The 13th Belgian symposium on the integration of molecular biology advances into oncology clinical practice (BSMO/Bordet meeting)

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SUMMARY

On the 22nd and 23rd of November 2019, the Jules Bordet Institute and the Belgian Society of Medical Oncology (BSMO) hosted the 13th Belgian symposium on the integration of molecular biology advances into oncology clinical practice. In the course of the symposium, a fine selection of Belgian and international key opinion leaders discussed the clinical impact of molecular biology advances in a plethora of cancer types.

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PRECISION ONCOLOGY

RARE TUMOURS AND HISTOLOGIES: CLINICAL MANAGEMENT PATHWAY *(C. JUNGELS, INSTITUT JULES BORDET)*

In Belgium, each year 660 patients are diagnosed with a rare cancer. These patients have a relative survival at five years of 48.5%, which is on average 15% worse than what is seen in patients with 'common' cancers (63.4%).[1] In addition to this, recent advances in sequencing techniques have subdivided more common cancers into several, sometimes rare, subtypes. Based on the tumour's genetic and molecular features, these tumours can sometimes be treated without regard to histologic type or localisation, in a tumour-agnostic approach. Unfortunately, this heterogeneous group of rare tumours are often diagnosed late and with a high level of uncertainty due to a lack of expertise, reference centres, therapies and research opportunities. Therefore, general practitioners as well as the public should be aware that second opinions and a multidisciplinary approach within centres of excellence are necessary to optimise the treatment pathways for those patients. These reference centres could provide the organisational structure and critical mass that is needed to propose an appropriate treatment plan, conduct clinical trials and develop alternative approaches for patients with rare cancers. Current examples of national and international collaborations are EURACAN, EORTC, the Oncodistinct network and the 'Rare Cancers Task Force' from the BSMO.

NEW ADVANCES IN AGNOSTIC ORGAN THERAPEUTIC APPROACHES *(M. LOLKEMA, ERASMUS MC CANCER INSTITUTE, ROTTERDAM)*

At the heart of every malignant disease are aberrations in the DNA. Unfortunately, the distribution of genetic aber-

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rations in patients with metastatic tumours is very heterogeneous (number of drivers, amplifications, fusions, *etc.*) and as a result, a complete tumour agnostic approach remains out of reach.[2] However, recent results of the I-Predict and Winther trial have demonstrated that patient selection based on genomic characterisation improves the selection for trial participation. In these trials, tailoring their treatment to the results of large-scale sequencing, even when they had no regular treatment options left, could approve the treatment outcome of patients. These trials thus represent the first steps towards a tumour agnostic and more pathway driven treatment approach.[3,4] In the *Erasmus MC Cancer Institute (Rotterdam, The Netherlands)*, whole genome sequencing (WGS) is now used as a selection tool for phase I studies. In accordance with their 'last resort protocol', fresh biopsies are taken from patients for whom there is no clear path towards a clinical trial and these samples are analysed by WGS (50-100 patients/year). In a next step, patients are allocated to a specific clinical study based on the alterations that are found in their DNA. The first patients are already included in the trial program and will hopefully benefit from this novel agnostic organ therapeutic approach.

GENOTYPE-DRIVEN MELANOMA: WHAT FIRST, TARGETED THERAPIES OR IMMUNOTHERAPY? *(J. KERGER, INSTITUT JULES BORDET)*

In malignant melanoma, *cKIT*, *NRAS* or *BRAF* are mutated in around 70% of the patients (usually mutually exclusive).[5] In melanoma patients, PD-L1 expression is not a good biomarker for response to immunotherapy. In contrast, data suggest that tumour mutational burden (TMB) as well as specific features in the microenvironment may be important. In addition, also the gut microbiome was found to influence the response to immunotherapy. However, until now there are no valid biomarkers that can assist in treatment selection, prediction of response to therapy or potential toxicity. Therefore, melanoma factors (mutational status, CNS involvement, metastatic sites, *etc.*), therapeutic factors (onset of action, objective response rate, toxicities, *etc.*) as well as patient factors (performance status, comorbidities, prior therapies, *etc.*) should be taken into account when selecting the optimal treatment. Durable responses can be obtained with *BRAF*-targeted, anti-PD-1 monotherapy and combined anti-PD-1 plus CTLA4 therapies. At the moment there are no prospective head-to-head comparative data from studies comparing immunotherapy to targeted therapy in the first-line treatment for *BRAF* mutated melanoma. Therefore, the optimal treatment sequence in this setting is still debated and phase III trials addressing this question are underway (NCT0222478 and NCT02631447). Finally, studies evaluating *BRAF*-targeted therapy combined with anti-PD(L)-1 drugs are ongoing. Preliminary results of these trials indicate that these combinations are associated with significant efficacy, but their high toxicity burden might limit their use in clinical practice.

GENOTYPE-DRIVEN NSCLC: WHAT FIRST, TARGETED THERAPIES OR IMMUNOTHERAPY? *(J. DE GRÈVE, UZ BRUSSEL)*

In the treatment of non-small cell lung cancer (NSCLC) patients harbouring mutations in validated oncogenic drivers and no or minimal smoking history, there is currently no place for immunotherapy. In fact, with this treatment modality, low response rates and a short progression-free survival are obtained. Therefore, sequential targeted therapies and chemotherapy remain the standard of care for these patients. Targeted therapies against mutant EGFR, ALK, *BRAF*, and ROS1 are already well established, and recently also *MET* exon 14 deletions, *RET* and *NTRK* have emerged as promising therapeutic targets. PD-L1 is not a predictor for immune response in oncogene addicted NSCLC while tumour mutational burden and tumour-infiltrating lymphocytes (TILs) are strong prognostic factors in NSCLC. Combining targeted therapies with immunotherapy is currently under clinical investigation but it is likely that excessive toxicity will pose a problem.[6] Interestingly, however, the $KRAS^{G12C}$ mutation, which is present in 13% of patients with NSCLC, was recently found to be 'druggable' with a clinical efficacy signal and a potential for synergy with immunotherapy.[7,8]

NEW THERAPEUTIC APPROACHES

NEW DRUG DEVELOPMENT IN METASTATIC BREAST CANCER: FROM EMPIRICAL TO MOLECULAR APPROACHES *(P. AFTIMOS, INSTITUT JULES BORDET)*

In metastatic breast cancer, 57% of the patients has one or more actionable molecular alterations.[9] A first example of this, which gained some attention in recent years, consists of mutant *FGFR*. Interestingly, aberrant FGFR signalling mediates resistance to CDK4/6 inhibitors in ER+ breast cancer, but this resistance can be reversed by adding lucitanib to the treatment. Lucitanib monotherapy showed modest antitumour activity in patients with HR+/HER2- metastatic breast cancer but came at the cost of major toxicity.[10] This toxicity can be explained by the fact that lucitanib not only inhibits FGFR-1 and -2 kinases, but also VEGFR-1, -2, and -3, which causes VEGFR-associated

toxicity. Therefore, the development of more specific, FGFR-targeting drugs is required.

Also PIK3CA is an actionable oncogene. As demonstrated in the SOLAR-1 trial, alpelisib significantly prolongs the PFS in *PIK3CA*-mutated patients while this agent did not induce any clinical benefit in *PIK3CA* wild-type patients.[11] Selective oestrogen receptor degraders have the advantage that they can be taken orally and have shown promising results in a patient-derived xenograft model.[12] Also the combination of epigenetic-targeting drugs with PARP-inhibitors seems to have a synergistic effect[13] and has now moved to a phase II clinical trial in patients with triple negative breast cancer (TNBC). Finally, antibody-drug conjugates are also gaining momentum in breast cancer, with sacituzumab govitecan, trastuzumab duocarmazine and trastuzumab deruxtecan being the most promising drugs.

RADIOTHERAPY AND IMMUNOTHERAPY: THE BASIS AND CLINICAL PERSPECTIVES *(P. LAMBIN, MAASTRICHT UNIVERSITY)*

For a long time it was believed that radiotherapy only provides local tumour control. However, recent evidence suggests that combining radiotherapy with immunotherapy could transform radiotherapy into a systemic treatment, ultimately leading to an improved survival. An important prerequisite for this 'abscopal effect' is the presence of CD8+ T-cells and dendritic cells.[14] Interestingly, fractionated radiation induces viral mimicry with cytosolic DNA accumulation, leading to cGAS/STING pathway activation and IFNb production, while high dose radiotherapy (20 Gy instead of 3x 8 Gy) abrogates the abscopal effect of radiation due to the activation of TREX1.[14] Also the combination of interleukine-2 (IL-2) with radiotherapy can be an interesting treatment option but the main disadvantage of IL-2 is its toxicity.[15] To overcome this toxicity, the L19-IL2 monoclonal antibody-cytokine fusion protein has been developed. In this fusion protein, IL-2 is fused to a single-chain antibody fragment directed against the extra-domain of fibronectin (L19), which makes the IL2 more tumour specific and less toxic.[16] Recently, *Zegers et al.* demonstrated that combining L19-IL2 with radiation has a synergistic effect.[17] Overall, it can be concluded that immunotherapy will revolutionise the way radiotherapy is used.

THE DILEMMA IN THE FIRST-LINE SETTING AND BEYOND

ADVANCED RENAL CELL CARCINOMA *(N. MARTINEZ-CHANZA, INSTITUT JULES BORDET)*

In the first-line treatment of renal cell carcinoma, impressive progress has been made in the last years; going from single agent VEGF blockade to combinations including checkpoint inhibitors. In treatment-naïve patients, dual checkpoint inhibitor combinations (nivolumab plus ipilimumab) or a checkpoint inhibitor in combination with a VEGF tyrosine kinase inhibitor (TKI) (pembrolizumab or avelumab plus axitinib) can be used. Based on results of the phase III CheckMate-214, Keynote-426 and Javelin-101 trials, patients classified to be at good risk (IMDC criteria) benefit the most from axitinib plus pembrolizumab in the first-line setting. On the other hand, patients with intermediate or poor risk are preferably treated with the nivolumab plus ipilimumab combination or with axitinib plus pembrolizumab.[18-21] No predictive biomarkers are available yet to guide the decision between both options. At the moment, only retrospective data are available on the post immunotherapy first-line setting so it is unclear what the impact of these new treatment options will be on subsequent treatment lines. Therefore, current guidelines recommend the use of VEGF TKIs in second-line. Cabozantinib is the most selective, and probably also the most active, TKI inducing an objective response rate of 35-40% in second-line. Other VEGF TKI and immunotherapy combinations in the frontline setting are currently being investigated. Also monotherapy *versus* combination therapy and sequential *versus* concurrent therapy are being evaluated in on-going clinical trials.

METASTATIC HORMONE SENSITIVE PROSTATE CANCER *(T. GIL, INSTITUT JULES BORDET)*

In metastatic hormone sensitive prostate cancer, patients should be treated as soon as possible. However, it remains difficult to choose between docetaxel, abiraterone, apalutamide or enzalutamide. According to toxicity profile, patient selection and drug availability, castration plus docetaxel can be offered to all M1 patients at diagnosis, independent of the tumour volume. Castration plus abiraterone can be offered to high-risk M1 patients, leading to a 36% reduction in the risk of death.[22] A newcomer in the treatment of metastatic hormone sensitive prostate cancer consists of apalutamide. As demonstrated in the TITAN trial, apalutamide plus androgen deprivation therapy results in a significantly improved survival in patients with metastatic castration-sensitive prostate cancer. In this study, the health-related quality of life was not improved with apalutamide and was comparable to what was seen with placebo.[23] In another study, the addition of enzalutamide to ADT resulted in a longer OS, PSA progression-free survival and clinical PFS. Of note, in patients who were previously

treated with docetaxel, the addition of enzalutamide was associated with a longer PFS, but this did not translate into a longer OS and came at the cost of additional toxic effects.[24] Finally, results of the STAMPEDE trial also learned that radiation therapy for local control can be provided for M1 patients with low volume disease.[25]

ADVANCED UROTHELIAL CANCERS *(P. BARTHÉLÉMY, INSTITUT DE CANCÉROLOGIE, STRASBOURG)*

Until recently, cisplatin-eligible patients with advanced urothelial cancer were treated with gemcitabine-cisplatin or high-dose MVAC in the first-line setting. For cisplatin ineligible patients, gemcitabine plus carboplatin was the standard of care.[26] At the moment, four phase III trials are assessing the potential of immunotherapy in the first-line setting; IMvigor 130, DANUBE, Keynote-361 and CheckMate-901. At ESMO 2019, the first results of the IMvigor 130 trial were presented. Data of this trial support the use of atezolizumab for cisplatin ineligible patients with a high PD-L1 expression level but data are not robust enough (yet) to support the use of atezolizumab for cisplatin eligible patients. In this patient group, chemotherapy remains the standard of care. The combinations of atezolizumab with chemotherapy led to a 1.9-month improvement in PFS (HR:0.82, p=0.007) but no difference in OS (HR:0.83, p=0.027) and response rates (47% *vs.* 44%) as compared to chemotherapy alone.[27] As for now, the combination of immunotherapy with chemotherapy is not yet ready to use in the front-line setting.

In the second-line setting, single-agent immunotherapy (preferably pembrolizumab) is currently the golden standard. However, new drugs such as the FGFR inhibitor erdafitinib or antibody-drug conjugates (ADCs) (enfortumab vedotin, sacitumab govitecan, ASG-ISME) are being evaluated. While the results of on-going trials with immunotherapy in combination with anti-angiogenic drugs or ADCs are still preliminary, the first data look promising.[28-30] In the future, molecular screening will most likely also gain momentum in this disease type, which will further facilitate a precision medicine approach.

RECURRENT HEAD AND NECK SQUAMOUS CELL CARCINOMA *(E. SERONT, CLINIQUES UNIVERSITAIRES SAINT-LUC, BRUXELLES)*

In head and neck cancer, 80-100% of the tumours express *EGFR*. As *EGFR* expression is associated with advanced stage carcinoma, decreased survival and decreased sensitivity to treatment, there is a rationale to treat head and neck cancer with the EGFR-inhibitor cetuximab. Both the EXTREME regimen (cisplatin/carboplatin + 5-FU + cetuximab) and the TPEx regimen (cisplatin + docetaxel + cetuximab) showed a better OS and ORR compared to chemotherapy alone with a favourable toxicity profile for the TPEx regimen.[31,32] The immune checkpoint inhibitors nivolumab and pembrolizumab are active in the second-line setting.[33,34] Also in the first-line setting, pembrolizumab is active against head and neck cancer, although there the efficacy seems to be dependent on the PD-L1 combined positive score (CPS). In the Keynote-048 trial, pembrolizumab plus chemotherapy had superior OS in the PD-L1 CPS ≥20 and CPS ≥1 and total population as compared to the EXTREME regimen. Moreover, pembrolizumab monotherapy demonstrated superior OS in the CPS ≥20 and CPS ≥1 populations.[35] Therefore, in asymptomatic patients who are in a stable condition and in whom there is no need for rapid tumour shrinkage, it is recommended to first determine the CPS. If the patient has a CPS of zero (15% of the patients), the EXTREME regimen should be the therapy of choice. In the 40-45% of patients with a high CPS (≥20), pembrolizumab alone was shown to be superior to the EXTREME regimen. In the patients with a CPS between 1% and 20%, physicians have the choice between pembrolizumab monotherapy or pembrolizumab plus chemotherapy. In the treatment of patients where rapid tumour shrinkage is warranted there seems to be no place for pembrolizumab monotherapy. In this setting, patients with a high or intermediate CPS level should preferably be treated with pembrolizumab plus chemotherapy while the patients without PD-L1 expression might benefit most from EXTREME.

TARGETED THERAPIES

PANCREATIC AND BILIARY TRACT CANCERS (JL. VAN LAETHEM, HÔPITAL ERASME)

In metastatic pancreatic ductal adenocarcinoma, chemotherapy (FOLFIRINOX, gemcitabine with or without nab-paclitaxel or nanoliposomal irinotecan) remains the standard of care. Unfortunately, failure of targeted therapy in unselected populations remains a reality. The phase III POLO trial demonstrated that olaparib maintenance therapy following first-line platinum-based chemotherapy could significantly improve the PFS in metastatic pancreatic cancer patients harbouring germline *BRCA* mutations.[36] Further attempts to target metabolic pathways and immune cells are on-going, but remain complex. The National Comprehensive Cancer Network nowadays recommends to routinely perform *BRCA* germline testing in newly diagnosed pancreatic cancer, irrespective of the family history. Somatic gene profiling is recommended

Trial	Patients	Setting	Comparison	1º endpoint	Outcome	HR - p vlalue
STARGATE	195	1st line	CX + Sorafenib CX	PFS	5.6 5.3	HR 0.92 p=0.609
FAST	161 (100% CLDN18.2)	1st line	EOX + Zolbetuximab EOX	PFS	7.5 5.3	HR 0.44 p<0.0005
NCT00982592	124	1st line	FOLFOX + Vismodegib FOLFOX	PFS	7.3 8.0	HR na p=0.64
PaFLO	87	1st line	FLO + Pazopanib FLO	6m PFS	31.4% 25.9%	HR 0.93 p=NS
ZAMEGA	64	1st line	FOLFOX + Aflibercept FOLFOX	6m PFS	60.5% 57.1%	HR 1.11 p=0.72
NCT01238055	107	2nd line	Docetaxel + Sunitinib Docetaxel	TTP	3.9 2.6	HR 0.77 p=0.206
SHINE	71 (FGFR2 amplified)	2nd line	AZD4547 Paclitaxel	PFS	1.8 3.5	HR 1.57 p=NS
INTEGRATE	152	2nd/3rd line	Regorafenib placebo	PFS	2.6 0.9	HR 0.40 p<0.001

FIGURE 1. Randomised phase II trials of targeted therapies in oesophagogastric cancers.[44]

for patients with locally advanced/metastatic disease who are candidates for anticancer therapy, in order to identify uncommon but actionable mutations.[37]

In biliary tract cancer, both the first- and second-line therapy consists of chemotherapy. Unfortunately, the efficacy of this approach is limited. Interestingly, approximately 50% of biliary tract tumours harbour mutations in targetable genes. As a result, molecular driven therapies have the potential to improve the survival of these patients.[38] For example, tyrosine kinase inhibitors such as regorafenib, infigratinib, pemigatinib and ivosidenib have already shown benefit in selected patient populations. Immunotherapy is not (yet) recommended in this setting as more consistent data are awaited.

ADVANCED OESOPHAGOGASTRIC CANCERS
(F. SCLAFANI, INSTITUT JULES BORDET)

With the increased understanding in the biology and genomic characterisation of oesophago-gastric cancers (OGCs), targeted therapies will become an important component of the therapeutic algorithm of advanced OGCs (HER-2, VEGF, EGFR).[39] However, a lack of optimal, biomarker-driven patient selection, intra-tumoural heterogeneity and the genomic complexity of OGCs resulted in the failure of many clinical trials evaluating targeted therapies in this disease type. For future studies, these issues should be kept in mind.

Several randomised phase II and III trials are currently on-going that evaluate other targeted therapies (apart from HER2, VEGF and EGFR targeting). As for now, only the phase II FAST-trial (zolbetuximab, mAb against Claudin-18.2) and the INTEGRATE trial (regorafenib, multi-kinase inhibitor), were able to show a significant improvement in PFS (*Figure 1*).[40,41] Immunotherapy in OGCs has demonstrated promising activity, mainly in patients with high levels of PD-L1 expression. As in 88% of cases where discrepant genomic alterations between primary tumour and metastasis were found, results were concordant between metastasis and circulating tumour DNA (ctDNA), ctDNA genomic profiling may represent a successful strategy to pursue in future clinical trials.[42] Recently presented data of the REGONIVO, EPOC1603 trial demonstrated that combination treatment with anti-angiogenic and anti-PD1 agents can potentially extend the benefit of immunotherapy to microsatellite stable tumours.[43]

NEUROENDOCRINE TUMOURS
(I. BORBATH, INSTITUT JULES BORDET)

Despite the fact that neuroendocrine tumours (NETs) are rare, their incidence is steadily increasing over the past

decades.[45] NETs are mostly prevalent in the pancreas and small intestine and it is also in these sites that the most advanced stage tumours are found.[46] Over the past decade, significant advances have been made in the treatment of pancreatic NETs (pNETs), where somatostatine analogues (SSAs) such as lanreotide autogel were found to significantly prolong the PFS compared to placebo (p=0.0002; HR[95%CI]: 0.47[0.30-0.73]).[47] Apart from SSAs, anti-angiogenesis and the mTOR pathway inhibition also proved to be successful (targeted by sunitinib and everolimus respectively).[48-51] In patients with a very high tumour burden, chemotherapy can be used. More recently, data of the phase II TALENT trial indicate that also lenvatinib can be used in the treatment of metastatic NETs.[52] In small-intestinal NETs (siNETs), there are less convincing data that demonstrate the efficacy of the different treatment options listed above. This is mainly caused by the fact that siNETs are very indolent, making it hard to demonstrate a treatment-benefit. Also in these cancers, SSAs and everolimus are currently the treatment options of choice.[53,54] Very recent data presented at ESMO also showed encouraging efficacy of surufatinib (small-molecule kinase receptor targeting VEGFR, FGFR1 and colony stimulating factor 1 receptor) in Asian patients with advanced extra-pancreatic NETs.[55] In the upcoming years, results from many interesting clinical trials in both pNETs and non-pNETs are expected.

IMMUNOTHERAPY: PROGRESS AND CHALLENGES

HOW TO OVERCOME IMMUNOTHERAPY RESISTANCE: THE NEW WAVE OF IMMUNOTHERAPY APPROACHES *(L. DIRIX, GZA)*

Despite what we learned from first-generation immune-checkpoint inhibitors, many questions still remain unanswered. One of these questions is whether the checkpoint blockade relies on the recruitment of novel T-cells or on the reinvigoration of tumour-infiltrating lymphocytes. Only very recently, *Yost et al.* could address this question and showed that PD-1 blockade led to a clonal replacement of tumour-specific T-cells.[56] Secondly, PD-L1 expression is predictive for increased sensitivity to immunotherapy, regardless of the mechanism of the increased expression level and regardless of whether PD-L1 is increased on tumour cells, immune cells or both.

Another open question relates to the relationship between tumour-mutational load and intra-tumour heterogeneity in the context of predicting benefit from our currently available immune checkpoint inhibitors. In this respect, data obtained in a melanoma mouse model show that the only predictor for OS was tumour heterogeneity. With an increased heterogeneity, there is a worse immune recognition and thus a lower benefit from immunotherapy.

In recent years, immune checkpoint blockade has been combined with chemotherapy, radiotherapy and targeted therapies but many clinical studies have overrun the progress in understanding the underlying basic science. On the other hand, this creates opportunities to synergise emerging science with clinical insight and an obligation for an integrated, high quality and scientifically sound translational program.

IMMUNOTHERAPY IN SPECIFIC CLINICAL SITUATIONS (HIV, AUTO-IMMUNE DISEASES, ELDERLY, ORGANS TRANSPLANTS, BRAIN METASTASES) *(S. HOLBRECHTS, CHU AMBROISE PARÉ)*

Despite the fact that the incidence of auto-immune diseases is increasing and the prevalence in cancer is not so rare, the clinical data on the use of ICI in cancer patients with auto-immune diseases are limited.[57,58] In fact, these patients were mostly excluded from randomised clinical trials and the level of evidence is therefore based on (retrospective) case series and some phase IV real world studies with numerous limitations. In brief, patients with the human immunodeficiency virus (HIV) on antiretroviral therapy with a controlled viral load and a CD-4 count of over 100 cells/mm^3 can safely be treated with ICI. In patients with organ transplants, organ rejection frequently occurs, leading to transplant failure. Nevertheless, disease control without organ rejection has been observed despite on-going immunosuppression. The decision to use ICI in this setting should however be taken with care and should balance the expected beneficial effect of ICI therapy to the potential risks.

In patients with brain metastases, the ORR to ICIs is similar to what is seen in patients with extra cranial tumours, although patients with symptomatic brain metastases have a worse disease outcome. Concurrent stereotactic radiotherapy is safe and leads to better outcomes as compared to non-concurrent stereotactic radiotherapy.

Finally, elderly patients treated with ICI have a similar efficacy and toxicity level than younger patients, except for patients with an ECOG performance status of ≥ 2 which benefit less.

IMMUNOTHERAPY AND PREDICTIVE BIOMARKERS *(V. SIOZOPOULOU, UZA)*

To date, PD-L1 immunohistochemistry retains its position as a predictive biomarker despite its heterogeneity and the

fact that the relationship of PD-L1 to prognosis is controversial and differs between tumour types. In the tumour micro-environment, the β-catenine pathway gives rise to a T-cell exclusion phenotype. Patients with an activation of β-catenine are therefore very unlikely to benefit from ICI therapy. β-catenine can thus be considered as a potential negative predictor for a response to ICI and represents an interesting biomarker candidate. Also specific mutations in *KRAS/STK11, PTEN, etc.* can be considered as predictive biomarkers.[59,60]

Interferon-γ (IFN-γ) is known for its positive effects on anti-tumour mechanisms but also has some controversial effects on the anti-tumour immunity. In fact, it may have a tumour promoting effect through IFN-γ insensitivity, the down-regulation of major histocompatibility complexes and loss of immunogenicity, the induction of indoleamine 2,3 dioxygenase and the expression of PD-L1.[61]

Microsatellite instability (MSI) positive tumours are a specific type of high TMB tumours. They generate numerous neopeptides which lead to a hypermutated phenotype. MSI-high tumours are highly sensitive to ICI therapy, regardless of the tissue of origin and therefore the MSI status represents a very interesting predictive biomarker.[62]

In the future, multicomponent predictive biomarkers will probably be used to predict which patients will benefit from immunotherapy.

CHALLENGES IN SOLID TUMOURS

CLINICAL RESEARCH CHALLENGES: THE ROLE OF THE ONCODISTINCT NETWORK *(A. GONÇALVES, IPC, MARSEILLES)*

Although recent progress in targeted therapies and immune-oncology agents provides lots of opportunities for patients, this wealth of novel therapeutics comes at the cost of several challenges in oncological clinical research. One of the most important challenges is the rapid evolution of early phase oncology trials forcing researchers to adapt the design of clinical trials. Also strategic issues must be overcome in order to prevent drug development from becoming more commercially-driven than patient-centred. To address these issues, the Oncodistinct network was set up. This network is currently active in 25 cancer centres and university hospitals with an expertise in oncology, divided over nine countries. The aim of this network is to accelerate oncology drug development and innovative strategies in clinical trials, particularly in settings with a high unmet medical need. The organisation is based on a close collaboration between all entities (investigators, industries, patients and scientists) contributing to a common project. The driving force of the network is the 'investigators' Think Tank', a forum for scientific discussions, ideas and strategies. At the moment, four Oncodistinct studies are on-going; the MiMe-A, PELICAN, AURA and Oncodistinct 005. In the future, the Oncodistinct network aims to improve its internal organisation, increase multidisciplinary partnership and develop a translational research group, further develop the collaboration with pharmaceutical companies and investigate novel tools and issues.[63]

HOW TO IMPROVE THE OUTCOME OF GLIOBLASTOMAS PATIENTS *(B. NEYNS, UNIVERSITY HOSPITALS BRUSSELS)*

Over the past decade, no progress has been made in the treatment of patients with glioblastoma. However, intensive research did result into a better insight into the molecular and genetic background of these central nervous system tumours. In clinical practice, this comes down to interrogating the mutation status of isocitrate dehydrogenase 1 (IDH1) since glioma patients with a mutation in IDH1 have a far better prognosis.[64] Within this subgroup, mainly those patients which are non-1p/19q deleted are highly sensitive to alkylating chemotherapy. The reference treatment for these types of high grade glioma consists of a maximal resection of the tumour, followed by combined radiation and temozolomide, and adjuvant temozolomide.[65-70] For lower grade tumours, there is still a place for the 'wait and see' approach.[71] Unfortunately, phase III trials with nivolumab failed to demonstrate a survival benefit in patients with glioblastoma.[72-74] More recently, results of the first study (GLITIPNI trial) demonstrating the safety and efficacy of combining surgical resection of recurrent glioblastoma with local intracerebral administration of immune checkpoint inhibitors were published. The results of this trial seem promising and justify further investigation.[75]

CNS METASTASES AND THE BRAINSTORM PROGRAM *(N. KOTECKI, INSTITUT JULES BORDET)*

Over the past decades, CNS metastases have become an increasing issue, in part due to the development of improved diagnostic tools. However, also the availability of newer, more effective anti-cancer therapies has led to an increased rate of CNS metastases. In fact, as these treatment modalities allow patients to live longer, there is also more time to develop brain metastases.[76-78] Importantly, brain metastases often harbour specific alterations that are not necessarily detected in the primary tumour. Therefore, genotyping of the primary tumour or extracranial metastatic sites can miss actionable oncogenic driver mutations

that are limited to the CNS metastasis.[79] *De Mattos-Arruda et al.* showed that cerebrospinal fluid-derived circulating tumour DNA (CSF ctDNA) follows the changes in brain tumour burden and might provide a biomarker to monitor brain malignancies and complement the diagnosis of leptomeningeal carcinomatosis.[80] The Brainstorm program of the Oncodistinct Network aims at a better understanding of the biology of CNS metastases using CSF ctDNA as a surrogate endpoint for CNS tumour tissue DNA. The trial will include patients from seven different cohorts of solid tumours with a high risk of developing CNS metastases; triple negative breast cancer, HER2-positive breast cancer, non-small cell and small-cell lung cancer, melanoma, other solid tumours and leptomeningeal carcinomatosis. The first patient inclusion is planned for early 2020 and the estimated study completion date is January 2028.[81]

CONTEMPORARY MANAGEMENT OF METASTATIC COLORECTAL CANCER: HOW TO EMERGE FROM THE "STATUS QUO"? *(A. HENDLISZ, INSTITUT JULES BORDET)*

In colorectal cancers, both tumour burden and the body mass composition of the patient are prognostic factors for treatment outcome. It is well-established that colon cancer is not just one disease. On a genomic, transcriptomic, proteomic, epigenomics and metagenomic level, colon cancers prove to be very heterogeneous. In metastatic colorectal cancer, around 45% of the cancers are *RAS*-mutated. For a long time, *RAS* has been considered to be 'undruggable' but recent work by *Canon et al.* has demonstrated that the novel compound AMG510 efficiently targets the $KRAS^{G12C}$ mutation and induces an immune-inflammatory phenotype.[82] Around 26% of colorectal cancer patients are *RAS/BRAF* wild-type. Interestingly, *Sadanandam et al.* have worked out a colorectal cancer classification system that associates cellular phenotype and responses to therapy. Each subtype shares similarities to distinct cell types within the normal crypt and shows differing degrees of 'stemness' and Wnt signalling.[83]

MSI high status is a positive predictive biomarker for immunotherapy. In MSI-high patients, nivolumab plus ipilimumab represents a promising new treatment option.[84] Of note, also within the subgroup of MSI-positive colorectal cancers, there is substantial molecular heterogeneity with clinical implications. For example, patients with *JAK1* mutations and the transcriptomic subgroup CMS1 have a better prognosis.[85] Finally, metastatic colorectal cancer patients with a $BRAF^{V600E}$ mutation seem to significantly benefit from treatment with a triplet combination of *BRAF*, MEK and EGFR inhibitors.[86]

NEW MULTIDISCIPLINARY APPROACHES

THE CURRENT LANDSCAPE OF GYNAECOLOGICAL CANCERS *(J. VERMORKEN, UZA)*

Two studies recently reported inferior survival with minimal invasive surgery in patients with early-stage cervical cancer *versus* open surgery.[87,88] Concurrent chemoradiotherapy is the standard of care in advanced-stage cervical cancer. Cisplatin dose and respective roles of neoadjuvant/adjuvant therapies are on-going research topics. Bevacizumab added to chemotherapy leads to a survival benefit in recurrent/metastatic disease. Checkpoint inhibitors (CPIs) are not very successful. A broader immune response, targeting both viral and non-viral antigens, may be necessary. Standard therapy of advanced ovarian cancer includes upfront cytoreductive surgery followed by six cycles of paclitaxel/carboplatin with or without bevacizumab followed by bevacizumab maintenance. For those patients not suitable for this regimen, neoadjuvant paclitaxel/carboplatin with or without bevacizumab with interval debulking surgery, followed by paclitaxel/carboplatin with or without bevacizumab (and maintenance bevacizumab) is recommended. PARP inhibitor maintenance is indicated when the tumour is *BRCA* mutated. Intraperitoneal chemotherapy and HIPEC need to be mentioned. PARP inhibitors are a breakthrough in recurrent/primary ovarian cancer. In endometrial cancer, surgery is the cornerstone. Adjuvant radiotherapy is indicated for intermediate and high-risk cases, radiotherapy plus chemotherapy in stage III (or serous tumours). Progestins are recommended for palliation in hormone-positive endometrial cancer, chemotherapy in case of hormone-failures. CPIs are efficacious in MSI-H endometrial cancer while combinations of anti-angiogenic drugs with CPIs are promising in MSS endometrial cancer.

RADIOISOTOPIC THERAPIES AND THERAGNOSTICS IN ENDOCRINE TUMOURS: AN EVOLVING FIELD *(I. KARFIS, INSTITUT JULES BORDET)*

Theragnostics, where the same or similar pharmacological agents can be used for diagnosis and treatment, has been standard practice in nuclear medicine for over 70 years. The most common used diagnostic agent in neuroendocrine tumours is ^{68}Ga-DOTATATE while ^{177}Lu-DOTATATE, targeting the somatostatine receptor, is the most frequently used therapeutic agent. Peptide receptor radionuclide therapy (PRRT) has a place in the treatment of siNETs and pancreatic NETs.[89] NETTER-1 is the first prospective, multicentre, randomised phase III trial

	PALOMA-2	MONALEESA-2	MONARCH 3	MONALEESA-7	PALOMA-3	MONARCH 2	MONALEESA-3
Study design	Phase 3, placebo-controlled **1st-line** (n=666)	Phase 3, placebo-controlled **1st-line** (n=668)	Phase 3, placebo-controlled **1st-line** (n=493)	Phase 3, placebo-controlled **1st-line** (n=672)	Phase 3, placebo-controlled **≥2nd-line** (n=521)	Phase 3, placebo-controlled **2nd-line** (n=672)	Phase 3, placebo-controlled **1st- or 2nd line** (n=726)
Prior therapy	No prior systemic therapy **for ABC**	No prior systemic therapy **for ABC**	No prior systemic therapy **for ABC**	No prior ET up to 1 chemo **for ABC**	Prior ET up to 1 chemo **for ABC**	**No more than one ET No prior chemo for ABC**	**≤1 line of ET for ABC**
Endocrine therapy	Letrozole	Letrozole	NSAI	Tamoxifen NSAI/ LHRHa	Fulvestrant	Fulvestrant	Fulvestrant
CDK4/6 inhibitor	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Abemaciclib	Ribociclib
HR PFS	**0.56**	**0.57**	**0.55**	**0.55**	**0.50**	**0.55**	**0.59**
Median PFS (mo)	**27.6 vs 14.5**	**25.3 vs 16.0**	**NR vs 14.7**	**23.8 vs 13.0**	**11.2 vs 4.6**	**16.4 vs 9.3**	**20.5 vs 12.8**

FIGURE 2. Progression-free survival data from CDK4/6 inhibitors in advanced breast cancer with luminal disease.
ABC = advanced breast cancer; LHRHa = luteinising hormone-releasing hormone agonist; mo = months; NR = not reached; NSAI = non-steroidal aromatase inhibitor.

for metastatic or unresectable somatostine receptor positive midgut NETs who progressed under standard octreotide treatment. Treatment with ^{177}Lu-Dotatate resulted in markedly longer PFS and a significantly higher response rate than high-dose octreotide LAR.[90] In order to further improve the PRRT efficacy, patients need to be optimally selected and PRRT can be combined with chemotherapy or SSAs.[91,92] Also in pheochromocytomas and paragangliomas PRRT has been investigated (mostly in retrospective case series). Also in this setting PRRT was found to be a safe and efficacious treatment option, even though response rates seem to be lower than in NET patients.[93] Key challenges for the upcoming years will be the personalisation, validation of new strategies and the registration and approval in other NETs.

HIPEC THERAPY AND PERITONEAL CARCINOMATOSIS: INDICATIONS AND LIMITATIONS *(G. LIBERALE, INSTITUT JULES BORDET)*

In colorectal carcinoma, a complete abdominal exploration with complete macroscopic resection of the tumour(s) is the standard of care. In clinical practice, complete resection and hyperthermic intraperitoneal chemoperfusion (HIPEC) are always combined. HIPEC therapy should not be performed in patients treated by six months of chemotherapy, as the addition of HIPEC does not influence the OS.[94] As for now, the role of HIPEC in chemotherapy naïve patients remains undetermined. The COLOPEC and PROPHYLOCHIP trial both assessed whether HIPEC therapy could prevent peritoneal metastases in patients with high risk. Both trials could not demonstrate a significant difference and could not proof a role of proactive complete surgical resection plus HIPEC.[95,96] In ovarian cancer patients with peritoneal metastases, the role of HIPEC remains undetermined in patients treated by upfront surgery. HIPEC is an option in France in interval debulking and it is recommended in the Netherlands, but in most other countries it is not yet accepted as a standard treatment. More clinical trials are needed to confirm the benefit of HIPEC in the treatment of ovarian cancer.

UPDATE ON BREAST CANCER SYSTEMIC THERAPY FOR CLINICAL PRACTICE *(A. AWADA, INSTITUT JULES BORDET)*

Based on the hormone receptor (HR) expression and the presence of specific genetic aberrations (*HER2*, *PIK3CA/AKT*, *ESR1*, *BRCA1/2*), breast cancers can be subdivided in at least seven molecular subtypes, each requiring a different therapeutic approach. In breast cancer patients with luminal disease, CDK4/6 inhibitors significantly and consistently improve PFS and ORR *(Figure 2)*.[97-103] In patients with HER2-positive breast cancer with residual disease after neoadjuvant therapy, trastuzumab emtansine reduced the risk of recurrence or death by 50% as compared to trastuzumab alone.[104] Moreover, promising results of neratinib and margetuximab were recently presented at ASCO 2019.[105,106] Several other ADCs targeting HER2 are cur-

rently under evaluation in phase II/III trials.[107-109] In the management of TNBC, checkpoint inhibitor-based combinations are currently being investigated in the neoadjuvant and metastatic setting.[110-112] Also the ADC sacituzumab govitecan as a single agent induced objective responses in heavily pre-treated $HR^+/HER2^-$ metastatic breast cancer patients.[113] Finally, in *BRCA* mutated breast cancer, much attention goes to the role of PARP inhibitors, both as a single agent (olaparib, talazoparib) or in combination with other drugs (*e.g.* veliparib).[114-116]

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