%), vomiting (17.2; 6.3%), fatigue (24; 14.3%), neutropenia (47.9; 19.2%) and febrile neutropenia (5.7; 0%) [17, 35].

More information is needed on the usefulness of granulocyte–macrophage colony-stimulating factor, the safety beyond 70 years and in patients with jaundice. Despite some uncertainties and data from a routine use, FOLFIRINOX may be considered a standard of care in patients with metastatic pancreatic cancer who fulfil the following selection criteria: normal bilirubin, good performance status (Eastern Cooperative Oncology Group 0 or 1) and no cardiac ischaemia. FOLFIRINOX is not yet easily available in many European countries, where gemcitabine remains the only standard of care. In the near future, the schedule of FOLFIRINOX may likely be optimised and simplified, with the role of 5-FU bolus being questioned. More information and data on its use in routine practice are also needed, as well as the relative contribution of each of its component. The oxaliplatin–5-FU-based
combination also appears to be a valuable alternative, as shown in the second-line setting [40].

Targeted therapy remains experimental in PDAC and there is no clearly relevant predictive marker to use erlotinib more selectively [41].

The future use of predictive biomarkers will likely help us to determine how and when such drugs have to be given in daily clinical practice and research settings [42].

specific considerations for trial designs in advanced pancreatic cancer

Randomised phase II studies are the best way to explore activity of drugs and/or strategies, before embarking on phase III studies. Single-arm phase II studies have many intrinsic flaws. The main disadvantage of single-arm studies is the fact that the results are very dependent upon patient selection, making it practically impossible to compare results with those of other single-arm studies.

Attention should also be paid to a proper selection of patients, based upon well-defined and uniform protocols of defining disease stage (metastatic versus locally advanced versus borderline resectable versus primarily resectable disease), performance status and predictive markers, if available. Study results should be reported by intention to treat. Moreover, international consensus should be sought on how to define and report pathological issues such as accurate distance to the retroperitoneal margin. Also, the reporting of end points should become more uniform than it is to date. Translational research should be added to as many prospective studies as possible, with the intention of identifying predictive markers for new therapies and acquiring a better understanding of the disease as such. In this respect, gemcitabine nucleoside transporters (hENT1, possibly hCNT3) and deoxycytidine kinase (dCK) involved in the metabolism of gemcitabine should be incorporated in all future trials, aiming to stratify patients for gemcitabine benefit once the assays have been standardised and validated [43–45].

Preferentially driven by predictive biomarkers, new targeted agents and perhaps combinations of targeted agents should be evaluated in combination with either gemcitabine or FOLFIRINOX, preferentially in phases II randomised studies.

executive summary

• Use preclinical genetically engineered mouse or xenograft models, and then human tumour tissue to support exploration and assessment of new drugs and targets.
• Collect tumour tissue and blood specimens in the setting of future research and trials; define standard operating procedures for the collection of these specimens, the extraction and preparation of DNA, RNA and proteins, and the storage.

Tumour tissue should be obtained by needle puncture, either preoperatively or in locally advanced or metastatic settings in the primary tumour or accessible metastases, preferably by sampling core-biopsies; all resected specimens should also be stored within a standardised biobanking process; and facilities for the assessment of prognostic and predictive markers.

Specific attention should be paid to standardised processing (inking) and pathological evaluation of the resected specimen in order to adequately determine R0 versus R1 resection, focusing on the accurate distance to the retroperitoneal margin.

• Develop and standardise a dynamic imaging platform (PET–CT, diffusion and perfusion MRI) to be incorporated in the early evaluation of new drugs and regimens according to the specific therapeutic intervention type, such as antiproliferative, antistromal and antiangiogenic. All the dynamic imaging parameters should be evaluated, standardised and validated to be used within a specific time schedule, a specific tumour setting and in a multicentre and reproducible way.
• Integrate optimal surgery (aiming at a true R0 resection) in a multimodal management and research setting by developing specific trials according to the resectability status of the tumour as assessed by a board of expert pancreatic surgeons, radiologists and pathologists; the best treatment of resectable tumours should be explored in both the adjuvant and the neoadjuvant settings; newer active regimens in advanced disease such as FOLFIRINOX should be tested after resection; neoadjuvant short-window pilot protocols incorporating new drugs or new regimens are encouraged in the setting of proof-of-concept studies in highly selected centres that can support the complex protocols (preoperative tissue sampling, biliary drainage, repeated functional imaging, delivery of new drugs, etc.).

Borderline resectable tumours should be accurately defined by the degree of vascular encasement and offered to downstaging therapeutic protocols combining either active multidrug regimens or RCT; R0 resectability rate, as a surrogate of disease-free survival or overall survival, is supported as the primary end point in randomised phase II trials.

• Consider the FOLFIRINOX regimen as a new standard option in selected patients; additional data from routine clinical practice and possible simplification of the regimen are both desirable; FOLFIRINOX may be evaluated in phase I/II studies with new partners in advanced disease; however, gemcitabine remains the gold standard and the backbone for new combinations in the general population of PDAC patients.
• Aim to identify patients who will derive particular benefit from gemcitabine exposure and those who should be treated with non-gemcitabine-based combinations; hENT1, dCK or ribonucleotide reductase M1/2 are credible candidates to be explored and then validated in clinical trials.
• Separate tumour settings for appropriate trials and end points, including metastatic, locally advanced, borderline resectable and resectable disease.
• Design randomised phase II proof-of-concept studies to explore new agents aiming to obtain positive signals of antitumour activity, supported by biomarker and functional imaging responses. Develop phase III designs that will enable more than one new agent and pathway to be assessed.
major conclusions, expectations and recommendations

The prognosis of patients with pancreatic cancer remains very poor. Surgery can yield long-term disease-free survival and further improvement is seen with adjuvant chemotherapy. Preclinical and early clinical research should focus on the mechanisms and prediction of response/nonresponse to therapeutic strategies. Attention should not only be paid to the pancreatic cancer cells but also to the microenvironmental factors and stem/stellate cells.

To move the field of clinical pancreatic cancer research forward, the expert panel recommends that the following steps should be taken:

- Define uniform classifications for disease stage and radiological resectability. The pathology of resection specimens and biopsies from unresectable local disease as well as metastases should be handled and reported uniformly. Define in a uniform manner specific groups of patients for various areas of clinical research, namely resectable, borderline resectable, locally advanced and metastatic. Define uniform criteria to report treatment results and end points in clinical studies. It is essential to analyse results by intention to treat.
- Treat as many patients as possible in the framework of prospective clinical studies. Studies should contain as many translational components as possible, including dynamic imaging. The expert panel embraces the concept of exploratory early proof of concept studies and randomised phase II studies. The choice of end points in phase II studies should be objective permitting the selection of the best therapeutic approach to go forward into phase III, where the recommended primary end point remains overall survival.
- Collection of tumour material and blood for translational research is warranted for all studied patients; preferably, core needle biopsies should be taken before treatment, also in patients with locally advanced disease and/or distant metastases participating in studies. Depending upon the study, tumour material should also be obtained after treatment. Biobanks should be set up using standardised operating procedures. Fundamental translational research with these tissues should be directed towards prognostic and predictive factors, response assessment and so on, specific for the study at stake. Not only the cancer cells but also the microenvironment should be taken into account. In addition, the biobanks should be used to find new pathways and eventually new targeted drugs. High-throughput in vitro systems and clever in vivo models should be used to increase the efficacy of bringing eventual new targeted therapies into clinical research.

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disclosure

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references


