

BJMO

Belgian Journal of
Medical Oncology

VOLUME 13 | ISSUE 2
MARCH 2019

clinic



Molecular test algorithms for breast tumours

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The Belgian Journal of Medical Oncology (BJMO) is the official scientific journal of the Belgian Society of Medical Oncology (BSMO) and the Belgian Association for Cancer Research (BACR). The BJMO aims to be a peer-reviewed cancer journal covering all aspects of the diagnostic and clinical management of cancer patients. Subscriptions are free for all specialists who are active in the fields of oncology, radiotherapy and adherent fields.

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Publication Frequency: 8 issues per year.
Edition: 3,000 copies.

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Science Photo

ISSN-NUMBER

1784-7141

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J. DE GRÈVE



DEAR COLLEAGUES,

We just had the 21st Annual Symposium of the Belgian Society of Medical Oncology (BSMO) with a score of exciting lectures and outstanding junior presentations, promising a bright future. Both translational science and clinical aspects in various malignancies came into view.

The **Review Oncology** article discusses the **molecular testing of breast cancer**, and the list of authors testifies to the intensive multidisciplinary and multi-stakeholder involvement. A. Hébrant and the Cancer Center deserve a lot of credit in the effort. NGS reimbursement seems on track for May 2019, a significant step forward but, as said in the previous issue, there is still a way to go to implementing the needed, broad panel, tumour-agnostic sequencing. In the **Pharmacotherapy section**, the role of **DOACs in the management of cancer-associated thrombosis** is reviewed. The drugs are all different and effective but with higher bleeding risk. Therefore, their use, as opposed to LMW heparin, should be weighed against the risks, and thus they are

not standard for all patients. Beyond the timeline of this article, two randomised trials appeared that evaluated the *preventive* use of DOACs in patients with a high risk for thrombosis.*

The **Oncothesis** is about the CD70-CD27 signalling pathway. CD70 is abnormally expressed on some cancer types and causes immune evasion. Drugs targeting CD70 are in clinical development.

The **Congress News** covers the 2018 annual conference of the **International Society of Geriatric Oncology** which took place in Amsterdam. We congratulate H. Wildiers, as the new president of SIOG. The next meeting will take place in Geneva (www.siog.org). H. Van Poppel reports the highlights from the **10th European Multidisciplinary Congress on Urological Cancers (EMUC18)**.

T. Feys (Ariez medical writer) has listed a series of **highlights from the SABCS 2018**. Some should affect our daily practice: low-dose tamoxifen chemoprevention, the importance of timing of adjuvant chemotherapy in TNBC, yet another reason for the generalised use of neoadjuvant chemotherapy in TNBC. Last but not least: the significant impact of adjuvant T-DM1 in patients with residual disease after neoadjuvant therapy in HER2 amplified breast cancer. T-DM1 largely outperforms adjuvant pertuzumab, and therefore we hope that our patients can access it as early as possible. To achieve this, we are prepared to trade in adjuvant pertuzumab entirely to make this possible (overwhelming member vote at BSMO annual meeting).

We also include the **winning abstracts from the BACR 2019 annual meeting** with the theme of **combination strategies**. I congratulate the **new BSMO board members** and wish them great success in their endeavours in the further development of our already busy society, in the service of our patients and our members.

Enjoy reading the BJMO,

Jacques De Grève, MD, PhD

*Khorana AA, et al. N Engl J Med. 2019;380(8):720-8 & Carrier M, et al. N Engl J Med. 2019;380(8):711-9.

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Molecular test algorithms for breast tumours

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SUMMARY

In order to advise the Federal Government on all matters related to personalised medicine in oncology, including the reimbursement of molecular tests, the Commission of Personalized Medicine (ComPerMed) has applied, for the breast tumours, the same methodology as previously applied for the digestive tumours. Meaning, the different molecular tests, represented in the shape of algorithms, are annotated with test levels – which aim to reflect their relevance based on current available data and to define the reimbursement – and are documented with recent literature, guidelines and a brief technical description.

(BELG J MED ONCOL 2019;13(2):40-45)

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: breast tumours, molecular tests, NGS, oncology.

TABLE 1. Test levels.

1	Standard of care biomarker for diagnosis and/or prognosis*
	Biomarker predictive of response or resistance to a reimbursed drug in Belgium for this indication
2A	Recommended standard of care biomarker for diagnosis and/or prognosis**
	Biomarker predictive of response or resistance to an EMA-approved drug for this indication
2B	Biomarker predictive of response or resistance to a reimbursed drug in Belgium for another indication (clinical trial available in Belgium or EU)
3	Compelling clinical evidence supporting the biomarker for diagnosis and/or prognosis Biomarker predictive of response or resistance to - a non-EMA-approved drug in this indication - a reimbursed drug in Belgium for another indication (clinical trial not available in Belgium or EU) - an EMA-approved drug for another indication Compassionate use of drug
*Standard of care: included in guidelines (WHO, etc.) AND consensus from experts ComPerMed, **Recommended standard of care: clinical evidence AND consensus from experts ComPerMed. EMA: European Medicines Agency, WHO: World Health Organization, ComPerMed: Commission of Personalized Medicine.	

INTRODUCTION

The treatment of patients with breast cancer has become more challenging with the advent of numerous innovative molecular tests giving the opportunity to the oncologists to tailor their patients' treatments based on prognosis and/or predictors of resistance or response to chemotherapy, endocrine therapy and targeted therapy.

METHODOLOGY

The Commission of Personalized Medicine (ComPerMed) has set up a methodology in order to systematically evaluate and prioritise the molecular tests currently performed in Belgium in clinical routine for each tumour type.¹

After having achieved a consensus for the digestive tumours, the same methodology has been applied to the breast tumours to ensure the relevance of a molecular test for a specific clinical question.¹

ALGORITHMS AND KEY MESSAGES

The different molecular tests used in clinical routine in Belgium are represented in algorithms (Figure 1 and 2) and are published on the website www.compermed.be. These algorithms will be reviewed annually. Some additional information has been noted, such as tumour incidence (provided by the Belgian Cancer Registry) and, for each molecular test, its utility (diagnostic, prognostic or therapeutic utility) and corresponding test level (Table 1) and a brief technical test description. Three test levels were determined, with level 1

representing the highest priority for the qualification of the test by the policy makers. These test levels are linked to the standard of care and to reimbursed treatments in Belgium.

Only molecular tests with a test level of 1 or 2A were retained. Some tests with a level 2B were, however, considered if the expert group estimated that they will acquire a test level 1 or 2A in the near future.

In the case of next generation sequencing (NGS) testing, the genes and regions that have to be sequenced were also evaluated.

Experts have agreed that:

- Only test level 1 and 2A molecular tests should be reimbursed by the Belgian reimbursement agency, INAMI/RIZIV.
- Immunohistochemical tests for oestrogen receptor (ER) and progesterone receptor (PgR) and determination of human epidermal growth factor receptor 2 (HER2) status by immunohistochemistry (IHC) and/or *in situ* hybridisation (ISH) are required for early breast cancers as well as for metastatic breast cancers. HER2 testing should follow the new 2018 ASCO-CAP guidelines, which highlights the importance of the quality assurance in HER2 IHC for therapeutic decision making.² Testing for ER, PgR and HER2 should be repeated in case of a biopsy in the metastatic setting.
- An official and mandatory government-led external quality assessment (EQA) for the immunohistochemical testing of HER2 overexpression and hormone receptor (ER/PgR) status is currently lacking in Belgium. It would en-

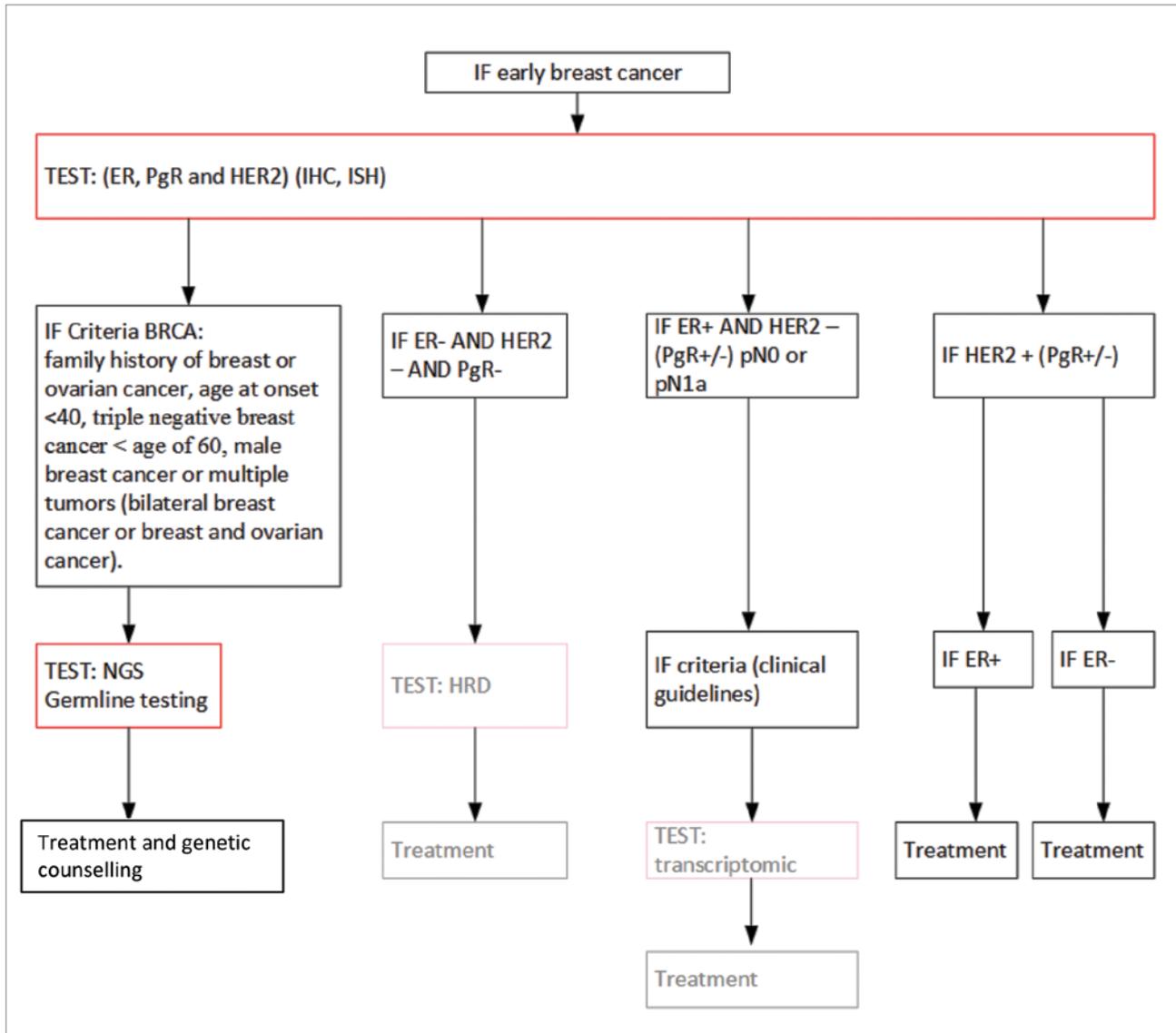


FIGURE 1. Breast algorithm: molecular tests with level 1 or 2A are represented in a red rectangle; molecular tests with a test level >2A are in shadow. ER: oestrogen receptor, PgR: progesterone receptor, HER2: human epidermal growth factor receptor 2, IHC: immunohistochemistry, ISH: in situ hybridisation, BRCA: breast cancer, NGS: next generation sequencing, pN0: no regional lymph node metastasis, pN1a: regional lymph node metastasis completely resected, HRD: homologous recombination deficiency.

sure the quality of these tests and standardised interpretation and reporting throughout Belgium. For the moment, commercial EQA schemes are followed by most laboratories. The lack of mandatory EQAs for the HER2 IHC test has led to upfront HER2 ISH testing in many laboratories.

- NGS germline tests on DNA from blood of breast cancer patients in the frame of a genetic counselling are required if the patient fulfils the criteria of the Belgian Society of Human Genetics for germline testing for hereditary breast and ovarian cancer. Recent changes include indication for germline testing in case of diagnosis of breast cancer ≤40

years or triple negative breast cancer ≤60 years, irrespective of familial history.³

- For the NGS tests, standardised wet lab and bioinformatics methods, as well as more uniform biological and clinical variant interpretation are mandatory.⁴
- *ESR1* and *PIK3CA* mutational status test by the analysis of DNA extracted from a metastatic biopsy or circulating tumour DNA (ctDNA) by polymerase chain reaction or NGS is recommended in routine management for metastatic ER+/HER2- cancers. The detection of pathogenic mutation in the ligand binding domain of *ESR1* is correlated with secondary resistance to aromatase inhibitors (level

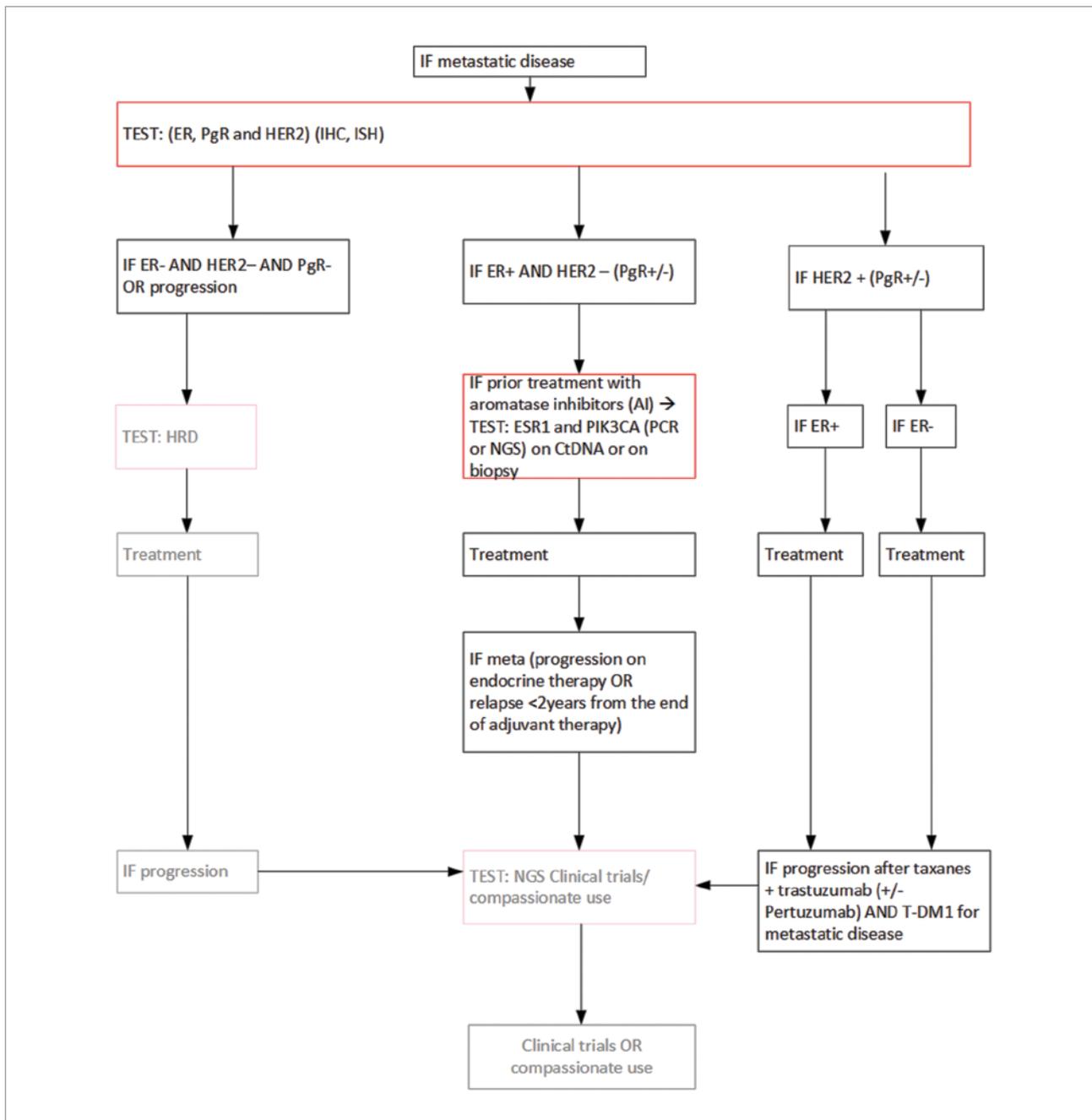


FIGURE 2. Breast algorithm: molecular tests with level 1 or 2A are represented in a red rectangle; molecular tests with a test level >2A are in shadow. *ER*: oestrogen receptor, *PgR*: progesterone receptor, *HER2*: human epidermal growth factor receptor 2, *IHC*: immunohistochemistry, *ISH*: in situ hybridisation, *HRD*: homologous recombination deficiency, *PCR*: polymerase chain reaction, *NGS*: next generation sequencing, *CtDNA*: circulating tumour DNA, *T-DM1*: trastuzumab emtansine.

2A).^{5,6} Detection of hotspot *PIK3CA* mutation, and other genetic alterations in the *PIK3CA*/*AKT*/*mTOR*-pathway can be predictive for a therapeutic effect of *PIK3CA*, *AKT* and/or *mTOR*-inhibitors (level 3).

- Tests for the detection of homologous recombination deficiency (HRD), also referred to as *BRCAness* tests, are emerging for the selection of patients who may require platinum-based chemotherapy or PARP inhibitors.⁷⁻⁹ The best

methodology to assess HRD status has yet to be determined, and several options are available:

- NGS based platforms investigating mutations in a broad panel of genes involved in the HRD pathway;
- commercially available assays based on MLPA and array-CGH technology;
- if feasible, whole genome or exome sequencing to detect mutational signatures linked to HRD.

KEY MESSAGES FOR CLINICAL PRACTICE

For an optimal management of breast cancer, it is essential to establish clear molecular test workflows.

It is recommended for breast cancer management to perform:

- Oestrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor 2 (HER2) analysis for early breast and metastatic breast cancers.
- Next generation sequencing germline tests on DNA from blood of breast cancer patients, if the patient fulfils specific criteria, in early and advanced breast cancer. This should be proposed in the frame of a genetic consultation. The test has prognostic, predictive and preventive utility, in addition to familial genetic counselling.
- ESR1 and PIK3CA mutational status test for the determination of endocrine resistance mechanisms and subsequent therapeutic strategy.

The following tests are emerging:

- large next generation sequencing panel tests for metastatic breast cancers that have progressed after therapy to direct patients to clinical trials;
- tests for the detection of homologous recombination deficiency for therapy selection;
- multigene signatures to select patients with ER+/HER2- tumours who may forego chemotherapy.

- There is currently insufficient evidence to classify other (emerging) prognostic and/or predictive biomarkers as level 1 or level 2A. Phase II-III clinical trials with several biomarker-specific drugs are now ongoing, and some of these already completed recruitment (e.g., ipatasertib in NCT03337724, alpelisib in NCT03056755 and NCT02437318, taselisib in NCT02340221, neratinib in NCT01953926). Other biomarkers demonstrated predictive value in phase III trials (e.g., somatic *BRCA* mutations predictive for carboplatin in NCT00532727). The classification of biomarkers in advanced breast cancers could then change rapidly. NGS with gene panels including these biomarkers can direct metastatic breast cancers patients to clinical trials or to ongoing compassionate use programs of the Federal Agency for Medicines and Health Product FAMHP (e.g., alpelisib for patients with a *PIK3CA* mutation). These molecular tests are currently not reimbursed by the reimbursement agency INAMI/RIZIV.¹⁰
- Multigene signatures (e.g., MammaPrint, Oncotype DX, Prosigna) are useful to select patients with ER+/HER2- tumours who may forego chemotherapy without relevant impact on survival.¹¹ However, the identification of the right target population is still a matter of debate, and, because these tests are performed in centralised foreign laboratories, their price is still high, which should be counterbalanced to the treatment-related side-effects and costs, sick-leave costs and psychosocial burden of adjuvant chemotherapy.

CONCLUSION

In conclusion, we have emphasised the importance of a clear workflow for an optimal clinical management of patients with breast cancer. Moreover, national quality control assessments of molecular tests linked with their reimbursements are crucial to ensure their quality (e.g., national EQA for HER2 IHC to be organised and national benchmark for NGS testing that is ongoing). Also, a more homogenous interpretation and annotation of the molecular test results as well as more homogenous test reporting throughout Belgium would increase Belgian healthcare quality.

Some of the molecular tests proposed here are not yet reimbursed by the Belgian reimbursement agency INAMI/RIZIV (e.g., multigene signature). As soon as the test levels increase for a particular biomarker, it is crucial that INAMI/RIZIV quickly updates the nomenclature. If not, these will result in higher expenses for laboratories.

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Belgian Journal of Medical Oncology (BJMO)

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In the section 'Research' an original research article is published. The structure of a contribution to this section should include 1. Title; 2. Key words; 3. Summary; 4. Introduction; 5. Body copy; 6. Conclusions; 7. Key messages for clinical practice; 8. References; 9. Name(s), title(s), position(s) and correspondence address(es) of author(s); 10. Disclosure statement(s) on author (or authors). Contributions must be no longer than 2,500 words (5 pages A4) including references, illustrations, tables, etc.

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The role of direct oral anticoagulants in the management of cancer-associated thrombosis

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SUMMARY

Cancer patients are at an increased risk of venous thromboembolism (VTE). The current standard initial treatment of an acute episode of VTE in cancer patients consists of the administration of three to six months of subcutaneous low molecular weight heparin (LMWH) at a dose adjusted to the body weight. The efficacy and safety profile of LMWHs are well established, but a drawback of these agents is that they require daily subcutaneous administration. In addition, they are mainly cleared through the kidneys, and their use in patients with severe renal insufficiency may require dose reduction or monitoring of the anti-Xa activity. To address the issues with LMWH, several direct oral anticoagulants (DOAC) have been developed for the treatment of VTE. In contrast to LMWHs and vitamin K antagonist, DOACs directly interfere with thrombin or activated factor X (FXa). DOACs have now become standard treatment options in the general management of VTE, but until recently, there were no results of clinical trials specifically assessing the role of DOACs in the treatment of cancer-associated thrombosis. Recently, the Hokusai VTE cancer study and preliminary data from the Select-D trial demonstrated that DOACs are non-inferior to LMWH in preventing recurrent VTE. However, both studies also show that this comes at the cost of an increased rate of both major and clinically-relevant non-major bleeding. Especially in the subgroup of patients with gastrointestinal cancer, the benefit in VTE recurrence with the DOAC seems to be outbalanced by a significantly increased bleeding risk. Based on the available results, DOACs might represent an interesting alternative for LMWH in certain subgroups of patients, but with an important list of exceptions. It seems reasonable not to use DOACs in patients with a high bleeding risk, and especially in patients with gastrointestinal cancer, DOACs should not be the first-line choice. In summary, while LMWHs are currently the standard of care in the acute management of cancer-associated thrombosis, the advent of DOACs is welcomed for patients at a low bleeding risk who are in need of long-term anticoagulation.

(BELG J MED ONCOL 2019;13(2):46-53)

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Conflict of interest: This publication is based on the Belgian expert consensus meeting logistically organised by Leo Pharma. Leo Pharma also provided editorial support for this paper.

Keywords: bleeding, cancer associated thrombosis, DOAC, LMWH, venous thromboembolism.

INTRODUCTION

It is well known that cancer patients are at an increased risk of venous thromboembolism (VTE), which includes both pulmonary embolism (PE) and deep vein thrombosis (DVT). The presence of malignancy increases the risk of VTE by a factor of 4.^{1,2} Importantly, VTE is strongly associated with short- and long-term mortality. In fact, in cancer patients, thromboembolism represents the second most common cause of death after cancer progression.^{2,3} The standard initial treatment of an acute episode of VTE in cancer patients consists of the administration of three to six months of subcutaneous low molecular weight heparin (LMWH) at a dose adjusted to the body weight. This recommendation is based on the outcome of large randomised controlled trials, indicating that treatment with a LMWH for six months is more effective than treatment with a vitamin K antagonist (VKA) and does not cause more bleeding.⁴⁻⁸ The two key studies attributing to this were the CLOT and the CATCH trial.^{5,8} CLOT demonstrated that dalteparin was more effective than a coumarin in reducing the risk of recurrent VTE in patients with cancer, without increasing the risk of bleeding.⁵ Similarly, CATCH showed that daily tinzaparin for six months was associated with a comparable VTE recurrence rate than six months of warfarin, with a lower rate of clinically relevant non-major bleeding among patients with active cancer and acute symptomatic VTE.⁸ There are no published studies addressing optimal anticoagulation beyond six months in patients with cancer. However, there is consensus that continuing anticoagulation beyond six months should be considered in patients with a persistent high-risk of recurrence and in patients with active cancer.⁷

The efficacy and safety profiles of LMWHs are well established, but a drawback of these agents is that they require daily subcutaneous administration. In addition, they are mainly cleared through the kidneys, and their use in patients with severe renal insufficiency may require dose reduction or monitoring of the anti-Xa activity. On the other hand, the narrow therapeutic window and variability in response of VKA imply the need for frequent anticoagulant monitoring to avoid a subtherapeutic anticoagulation associated with an increased risk of thrombosis or an excessive anticoagulation that increases the risk of bleeding. To address the issues with LMWH and VKA, several direct oral anticoagulants (DOAC) have been developed for the treatment of VTE. In contrast to LMWHs and VKA, DOACs directly interfere with thrombin or activated factor X (FXa), an important serine protease in the coagulation cascade.^{9,10} Several studies on patients with acute VTE have demonstrated comparable efficacy of DOACs in comparison to VKAs in terms of VTE recurrence rates, with lower risks of bleeding complications.¹¹⁻¹⁶ Based

on these data, DOACs have now become standard treatment options in the general management of VTE. Currently, four DOACs are approved for the treatment of VTE in the European Union: the oral direct FXa inhibitors rivaroxaban, apixaban and edoxaban and the oral direct thrombin inhibitor dabigatran etexilate.

Until recently, there were no results of clinical trials specifically assessing the role of DOACs in the treatment of cancer-associated thrombosis (CAT). This changed with the publication of the Hokusai VTE cancer data in the *New England Journal of Medicine* and with the presentation of the smaller Select-D trial during the 2017 annual meeting of the American Society of Hematology (ASH).^{17,18} In this review article, the pharmacokinetic differences between the different DOACs will be discussed as are the potential drug-drug interactions that need to be considered when using DOACs in cancer patients. In addition to this, the clinical data generated with DOACs in CAT patients will be critically reviewed.

PHARMACOLOGICAL AND PHARMACOKINETIC PROPERTIES OF DIRECT ORAL ANTICOAGULANTS

While DOACs are often referred to as being a uniform group of drugs, there are some important pharmacological and pharmacokinetic differences between these agents (*Table 1*).

PHARMACOKINETICS

First of all, not all DOACs have the same molecular target. In fact, rivaroxaban, apixaban and edoxaban are targeting factor Xa, whereas dabigatran is a direct inhibitor of thrombin. Given their direct mode of action, the factor targeting agents can inhibit both free and prothrombinase-bound FXa as well as fibrin-bound FXa. Similarly, dabigatran is able to inhibit both free and fibrin-bound thrombin. Also important to note is that, in contrast to the three anti-FXa agents, dabigatran is administered under the form of a pro-drug (dabigatran etexilate). This pro-drug is a hydrophilic molecule, with poor intestinal absorption after oral administration and low bioavailability (about 7%). The pro-drug needs to undergo an ester cleavage in order to be transformed into its active form, dabigatran.^{19,20}

The direct effect of DOACs on coagulation proteins allow these drugs to reach their peak concentrations after only two to four hours after intake. Conversely, the half-lives of the DOACs are short, in the order of hours, rather than days as with VKAs (*Table 1*). As such, the anticoagulant effects more quickly dissipate when therapy is stopped.²¹ The latter is beneficial when anticoagulation must be reversed for an elective invasive procedure but also makes the DOACs less

TABLE 1. Overview of pharmacokinetic properties of the different direct oral anticoagulants approved in the European union (based on summaries of product characteristics (SmPCs) of the different products).²⁸⁻³¹

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Pro-drug	Yes	No	No	No
Bioavailability	6%	90% (with food)	50%	60%
Time to peak levels (hours)	2	2-4	2-4	2
Terminal half-life (hours)	12-14	5-14	13	10-14
Metabolism	esterase hydrolysis of pro-drug for activation CYP-independent glucuronidation	CYP3A4 CYP2J2	CYP3A4 CYP1A2 CYP2C8 CYP2C9 CYP2C19 CYP2J2	<4% CYP3A4
Renal elimination	80%	35% (65% [*])	25%	50%
P-gp substrate	Yes	Yes	Yes	Yes
Initial treatment of acute VTE	LMWH for at least 5 days	15 mg BD 3 weeks	10 mg BD 1 week	LMWH for at least 5 days
Continued treatment	150 mg BD	20 mg OD	5 mg BD	60 mg OD
Dose reduction	110 mg BD: Reduced dose has not been studied but is suggested for patients >80 years, with CrCl 30-50 mL/min or high bleeding risk	15 mg OD: Reduced dose has not been studied, can be considered for patients with high bleeding risk and CrCl 30-50 mL/min	Reduced dose has not been studied for acute VTE treatment	30 mg OD: CrCl 15-50 mL/min Weight ≤60 kg Concomitant use of cyclosporine, dronedarone, erythromycin, or ketoconazole
Use not recommended	CrCl <30 mL/min Concomitant use of P-gp inhibitors ketoconazole, itraconazole, dronedarone, cyclosporine Concomitant use of P-gp inducers rifampicin, carbamazepine, phenytoin	CrCl <15 mL/min Concomitant use of antiretroviral protease inhibitors and azoles (except fluconazole) Concomitant use of P-gp inducers rifampicin, carbamazepine, phenytoin	CrCl <15 mL/min Concomitant use of antiretroviral protease inhibitors and azoles (except fluconazole) Concomitant use of P-gp inducers rifampicin, carbamazepine, phenytoin	CrCl <15 mL/min Concomitant use of P-gp inducers rifampicin, carbamazepine, phenytoin

*Approximately half eliminated unchanged in the urine. VTE: venous thromboembolism, LMWH: low molecular weight heparin, CrCl: creatinine clearance, CYP: cytochrome P450 protein, P-gp: P-glycoprotein, OD: once daily, BD: twice daily.

forgiving drugs in patients who are inconsistently compliant with their therapy.

Renal function is of crucial significance for the plasma concentration and duration of action of DOACs. Pharmacokinetic studies indicate that DOACs are eliminated to a varying extent via the kidneys. The risk of accumulation in the case of renal failure is highest for dabigatran (80% renal elimination), followed in descending order by edoxaban, rivaroxaban and apixaban.²²⁻²⁴ This is of particular importance in the context of CAT, given the high incidence of renal impairment in cancer patients.

Routine laboratory monitoring is not required with DOACs due to their wide therapeutic window, which creates a more consistent relationship between dose and pharmacodynamic effect in most patients.

DRUG-DRUG INTERACTIONS

Although DOACs have significantly fewer drug-drug interactions than VKAs, drugs that strongly affect the CYP3A4 enzyme and/or P-glycoprotein (P-gp) can alter the plasma concentration of the DOACs and lead to clinically significant alterations in their anticoagulant effects. CYP3A4 is a member of the hepatic cytochrome P450 enzyme system and is responsible for the oxidative metabolism of both apixaban and rivaroxaban (only minimal involvement in metabolism of edoxaban). In contrast, the dabigatran pro-drug is metabolised by esterases in the plasma and liver without significant involvement of CYP3A4. As substrates of CYP3A4, rivaroxaban and apixaban are vulnerable to both inducers and inhibitors of this enzyme when given concomitantly, leading to potential increased toxicity or decreased efficacy.²⁵

P-gp is an ATP-dependent efflux transporter belonging to the ATP-binding cassette transporter superfamily. It mediates drug absorption and excretion and is a mechanism of chemotherapy resistance, as its activity decreases uptake of chemotherapeutic agents in some cancer cells.²⁶ P-gp is present in many normal human tissues, most notably the luminal membrane of enterocytes and the apical membrane of both hepatocytes and renal tubular cells.²⁷ In the intestines, it causes efflux of absorbed substances and drugs back into the intestinal lumen, decreasing net gut absorption. Inhibitors of P-gp increase plasma levels of its substrates, whereas inducers decrease levels. All DOACs are substrates of P-gp and are therefore susceptible to strong inhibitors or inducers of this transporter.

The clinical impact of the potential drug-drug interactions of DOACs with inducers and inhibitors of P-gp and/or CYP is not clear. Nevertheless, the summaries of product characteristics (SmPCs) of the different DOACs include some recommendations for their concomitant use with such drugs.²⁸⁻³¹

Specifically looking at drugs that are used in cancer patients, it becomes clear that many chemotherapy or molecular-targeted drugs induce or inhibit the activity of CYP3A4, P-gp or both. In fact, some classes of anti-cancer drugs appear to nearly universally interact with CYP3A4 and/or P-gp. These include the antimetabolic microtubule inhibitors (e.g., vinca alkaloids and taxanes), tyrosine kinase inhibitors (with the exception of erlotinib, gefitinib, and sorafenib) and the immune-modulating agents, including glucocorticoids and mammalian target of rapamycin (mTOR) inhibitors (with the exception of everolimus). In contrast, none of the frequently used anti-metabolites, platinum-based agents, intercalating agents or monoclonal antibodies have significant inhibitory or inducing effects on CYP3A4 or P-gp.

Two strong inhibitors of CYP3A4 deserve special attention: enzalutamide, an androgen receptor antagonist used to treat castration-resistant prostate cancer, and dexamethasone, a glucocorticoid used for its anti-tumour effects in many lymphoid malignancies and for the treatment and palliation of various cancer-related complications, including nausea, vomiting and oedema of brain metastases. These agents could potentially increase the plasma concentration of rivaroxaban or apixaban if used in combination with these DOACs. In addition to these strong inhibitors, two other hormonal agents, bicalutamide and abiraterone acetate, were identified as moderate inhibitors of CYP3A4. No strong inducers of CYP3A4 were identified. Four moderate inhibitors of both CYP3A4 and P-gp activity were identified: imatinib, crizotinib, abiraterone acetate and cyclosporine. The use of these drugs in combination with any of the DOACs could result in increased plasma concentrations of the DOAC. Drugs that exert moderate induction of CYP3A4 activity without significant influence on the P-gp transporter include paclitaxel, vemurafenib, prednisone and bexarotene. Use of these agents in combination with rivaroxaban or apixaban could lead to decreased plasma concentration of the anticoagulant. Of note, the vemurafenib SmPC also calls for caution and potential additional monitoring when using it in combination with dabigatran.³² With respect to supportive care agents, the neurokinin receptor 1 antagonists, aprepitant and fosaprepitant, can both moderately induce and inhibit CYP3A4 activity. However, their effect on DOAC plasma concentrations is not clear. Most other supportive care agents have little drug interaction potential, with the exception of some of the pain palliation agents (e.g., fentanyl, methadone and acetaminophen).²⁵ An extensive table of anti-cancer drugs and their potential to interfere with DOACs is provided in the 2018 European Heart Rhythm Association (EHRA) practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation.³³ In addition, www.drugs.com

TABLE 2. Inclusion and exclusion criteria of the Hokusai venous thromboembolism study.¹⁷

Inclusion criteria	Exclusion criteria
Adult cancer with acute VTE confirmed by imaging: <ul style="list-style-type: none"> • symptomatic or incidentally detected proximal DVT • symptomatic PE • incidental PE of a segmental or larger pulmonary artery Cancer other than basal-cell or squamous-cell skin cancer Cancer either active or diagnosed within 2 years Active cancer: <ul style="list-style-type: none"> • diagnosed or treatment given within last 6 months • recurrent or regionally advanced or metastatic • haematological cancer not in complete remission Intention for LMWH treatment for at least 6 months	<ul style="list-style-type: none"> • More than 72 hours pre-treatment with therapeutic dosages of anti-coagulant treatment to treat the current episode • Active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban • ECOG PS 3-4 at the time of randomisation • Platelet count <50,000 mL • Calculated creatinine clearance (CrCl) <30 mL/min • Acute hepatitis, chronic active hepatitis, liver cirrhosis • History of heparin-associated thrombocytopenia • Life expectancy less than 3 months

VTE: venous thromboembolism, DVT: deep vein thrombosis, PE: pulmonary embolism, LMWH: low molecular weight heparin, ECOG PS: Eastern Cooperative Oncology Group performance status, CrCl: creatinine clearance.

allows physicians to rapidly check for potential drug-drug interactions.

TREATING VENOUS THROMBOEMBOLISM WITH DIRECT ORAL ANTICOAGULANTS

Before discussing the clinical data that were generated with DOACs, it is important to underscore that the administration schemes vary between the different DOACs. In fact, with dabigatran and edoxaban, patients are initially treated with a LMWH for five to seven days. After this initial phase, dabigatran is given twice daily at a dose of 150 mg, while edoxaban needs to be taken once daily at a dose of 60 mg. With rivaroxaban and apixaban, the treatment scheme does not include a LMWH phase, but does include an acute phase in which the DOAC is given at a higher dose. With rivaroxaban, patients first receive 15 mg twice daily for three weeks, after which the dose is reduced to 20 mg once daily. Patients on apixaban first receive the drug twice daily at a dose of 10 mg for one week after which the dose is cut in half (5 mg twice daily). After six months, the dose of apixaban can be lowered even further to 2.5 mg twice daily. The rationale for the more intensive anti-coagulation during the first week(s) is that patients are at the highest recurrence risk in the first weeks. The higher DOAC dose, or the initial LMWH, offers extra protection in this acute, high-risk phase.

DOACs IN GENERAL VTE MANAGEMENT

Several clinical studies in patients with acute VTE have demonstrated comparable efficacy of DOACs in comparison with VKAs in terms of VTE recurrence rates, with lower risks of bleeding complications.¹¹⁻¹⁵ These findings were confirmed in a meta-analysis grouping the data of the pivotal trials comparing DOACs with VKA in the treatment of acute VTE. This meta-analysis included data from 24,455 patients and demonstrated that DOACs were as effective as VKA in the prevention of recurrent VTE, or fatal pulmonary embolism. Interestingly, DOACs were associated with a 40% lower risk of experiencing a major bleeding. Also, the risk for fatal bleeding, bleedings at critical sites and the risk for intracranial bleeding were significantly lower with DOACs compared to VKA in this meta-analysis.¹⁶

CANCER PATIENTS IN PIVOTAL RANDOMISED TRIALS WITH DOACs

The percentage of patients with cancer that were enrolled in the pivotal DOAC trials was limited, ranging from 3-9%.¹¹⁻¹⁶ In a meta-analysis with all cancer patients included in the AMPLIFY (apixaban), Einstein-DVT, Einstein-PE (rivaroxaban), Hokusai (edoxaban) and RECOVER I and II (dabigatran) trials (n=1132), similar efficacy results were observed as in the general trial populations. In fact, in this meta-analysis, DOACs seemed to be as effective and safe as conventional

treatment for the prevention of VTE in patients with cancer. The odds ratio for VTE recurrence with DOACs versus VKA was 0.63 (95% confidence interval [CI]: 0.37-1.10), while the odds ratios for major and clinically-relevant non-major (CRNM) bleedings were 0.77 (95% CI: 0.41-1.44) and 0.85 (0.62-1.18), respectively.³⁴

However, this meta-analysis has some important drawbacks. First of all, the definition of cancer varied significantly between the different studies included in the analysis. Secondly, the VTE recurrence rate in the cancer patients included in this meta-analysis was only 6%. This recurrence rate is much lower than what was reported in the clinical trials assessing the use of LMWHs in the treatment of CAT (CLOT trial: recurrence rate 17% with VKA and 9% with dalteparin; CATCH trial: 6-month recurrence rate of 7.2% with tinzaparin and 10.5% with warfarin).^{5,8,34} This indicates that the patient population used in this meta-analysis is not representative for the overall cancer population. Of note, also the bleeding risk was higher in pure cancer VTE trials than in this meta-analysis. This underlines the need for dedicated clinical trials with DOACs in cancer patients.

CLINICAL TRIALS EVALUATING DOACS IN THE TREATMENT OF CAT

The first results of a randomised phase III trial specifically evaluating a DOAC in the treatment of CAT came from the Hokusai VTE cancer study. The objective of this study was to evaluate whether initial LMWH followed by edoxaban is non-inferior to dalteparin for the prevention of recurrent VTE or major bleeding in patients with VTE associated with cancer. In the study at hand, patients with active cancer and objectively confirmed VTE were randomised between treatment with a LMWH for at least five days followed by edoxaban (orally 60 mg QD, 2x 30 mg tablets, 30 mg QD for patients requiring dose adjustment) or dalteparin (200 IU/kg for 30 days, from approximately day 31 onwards 150 IU/kg). In *Table 2*, an overview of the inclusion and exclusion criteria of the Hokusai VTE study are depicted.¹⁷ The primary endpoint of the Hokusai VTE cancer study consisted of a composite of recurrent VTE and major bleeding. For this endpoint, recurrent VTE was defined as a symptomatic confirmed (new) DVT or (new) PE, an unsuspected (new) proximal DVT of the legs or unsuspected (new) PE located in segmental or more proximal arteries or a fatal PE (including unexplained death for which PE cannot be ruled out). Major bleeding was defined as overt bleeding associated with a decrease in haemoglobin of ≥ 2 g/dL, leading to a transfusion of ≥ 2 units of packed red blood cells or whole blood, a bleeding occurring in a critical site (i.e., intracranial, intraspinal, in-

traocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal) or a bleeding contributing to death.¹⁷

The trial enrolled 1,050 individuals from 114 centres in thirteen countries. Patients had a wide range of cancer types and were treated with different chemotherapy regimens. About 10% of patients had a haematological malignancy and the rest had solid tumours. At study entry, PE with or without DVT was present in 657 patients (63%), while the remainder had isolated DVT. Of the 1,050 patients, 706 (67%) had symptomatic VTE and the rest was incidental. Active cancer at entry was present in 97% of the patients and 53% had metastatic disease.

The study showed that edoxaban is non-inferior to dalteparin with respect to the composite endpoint of recurrent clots and bleeding, which occurred in 12.8% of patients receiving edoxaban and in 13.5% of patients treated with dalteparin (HR [95% CI]: 0.97 [0.70-1.36], $p=0.006$). Looking at recurrent VTE or the incidence of major bleeding individually, it becomes clear that edoxaban was associated with a (non-significant) lower rate of recurrent VTE compared to dalteparin (7.9% vs 11.3%; HR [95% CI]: 0.71 [0.48-1.06]; $p=0.09$), but this benefit was balanced by a significantly higher rate of major bleedings under edoxaban (6.9% vs 4.0%; HR [95% CI]: 1.77 [1.03-3.04]; $p=0.04$). This difference in major bleeding was mainly due to the higher rate of upper gastrointestinal bleeding with edoxaban. Of note, the frequency of severe major bleeding events (categories 3 and 4) was similar during treatment with edoxaban and dalteparin (12 patients, corresponding with 2.3% in both treatment arms). The investigators did observe a higher rate of CRNM bleeding with edoxaban compared to dalteparin (14.6% vs 11.1%; HR [95% CI]: 1.38 [0.98-1.94]). The incidence of major and CRNM bleedings together was 18.6% with edoxaban, which is significantly higher than the 13.9% seen with dalteparin (HR [95% CI]: 1.40 [1.03-1.89]).¹⁷

The increased risk for major bleeding with edoxaban seemed more pronounced in the subgroup of patients with gastrointestinal cancer. The incidence of major bleeding in this subgroup was 2.4% with dalteparin as compared to 13.2% in patients treated with edoxaban (vs 4.5% and 4.7% in patients with no gastrointestinal cancer).¹⁷

On a final note we would like to underline the fact that patients with catheter-associated thrombosis were not included in the Hokusai VTE cancer study. This is important for the translation of these data to clinical practice, where this type of VTE is common among cancer patients.

A second clinical trial specifically assessing a DOAC in cancer patients was the Select-D trial.¹⁸ This ongoing trial, including 406 patients, compares rivaroxaban (15 mg twice daily for

KEY MESSAGES FOR CLINICAL PRACTICE

- 1. Direct oral anticoagulants (DOACs) are not all the same: there are important pharmacokinetic differences, and also the dosing schedules are different.**
- 2. Drug-drug interactions of DOACs are important and need to be considered. Education will be key.**
- 3. DOACs appear to be as effective as LMWHs in protecting CAT patients from recurrent VTE but seem to be associated with a higher rate of major bleeds.**
- 4. Clinical trials with DOACs in CAT indicate a particularly higher gastrointestinal bleeding risk.**
- 5. Whereas LMWHs will currently remain the standard of care in the acute management of CAT in many patients, the advent of DOACs is welcomed for patients at low bleeding risk who are in need for long-term anticoagulation.**

3 weeks, then 20 mg once daily, for 6 months in total) with dalteparin (200 IU/kg daily, month 1, and 150 IU/kg, months 2-6) for the treatment of cancer patients with VTE (symptomatic or incidental PE, or symptomatic lower extremity proximal DVT).¹⁸ The first results of this study, presented during ASH 2017, are very similar to what was seen in the Hokusai VTE cancer study. In fact, rivaroxaban was associated with a lower rate of VTE recurrence (6-months VTE recurrence rate 11% with dalteparin vs 4% with rivaroxaban). Also in this trial, the VTE recurrence benefit came at the cost of an increased incidence of major bleeding: 2.9% with dalteparin versus 5.4% with rivaroxaban. Also the incidence of CRNM bleeding was significantly higher with rivaroxaban than with dalteparin in Select-D (12% vs. 3%). Similar to what was seen in the Hokusai VTE cancer study, most bleedings were gastrointestinal in nature.¹⁸ This is also in line with the higher bleeding rate in gastrointestinal cancer patients in the Hokusai cancer VTE study.

DISCUSSION AND CONCLUSIONS

Several clinical studies in patients with acute VTE have demonstrated comparable efficacy of DOACs and VKAs in terms of VTE recurrence rates, with lower risks of bleeding complications. This comparable efficacy in combination with the oral administration route and the fact that laboratory monitoring is not required, led to the rapid uptake of DOACs in the treatment schemes for acute VTE in the general population. However, there were no data from clinical trials specifically evaluating DOACs in the setting of CAT and, as a result, there was no place for DOACs in the management of VTE in cancer patients. Recently, the Hokusai VTE cancer study and preliminary data from the Select-D trial demon-

strated that DOACs are non-inferior to LMWH in preventing recurrent VTE. However, both studies also show that this comes at the cost of an increased rate of both major and CRNM bleeding. The subgroup of patients with gastrointestinal cancer seemed to be most vulnerable. In these patients, the benefit in VTE recurrence with the DOAC seems to be outbalanced by the increased bleeding risk. Also, among patients with other tumour types, gastrointestinal bleeds account for the majority of bleeding. A possible explanation for this could be that DOACs are oral drugs. Given their oral administration route, it could be that the local concentration of the drug is higher in the gastrointestinal tract, leading to more bleedings at that site, especially in patients with frailty of the mucosal membranes.

In conclusion, more data will be needed to fully elucidate the potential role of DOACs in the treatment of CAT. Based on the results that we have now, DOACs might represent an interesting alternative for LMWH in certain subgroups of patients, but with an important list of exceptions. It seems reasonable not to use DOACs in patients with a high bleeding risk (i.e., patients with very active cancer, patients with a bleeding history). In patients with gastrointestinal cancer, DOACs should be used with caution. It is also important to stress that the patients included in these clinical trials are not fully representative for the typical cancer patients encountered in real life. In everyday clinical practice, patients often present with comorbidities (i.e., renal impairment) and often have a poorer performance status than patients included in clinical trials. Therefore, it is important to see how these DOACs will perform in a real world setting. In addition to this, DOACs have not yet been evaluated in patients with catheter-associated thrombosis, and we also lack data on the

use of DOACs in the new era of immunotherapeutics. Finally, physicians also need to take into account the potential drug-drug interactions between DOACs and some anti-cancer drugs. These potential interactions differ between the different DOACs and require proper physician education.

In conclusion, three to six months of LMWH remains a standard of care in the management of CAT. For patients that are in need for long-term anti-coagulation who are at low bleeding risk, the advent of oral DOACs provides an alternative to continued subcutaneous LMWHs. However, more data on the bleeding risk of DOACs in cancer patients are needed before LMWH are abandoned in this setting.

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Unravelling the immunotherapeutic potential of CD70 as a target in solid malignancies

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SUMMARY

Under normal conditions, CD70, member of the tumour necrosis factor family, is only transiently expressed on activated T and B cells. Instead, constitutive expression of CD70 has been described on malignant cells in a range of solid and haematological malignancies. Through its receptor, CD27, the expression of CD70 can facilitate evasion of the immune system by three important mechanisms: induction of T cell apoptosis, T cell exhaustion and increasing the amount of suppressive regulatory T cells. The general aim of this thesis was to investigate the role of CD70 in solid tumour types and explore promising combination strategies for anti-CD70 therapy. Thereby, we focused on the role of CD70 in non-small cell lung cancer and colorectal cancer.

(BELG J MED ONCOL 2019;13(2):54-59)

INTRODUCTION

Cancer represents one of the largest unmet medical needs of western societies. Over the last decades, improvements in molecular profiling techniques have led to the identification of distinct molecular subtypes, for which biology-driven targeted therapies can be harnessed.¹ Despite these novel therapies, clinical anti-tumour responses remain of limited duration and are only observed in a minority of patients.² Hence, chemotherapy remains the backbone of treatment in solid malignancies but is often associated with therapy resistance and intolerable side effects, underscoring the need for new therapeutic strategies. Immunotherapy in which the patient's immune system is used selectively towards cancer cells is considered a very promising candidate in this regard and

may lead to a paradigm shift in current standard of care.³ A major breakthrough in cancer immunotherapy was the discovery of immune checkpoint proteins, which function to effectively inhibit the immune system.⁴ Immune checkpoint inhibitors targeting the cytotoxic T-lymphocyte associated protein-4 (CTLA-4) and programmed cell death 1 (PD-1) receptors have shown impressive activity in different tumour types such as melanoma and lung cancer but also left room for improvement.^{5,6}

CD70: AN EMERGING IMMUNOTHERAPEUTIC TARGET

In this study, we have focused on the CD70-CD27 signalling pathway as an interesting new immunotherapeutic target.

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Conflict of interest: This work was supported by the agency for Flanders Innovation & Entrepreneurship under Grant number 120-128. In addition, part of this research was supported by the Flemish Gastroenterology Association, Belgian Group of Digestive Oncology, Kom op tegen Kanker (Stand up to Cancer), the Flemish cancer society, BOF-KP (2015) and a private donation by Mr Willy Floren (Schilde, Belgium).

Keywords: CD27, CD70, colorectal cancer, immunotherapy, non-small cell lung cancer, Tregs.

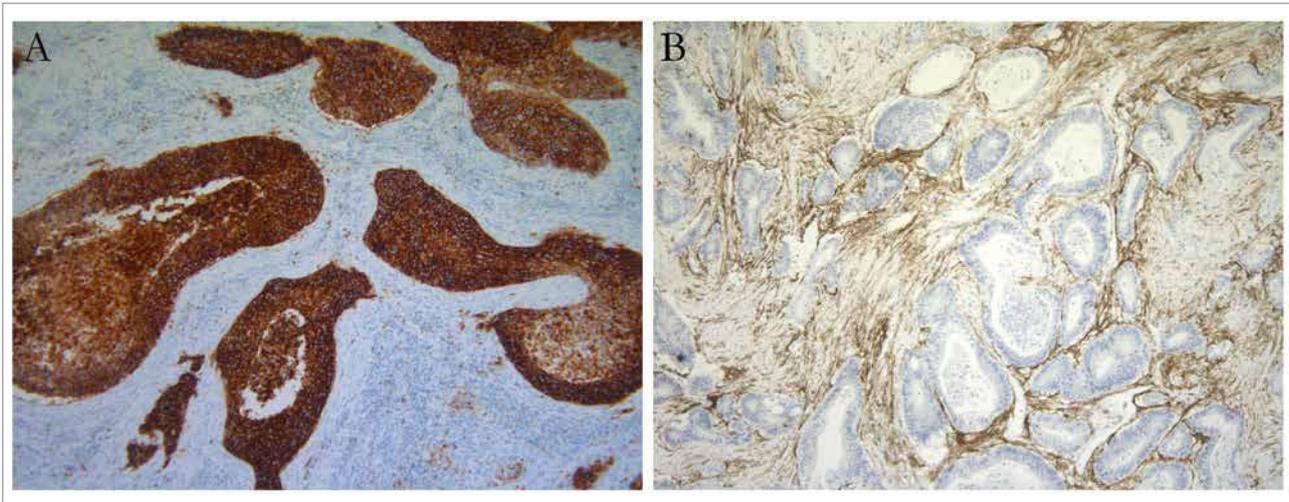


FIGURE 1. Representative immunohistochemical stainings of (A) CD70-positive tumour cells in non-small cell lung cancer and (B) CD70-positive cancer-associated fibroblasts in colorectal cancer specimens.

Under normal conditions, CD70, member of the tumour necrosis factor (TNF) family, is only transiently expressed on activated T and B cells. In addition, CD70 is absent from normal epithelial cells, but was found overexpressed on malignant cells in different tumour types⁷. Through its receptor, CD27, the expression of CD70 can facilitate evasion of the immune system by three important mechanisms: induction of T cell apoptosis, T cell exhaustion and increasing the amount of suppressive regulatory T cells (Tregs).^{7,8} Therefore, targeting CD70 has also emerged as an immunomodulatory therapy that can enhance anti-tumoural immune responses and specifically attack the malignant cells, opening a new therapeutic window, which was explored throughout this thesis.⁸

NON-SMALL CELL LUNG CANCER

Non-small cell lung cancer (NSCLC) retains its position as the most lethal type of cancer worldwide with around 1.3 million deaths each year and a marginally improving 5-year overall survival rate that remains below 20%.⁹ These data point towards the continued need for new therapeutic modalities. We have assessed the expression of CD70 in NSCLC by immunohistochemistry (IHC). We revealed CD70 expression in 16% of NSCLC specimens (Figure 1A). We have shown particular CD70 expression in late stage diseases and squamous cell carcinoma with stable CD70 expression over metastatic tissue in 80% of cases. In addition, we did not find concurrent expression of CD70 with common targetable gene arrangements (including EGFR and ALK), making it an interesting therapeutic tool for patients that currently lack specific treatment options.¹⁰ To unravel a role of CD70 in thriving immune escape, we examined the expression of its receptor, CD27, and FOXP3, a prominent marker for Tregs, on these

NSCLC specimens. Interestingly, we were able to detect infiltration of CD27⁺ lymphocytes in 90% of NSCLC specimens. Furthermore, tumour infiltrating lymphocytes surrounding CD70⁺ tumour cells showed a strong trend towards increasing FOXP3 expression, supporting our hypothesis that CD70 can cause immune escape. Although we could detect the expression of CD70 in NSCLC specimens by IHC, it was important to investigate whether monoclonal antibodies directed to CD70 could bind these CD70-positive malignant cells. One interesting antibody that was further investigated in this dissertation is ARGX-110 (kindly provided by ARGEN-X BVBA). ARGX-110, a human monoclonal antibody, is currently in clinical testing and is able to block the CD70/CD27 interaction and target CD70-expressing tumour cells by antibody-dependent cellular cytotoxicity (ADCC). Our data show a strong correlation between IHC and the capacity of ARGX-110 to bind these cells by flow cytometric analysis. Using a low dose of ARGX-110, we could detect efficient natural killer (NK)-cell based tumour lysis in CD70-expressing tumour cells, demonstrating the potential of ADCC-inducing antibodies to deplete CD70-positive tumour cells. Furthermore, these results imply that IHC is a suitable tool to screen patients for ARGX-110 treatment.¹⁰

It has been demonstrated that upon irradiation, CD70 expression becomes exposed onto the surface of the cells, broadening the applicability of anti-CD70 therapy.¹¹ Therefore, we explored the potential of the first-line chemotherapeutic cisplatin (CDDP) to induce CD70 expression in NSCLC. Our results demonstrated an induction of CD70 protein levels upon CDDP treatment with the highest levels of CD70, 24 hours after treatment. Interestingly, this induction of CD70 could be achieved using medium doses of CDDP and even demonstrated effective upregulation of CD70 in a CD70-neg-

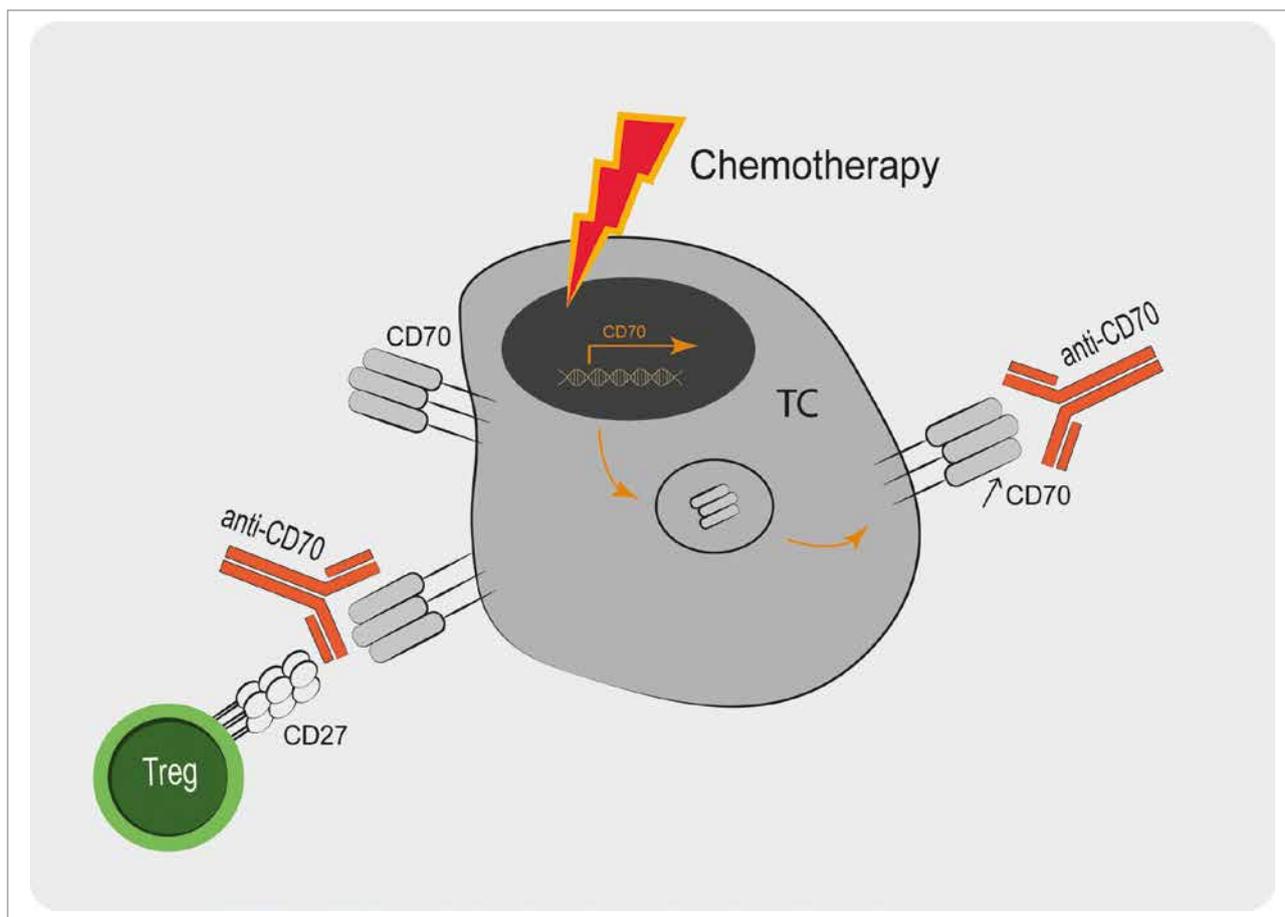


FIGURE 2. Schematic overview demonstrating the potential of combinatorial treatment with chemotherapeutics and anti-CD70 therapy in non-small cell lung cancer.

ative cell line. Moreover, by the sequential administration of CDDP and ARGX-110, we observed a significant decrease in cell survival compared to single treatment regimens. Since it was demonstrated that hypoxic tumour regions often contain viable cells that are more resistant to different types of therapy, these experiments were repeated under hypoxic conditions (0.1-1% O₂). Here, we have demonstrated an identical pattern of CD70 upregulation upon CDPP treatment as opposed to normoxic conditions. Moreover, under hypoxic conditions the combination regimen of CDDP and ARGX-110 yet again displayed a significant decrease in cell survival as opposed to monotherapies.¹² Consequently, this study provides a new combination strategy that can ultimately result in increased tumour-specific cytotoxicity, reduce side effects and reinvigorate the anti-tumour immune response in NSCLC patients (Figure 2).

Lastly, serum samples of NSCLC patients were examined for soluble CD27 (sCD27), which is shed in body fluids upon activation of CD27 by CD70.¹³ We revealed a potential role of sCD27 as a prognostic marker in NSCLC and demonstrated an even worse prognosis when CD70 was also found on the malignant cells. This highlights the activation of the CD27

signalling cascade in patients with NSCLC and the use of sCD27 as a prognostic biomarker for NSCLC.¹⁰

COLORECTAL CANCER

Colorectal cancer (CRC) is the fourth leading cause of cancer-related deaths, mainly due to the development of metastases in the liver and lungs, with a median survival of two years.^{14,15} Despite the clinical successes of immunotherapy in NSCLC, early signals of activity in CRC are largely seen in a small subset of patients, involving microsatellite unstable (MSI) tumours.¹⁶ In CRC, 50% of the tumour microenvironment (TME) consists of cancer associated fibroblasts (CAFs). CAFs reside within the tumour margins or infiltrate the tumour mass and contribute to tumour progression by invasion, angiogenesis and manipulation of the immune response.¹⁷⁻²⁰ On the other hand, the pro-tumorigenic role of CAFs in cancer progression has recently been challenged as complete depletion of CAFs, by its general marker α -smooth muscle actin (α -SMA), led to more aggressive tumours.²¹⁻²³ This heterogeneity of CAFs makes it challenging to develop stromal cell targeted therapies, engineered for distinct subsets of pro-tumorigenic CAFs.²⁴

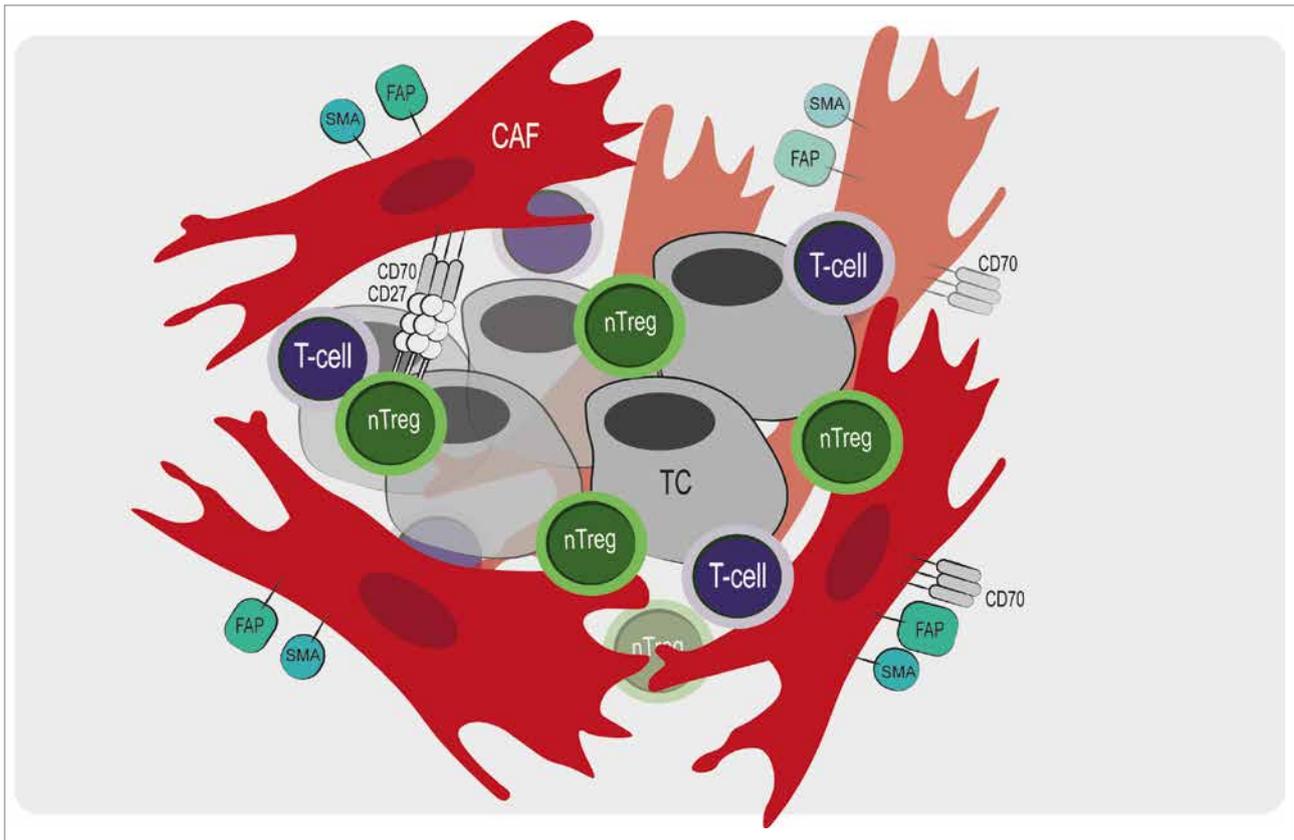


FIGURE 3. Schematic overview of CD70-mediated immune suppression in colorectal cancer.

We are the first to demonstrate the expression of the immune checkpoint molecule CD70, hardly on tumour cells, but on CAFs in CRC specimens (Figure 1B). Moreover, we have found that CAF CD70-positivity was significantly associated with poor clinicopathological parameters and served as an independent prognostic marker in CRC. CD70-positive CAFs displayed no association with MSI status, highlighting the potential of targeting CD70 in CRC subsets that do not benefit from immune checkpoint blockade. In addition, we could demonstrate the expression of CD70 on a specific subset on CAFs as opposed to general CAF markers such as α -SMA and fibroblast-activation protein α . This CD70-positive subset of CAFs was mainly located at the invasive margin of the tumour, suggesting a role of these CAFs in cancer cell migration/invasion. We analysed the migratory capacities of a primary CAF cells line, divided into a CD70^{high} and CD70^{low} subset by flow cytometry. Using real-time analysis of wound closure, we revealed a significant increase in migration when CRC cells were co-cultured with the CD70^{high} CAFs, compared to CD70^{low} CAFs, providing a strong rationale for investigating anti-CD70 therapy in CRC.²⁵ Targeting the CD70/CD27 axis can also release the brakes on the immune system.⁷ In support of this view, we detected a significant association between high CD70 scoring and

increased Treg amounts in primary CRC specimens. However, this present study is the first to reveal such a crosstalk with Tregs by the presence of CD70 on the CAFs instead of the cancer cells. *In vitro* analysis has demonstrated that this presence of CD70^{high} CAFs nearly doubled the proportion of naturally occurring Tregs when co-cultured with T cells, indicating that targeting CD70-positive CAFs can also release the immunosuppressive effect of Tregs in CRC (Figure 3).

CONCLUSION

The main research objective of this thesis was to identify interesting tumour types for anti-CD70 therapy and to provide new combination strategies. We have demonstrated a strong positivity of CD70 on tumour cells in NSCLC specimens, also in patients that lack other targeted treatment options. We could demonstrate the capacity of ARGX-110 to bind these CD70-positive cells and enable NK cell mediated cytotoxicity. In addition, we have revealed that low doses of chemotherapeutics can increase membrane CD70 expression and enhance cytotoxicity of anti-CD70 therapy, hence providing a new combination strategy that can ultimately increase tumour-specific cytotoxicity, reduce side effects and reinvigorate the anti-tumour immune response in NSCLC patients.

KEY MESSAGES FOR CLINICAL PRACTICE

1. CD70 is an interesting immunotherapeutic target for non-small cell lung cancer and colorectal cancer.
2. CD70 is constitutively expressed on tumour cells in 16% of non-small cell lung cancer patients and can be targeted by antibody-dependent cellular cytotoxicity inducing antibodies.
3. Chemotherapy can enhance the efficacy of anti-CD70 therapy.
4. Soluble CD27 can possibly be used as a prognostic blood-based biomarker in non-small cell lung cancer.
5. CD70-positive cancer associated fibroblasts are an inferior prognostic biomarker for colorectal cancer patients.
6. Targeting CD70-positive cancer associated fibroblasts can neutralise the suppressive tumour microenvironment in colorectal cancer.

In CRC, we discovered an entirely different mode of CD70 expression. Contrary to its expression in NSCLC, we could find almost no expression on tumour cells in CRC specimens. Nonetheless, we uncovered CD70 expression on CAFs in the tumour microenvironment that are known to play a tremendous role in cancer progression. Our research led to the identification of CD70-positive CAF in invasive CRC specimens and their role as a prognostic marker for CRC patients. Moreover, we found evidence of a cross-talk between CD70-positive CAFs and naturally occurring Tregs, paving the way towards immune escape in CRC. We also displayed the pro-tumorigenic features of CD70-positive CAFs by their strong migratory capacities, providing a strong rationale for further investigation of anti-CD70 therapy in CRC.

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Geriatric oncology: becoming mainstream cancer care

REPORT FROM THE 2018 ANNUAL CONFERENCE OF THE INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

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SUMMARY

The 2018 annual conference of the International Society of Geriatric Oncology took place in Amsterdam, the Netherlands from November 16-18th. More than 500 delegates from 41 countries with a special interest in the care for older patients with cancer attended this conference. The meeting provided an overview of current advances in geriatric oncology.

(BELG J MED ONCOL 2019;13(2):60-62)

INTRODUCTION

The 2018 annual conference of the International Society of Geriatric Oncology (SIOG) focused on the incorporation of geriatric oncology in mainstream cancer care. This is essential to improve the care of the growing group of older patients with cancer. An optimal care for older patients with cancer implies a close collaboration between oncologists and geriatricians but also the involvement of nurses and allied health care professionals in the care plan of these patients.

ADVANCEMENTS IN THE FIELD OF GERIATRIC ONCOLOGY

In an ageing world, oncologists are required to make difficult and complex treatment decisions regarding the treatment of older patients with cancer for which they cannot rely on chronological age alone. In a review paper published by

Soto-Perez-de-Celis *et al.*, the authors give a clear overview of the heterogeneous ageing process and discuss a geriatric assessment (GA)-based approach to cancer care for older patients.¹

At the SIOG meeting, two important studies on GA were presented orally. In the first presentation, Cindy Kenis presented data from a large Belgian study on unplanned readmissions in older patients with cancer.² In this study, the incidence of unplanned admissions was significantly higher in patients with an abnormal result on the G8 screening tool compared to patients with a normal result (22.9% versus 12.4%, respectively, $p < 0.0001$). In a multivariate analysis limited to patients with an abnormal G8, different baseline treatment-related (e.g., chemotherapy) and GA-related risk factors (e.g., presence of comorbidities, malnutrition and polypharmacy) for unplanned readmissions were identified.

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: 2018 SIOG congress, geriatric oncology.

KEY MESSAGES FOR CLINICAL PRACTICE

1. Patients with an abnormal G8 screening have a higher incidence of unplanned admissions.
2. Geriatric assessment improves patient-centred outcomes such as communication.
3. Every physician/nurse/allied health care professional dealing with patients with cancer should become a specialist in 'geriatric oncology'.
4. Join the geriatric oncology family by becoming a SIOG member or by attending the 2019 SIOG Annual Conference in Geneva in order to learn how to improve the care of older patients with cancer.

In the second presentation, Supriya Mohile from the United States presented a randomised controlled trial evaluating the effect of GA.³ In this study, performance of GA with recommendations for interventions improved patient-centred outcomes including patient communication and caregiver satisfaction. This study gives further support to the American Society of Clinical Oncology (ASCO) geriatric oncology guideline, which recommends GA for older adults undergoing chemotherapy.⁴

An important factor in the care of older patients with cancer is physical resilience, which is an individual's ability to recover their basic functional level after experiencing acute or chronic health stressors such as cancer treatment. Functional resilience is influenced by many factors including baseline frailty, the magnitude of the stressor, the support system, the care and interventions as well as the mind-set of the person. In older women receiving adjuvant chemotherapy for breast cancer, a functional decline was observed in 42% of patients at the end of chemotherapy. This functional decline did not recover in 53% of these patients at twelve months. Further research on resilience in older patients with cancer is essential for decision making in these patients.⁵

IMMUNOTHERAPY IN OLDER PATIENTS WITH CANCER

Checkpoint inhibitors have reshaped the therapeutic landscape of many tumours, including melanoma, non-small cell lung cancer, renal cancer and bladder cancer. This has led to an increase in the prescription of immunotherapy, also in older patients with cancer. In a meta-analysis of the pivotal clinical trials, the efficacy and toxicity of checkpoint inhibitors is similar in older versus younger patients, but there are relatively low numbers of very old and/or unfit patients in these clinical trials.⁶ There is therefore a need of real life data. At SIOG, dr Baldini presented the results of a large French real life analysis of anti-PD-(L)1 therapy in older patients with

cancer.⁷ She concluded that age was not predictive for progression-free survival or overall survival. However, adverse events were more frequent in the older population (≥ 70 years) compared to the younger population (< 70 years) with a frequency of 25 versus 33% respectively of grade 2 or more immune related adverse events ($p=0.035$). It seems therefore important to monitor these patients closely for adverse events.

PRESIDENTIAL SESSION

Finally, at the 2018 annual meeting, prof. dr Hans Wildiers from Belgium became the president of SIOG. In his presidential speech, he revealed his ambitious plan to push the boundaries of SIOG. In order to see geriatric oncology become mainstream cancer care for all older patients, there is a need for every physician/nurse/allied health care professional dealing with patients with cancer to become a specialist in 'geriatric oncology'. To do so, SIOG will need to increase its educational activities and integrate with regular oncology organisations. Wildiers stretched the fact that SIOG is a fantastic family of health care professionals with the same goal: to improve care for older patients with cancer. He invites us all to Geneva next year for the 2019 Annual Meeting of SIOG.

CONCLUSION

In November 2018, just before the annual conference, the SIOG family lost a great member, dr Arti Hurria, who was an inspiring role model and mentor. SIOG 2018 has demonstrated that the geriatric oncology community will continue her legacy and advocate strongly for the optimal care of older patients.

The continuous education of all health care professionals involved in the treatment of older patients with cancer is essential to improve this care. The SIOG advanced course in geriatric oncology will again be held in Treviso, Italy, from June 26-29th, 2019. This four-day course is designed to provide specific skills in assessment care pathways and ther-

apeutic choices for older patients with cancer. It includes geriatrics teaching for oncologists and oncology teaching for geriatricians. It gives the opportunity to be part of the international geriatric network.

Finally, all interested physicians, nurses and other health care professionals are more than welcome to join the community of geriatric oncology by becoming a SIOG member. In addition, we all can increase our knowledge on geriatric oncology at the next SIOG annual conference, which will be held in Geneva, Switzerland (date to be confirmed). Further information for the Treviso course, the SIOG membership and the SIOG annual conference can be found at www.siog.org.

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EMUC18: Synergy of disciplines for optimal genitourinary cancer care

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SUMMARY

Marking its decade-long dedication to the goal of pursuing multidisciplinary collaboration, the 10th European Multidisciplinary Congress on Urological Cancers (EMUC18) examined the best practices, advances and future prospects in managing genitourinary malignancies. The congress also identified current dilemmas and addressed gaps in clinical practice.

(BELG J MED ONCOL 2019;13(2):63-65)

INTRODUCTION

Around 1,400 healthcare professionals from 67 countries congregated at the 10th European Multidisciplinary Congress on Urological Cancers (EMUC18) from November 8 to 11, 2018, in Amsterdam, The Netherlands. The synergy of diverse disciplines illustrated that comprehensive genitourinary (GU) cancer care is optimised when various experts such as medical and radiation oncologists, oncologic urologists, pathologists, radiologists, nuclearists and patients work together to identify and achieve prime treatment strategies. Selected key messages of EMUC18 are collated in this article.

PROCUREMENT OF QUALITY DATA

Plenary Session 01 – *Prostate cancer management: Implementation without good evidence?* – underscored the relevance of performing more randomised and multi-centre studies to produce more robust and quality data. The advantages of using digital (virtual) slides such as image sharing for teaching, consultation and quality assurance, interactive publication, quantitative image analysis and information fusion were also expounded.

In generating good evidence in the coming decade, it was inferred that patient-centric trials are the future, as are multi-stakeholder collaborations with the industry. In addition, effective digitalisation of results will lead to bigger data for researchers.

KIDNEY CANCER

In the point-counterpoint discussion during Plenary Session 04 – *Evolving paradigms in GU cancers* – Dr. Laurence Albiges presented insights in favour of immunotherapy as first-line treatment in kidney cancer. Overall survival benefits from the combination nivolumab + ipilimumab, which is the new benchmark. Some good-risk patients can achieve complete response with the immunotherapy approach. Prof. Manuela Schmidinger stated that the debate was not about immunotherapy *per se* but on the timing of immunotherapy as it does not need to be the first-line treatment for all patients. Favourable-risk and some intermediate-risk patients may be better off with delayed immune-checkpoint inhibitors.

In Plenary Session 5 – *Kidney cancer in the frail patient* – two main theoretical concepts of frailty were identified: the frail-

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Conflict of interest: The author has nothing to disclose and indicates no potential conflict of interest.

Keywords: bladder cancer, imaging, kidney cancer, medical treatment, prostate cancer, radiotherapy, surgical treatment.

Acknowledgement: The author would like to thank the Steering and Scientific Committee of the European Association of Urology (EAU), European Society for Medical Oncology (ESMO) and European Society for Radiotherapy and Oncology (ESTRO) and Erika de Groot, Editor and Copywriter, EAU Central Office, Arnhem, The Netherlands.

TAKE HOME MESSAGES

The concluding Plenary Session included the following selected take-home messages:

On Radiation Oncology (Prof. Anne Kiltie):

1. The use of protons in prostate cancer is still unproven and could be detrimental to patients.
2. Salvage radical prostatectomy is underused but has significant caveats in terms of severe side effects.
3. Local radiotherapy to the primary in low-burden oligometastatic prostate cancer is a new standard of care.

On Urology Highlights (Prof. Evangelos Xylinas):

1. ¹¹C-choline PET/CT shows that up to 60% of the cases was pelvic soft tissue recurrence only.
2. Pre-MRI radical prostatectomy (RP) and RP specimens show that radiorecurrent prostate cancer predominantly occurs at initial tumour location on the RP specimens.
3. Pembrolizumab for high-risk non-muscle invasive bladder cancer unresponsive to Bacillus Calmette-Guérin achieves a 38.8% complete response.

On Radiology (Prof. Raymond Oyen):

1. For the characterisation and staging of renal masses, the key modalities are still CT and MRI in differentiation between clear cell carcinoma and urothelial cancer.
2. For multiparametric MRI of solid renal tumours, a practical algorithm can be used to differentiate almost all subtypes of renal cell carcinoma based on MRI sequences.

On GU Pathology (Prof. Rodolfo Montironi):

1. The application of neo-adjuvant chemotherapy should beforehand identify variants and molecular subtypes of bladder cancer.
2. Gleason Score 3 + 3 does not metastasise, and the rare occurrence of extraprostatic extension in such tumours does not have prognostic significance.

On Medical Oncology (Dr. Laurence Albiges):

1. Abiraterone + prednisolone + androgen deprivation therapy should be considered for metastatic hormone-naïve prostate cancer irrespective of risk and/or volume classification.
2. Enzalutamide and apalutamide demonstrate a meaningful improvement of metastasis-free survival in non-metastatic castration-resistant prostate cancer.
3. The ongoing ARAMIS trial will help substantiate the overall survival benefit with darolutamide.
4. Both EAU and ESMO guidelines recommend the combination of checkpoint inhibitor nivolumab + ipilimumab as first-line standard treatment for intermediate-risk and poor-risk patients with clear cell renal cell carcinoma.

ty phenotype and the accumulation of deficits. The frailty phenotype is based on five criteria: shrinking (weight loss), weakness (declining grip strength), self-reported fatigue, a decrease in walking speed and self-reported low activity. Geriatric 8 screening tool and cross-sectional imaging are some of the ways to establish frailty and select patients that will optimally benefit from a given kidney cancer treatment.

TRIAL UPDATES

EMUC18 delivered updates on notable trials such as the Clinical Trial to Assess the Importance of Nephrectomy (CARMENA; NCT00930033) and PeriOperative chemotherapy or sUrveillance in upper Tract urothelial cancer

(POUT; CRUK/11/027; NCT01993979, NIHR portfolio).

The findings of the CARMENA trial stated that sunitinib alone was not inferior to cytoreductive nephrectomy (CN), and CN should not always be considered the standard of care any longer in metastatic renal cell carcinoma and could be omitted in selected patients when medical treatment is required.

The POUT trial showed that adjuvant platinum-based chemotherapy following nephron-ureterectomy improved disease-free and metastasis-free survival in upper tract urothelial carcinoma (UTUC). Its successor trial, POUT 2: Chemotherapy with or without immunotherapy following nephron-ureterectomy for upper tract urothelial cancer, was also announced at the congress. The rationale for POUT

2 is that the high incidence of microsatellite instability in UTUC may predispose to immunotherapy sensitivity while it has been proven feasible to combine immunotherapy with chemotherapy.

PROSTATE CANCER EVALUATION

Plenary Session 08 – *New developments in prostate cancer evaluation* – provided a forum wherein confusing and clinically important issues related to prostate pathology were addressed. Pathology experts stated that urological tumours are classified more precisely based on a combination of morphology, immunohistochemistry and molecular findings. Treatment regimens can be tailored more accurately to the specific subtype of the tumour due to new developments. Further into the session, Prof. Philippe Lambin showed that radiomics is an emerging field that can translate medical images into quantitative data to enable phenotypic profiling for diagnosis, treatment decisions and treatment evaluation. He said: “There are several potential applications that relate to prostate cancer, such as screening, image-guided biopsies and active surveillance. It’s time to test these radiomic approaches much more systematically in clinical trials.”

CURRENT DILEMMAS IN METASTATIC PROSTATE CANCER

In Plenary Session 12 – *Current dilemmas in the management of metastatic prostate cancer* – it was articulated that one of the strengths of plasma cell-free DNA analysis is the eligibility of

all patients for blood-drawing while some patients may be ineligible to undergo a metastatic tissue biopsy, for example those with aggressive disease that have rapid deterioration. Later in the session, dr Ganesh Palapattu underlined to treat the patients, not the diseases; and noted that there is a significant benefit for risk-based treatment allocation. He stated: “We can’t treat all patients the same way. The diseases don’t behave in the same way.”

EUROPEAN SCHOOL OF UROLOGY COURSES AND HANDS-ON TRAINING SESSIONS

The European School of Urology (ESU) offered two complementary frontline courses, which were ‘Daily practice in the management of metastatic prostate cancer’ and ‘Immunotherapy for urological tumours’ as well as the Hands-on Training (HOT) courses ‘ESU/ESUI HOT course Prostate MRI reading for urologist’, ‘ESU/ESUT/ESUI HOT Course in MRI Fusion biopsy’ and ‘ESU/ESUI HOT course in Prostate PET in urologists’.

WHAT TO EXPECT AT EMUC19

Hot topics for EMUC 2019 will include results of the combination vascular endothelial growth factor receptor + tyrosine kinase inhibitor and immunotherapy in first-line renal cell carcinoma setting across all subgroups; and close collaboration between urologists and medical oncologists with regard to immunotherapy use in non-muscle invasive bladder cancer.

Highlights from the 2018 annual meeting of the San Antonio Breast Cancer Symposium (SABCS)

DEC 4-8 2018, SAN ANTONIO, TX, USA

T. Feys, MSc, MBA

SUMMARY

From the 4-8th of December, the San Antonio Riverwalk again formed the background of the most important breast cancer congress in the world. This report will summarise eight top stories presented during the 2018 San Antonio Breast Cancer Symposium (SABCS). For a more complete overview of studies presented at the meeting, we refer to the congress website www.sabcs.org.

(BELG J MED ONCOL 2019;13(2):66-71)

ADJUVANT T-DM1 IMPROVES THE INVASIVE DISEASE-FREE SURVIVAL IN PATIENTS WITH HER2-POSITIVE EARLY BREAST CANCER WITH RESIDUAL INVASIVE DISEASE AT SURGERY FOLLOWING NEOADJUVANT CHEMOTHERAPY AND TRASTUZUMAB

The goal of the phase III KATHERINE trial was to determine if treating patients at higher risk for recurrence following neoadjuvant therapy (i.e. patients with persisting invasive breast cancer at surgery) with the antibody-drug conjugate T-DM1 instead of the standard therapy of trastuzumab would reduce the risk of recurrence without an unacceptable increase in toxicity.¹ KATHERINE is an open-label study of 1,486 patients with HER2-positive early-stage breast cancer who received neoadjuvant chemotherapy plus HER2-targeted therapy that included a taxane and trastuzumab, followed by surgery. All patients had residual invasive disease

in the breast or axillary lymph nodes. Within 12 weeks of surgery, patients were randomly assigned (1:1) to T-DM1 (3.6 mg/kg IV every three weeks) or trastuzumab (6 mg/kg IV every three weeks), for 14 cycles. The primary endpoint was invasive disease-free survival (IDFS). The median age of patients in KATHERINE was 49 years, with one out of five patients being younger than 40 years of age. Three quarters of patients previously received anthracyclines and 22% had residual disease of 1cm or less and negative axillary nodes (ypT1a, ypT1b, ypT1mic and ypN0). IDFS events occurred in 12.2% of patients in the T-DM1 arm as compared with 22.2% on the trastuzumab arm (HR[95%CI]: 0.50[0.39-0.64]; $p < 0.001$) (Figure 1) and this IDFS benefit was seen irrespective of age, race, the clinical stage at diagnosis, the hormone-receptor status, the type of preoperative HER2-directed therapy, the pathological nodal status after preoperative therapy and the primary tumour stage. At 3-years the IDFS rate with T-DM1 was 77%, which was 11.3% less

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Conflict of interest: The author has nothing to disclose and indicates no potential conflict of interest.

Keywords: breast cancer, T-DM1, adjuvant, triple-negative breast cancer, pathological complete response, tamoxifen, carcinoma in situ, circulating tumor cells, axilla, whole breast irradiation, partial breast irradiation.

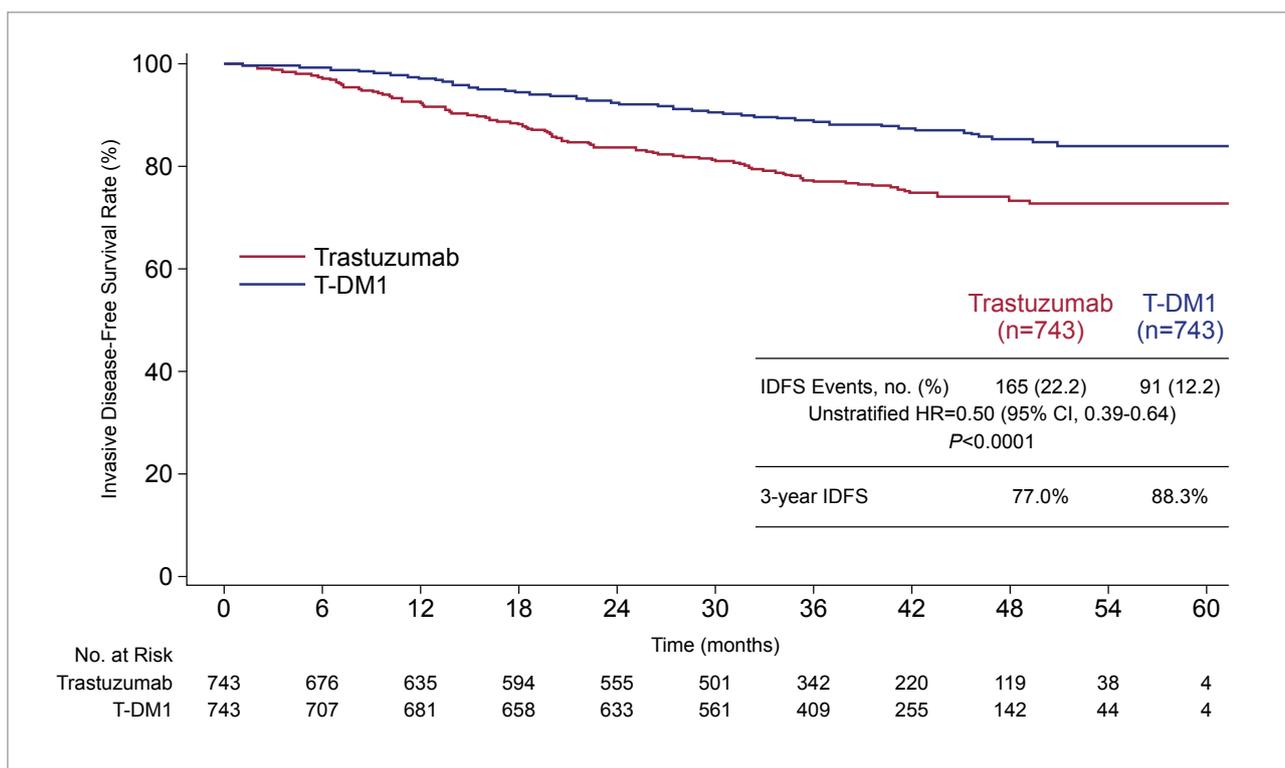


FIGURE 1. IDFS in the phase III KATHERINE trial.¹

than the 88.3% seen with trastuzumab. T-DM1 also outperformed trastuzumab with respect to the incidence of distant recurrence (10.5 vs. 16.3%; HR[95%CI]: 0.60[0.45-0.79]) and locoregional recurrence (1.1% vs. 4.6%). The safety data were consistent with the known manageable toxicities of T-DM1, with expected increases in adverse events (AEs) associated with T-DM1 compared to trastuzumab (more fatigue, nausea, decreased platelet count, ALS/AST increase, epistaxis and sensory neuropathy). The incidence of grade 3/4 AEs with T-DM1 was 25.7% as compared to 15.4% with trastuzumab with a rate of AE-related treatment discontinuation of 18.0% with T-DM1 and 2.1% with trastuzumab.¹

The authors concluded that the KATHERINE data could form the foundation of a new standard of care in this population and increase the use of neoadjuvant therapy in HER2-positive early breast cancer.

ADJUVANT CAPECITABINE DOES NOT LEAD TO A SIGNIFICANT OUTCOME IN PATIENTS WITH EARLY-STAGE TRIPLE-NEGATIVE BREAST CANCER

Results of the phase III GEICAM/CIBOMA trial indicate that adjuvant capecitabine for patients with early-stage triple negative breast cancer (TNBC) after completion of surgery and standard chemotherapy does not result in a significant improvement in the disease free (DFS) and overall survival

(OS).² In total, 876 patients with operable, node-positive (or node-negative with tumour size ≥ 1 cm), centrally confirmed hormone receptor-negative, HER2-negative early breast cancer who had received 6-8 cycles of standard anthracycline and/or taxane-containing chemotherapy or 4 cycles of doxorubicin-cyclophosphamide (for node-negative disease) in the (neo)adjuvant setting, were included in the trial. Patients were randomized to either 8 cycles of capecitabine (1,000 mg/m² bid, days 1-14, every 3 weeks) or observation. The primary endpoint was DFS.²

The median age of patients in the trial was 50 years, approximately 30% of women were premenopausal and 60% had stage II disease (15% stage I, 20% stage III). The majority of patients (55%) was node-negative while an additional 30% had 1-3 positive nodes (approximately 15% had 4 or more positive nodes). In total, 71.7% had a basal phenotype and 67.5% received chemotherapy based on anthracyclines and taxanes. Three quarters of patients underwent an axillary lymph node dissection and approximately 80% also received radiotherapy. After a median follow-up of 7.4 years, the DFS was not significantly improved in patients treated with capecitabine (5-year DFS rate 79.6% vs. 76.8%; HR[95%CI]: 0.82[0.63-1.06]; p= 0.136). Also with respect to OS there was no difference between adjuvant capecitabine and observation (5-year OS: 86.2% vs. 85.9%; HR[95%CI]: 0.92[0.66-1.28]). In subgroup analyses, the investiga-

tors found that among the 248 patients with non-basal-like disease, as defined by immunohistochemistry, patients randomized to adjuvant capecitabine were 49% less likely to experience a disease event (5-year DFS: 82.6% vs. 72.9%; HR[95%CI]: 0.53[0.307-0.913]) and 52% less likely to die (5-year OS: 89.5% vs. 79.6%; HR[95%CI]: 0.42[0.21-0.81]) compared with those randomized to observation. This is an intriguing finding but should be interpreted with caution because the interaction test was negative for DFS ($p=0.0694$), although it was statistically significant for OS ($p=0.0052$).²

PATHOLOGICAL COMPLETE RESPONSE AFTER NEOADJUVANT CHEMOTHERAPY AND IMPACT ON BREAST CANCER RECURRENCE AND MORTALITY

While the prognostic significance of pathological complete response (pCR) after neoadjuvant chemotherapy is relatively well established, the impact of adjuvant therapy in modulating relationship between pCR and long-term outcomes is less clear. To address this question, a meta-analysis of 52 studies including 27,895 patients was performed. Attainment of pCR, as compared to absence of pCR, was associated with significantly reduced disease recurrence overall (HR[95%CI]: 0.31[0.24-0.39]), and in triple negative (HR[95%CI]: 0.18[0.10-0.31]), human epidermal growth factor 2-positive (HER2+) (HR[95%CI]: 0.32[0.21-0.47]), and trended towards significance for HR-positive breast cancer (HR[95%CI]: 0.15[0.02-1.10]). Similarly, pCR after neoadjuvant chemotherapy was also associated with reduced mortality overall (HR[95%CI]: 0.22[0.15-0.30]), and among all three major disease subtypes. The association of pCR with reduced recurrence was similar among studies where patients received subsequent adjuvant chemotherapy (HR[95%CI]: 0.34[0.18-0.61]) and those without adjuvant chemotherapy (95% HR[95%CI]: 0.36[0.27-0.54]) (Figure 2). The investigators concluded that the similar outcomes with/without adjuvant chemotherapy in patients who attain pCR after neoadjuvant chemotherapy likely reflects tumour biology and suggests adjuvant chemotherapy could potentially be abbreviated in certain circumstances and highlights the need for further research to evaluate clinical utility of escalation/de-escalation strategies in the adjuvant setting based on neoadjuvant response for patients with localized breast cancer.³

DELAYING THE INITIATION OF ADJUVANT CHEMOTHERAPY NEGATIVELY IMPACTS THE OUTCOMES OF TNBC

Morante *et al.* retrospectively analysed the medical records of 687 TNBC patients who received adjuvant chemotherapy at Instituto Nacional de Enfermedades Neoplásicas between

2000 and 2014.⁴ The mean age at diagnosis of the included patients was 49 years and most patients had stage II (60.1%) or III (29.45%) disease. They received either anthracyclines or anthracyclines and taxane-based chemotherapy (96.1%). The median follow-up was 101 months and the median time to starting adjuvant chemotherapy (TTC) was 41 days. In total, 189 patients started the treatment at or before 30 days, 329 started it from 31 to 60 days, 115 started it between days 61 to 90 and 54 started it more than 90 days after surgery.⁴ As the time to starting adjuvant chemotherapy increased, the 10-year DFS rate decreased. In fact, the 10-year DFA rate was 81.4%, 68.6%, 70.8%, and 68.1% among patients who started the treatment at or before 30 days after surgery, 31 to 60 days after surgery, 61 to 90 days after surgery, and more than 90 days after surgery, respectively. The 10-year OS rate also decreased with a longer TTC at 82%, 67.4%, 67.1%, and 65.1% for the four groups of patients, respectively. The researchers then studied how the extent of delay in starting chemotherapy was associated with an increased risk for disease recurrence and death. They found that compared with patients who started adjuvant chemotherapy in the first 30 days after surgery, risk for disease recurrence was increased by 92% for those who delayed starting the treatment for 31 to 60 days after surgery, by 138% for those who delayed starting the treatment for 61 to 90 days after surgery, and by 147% for those who delayed starting the treatment for more than 90 days after surgery. The risk of death compared with patients who started adjuvant chemotherapy in the first 30 days after surgery increased by 94%, 145%, and 179% for the three groups, respectively.⁴

It needs to be stressed that this was only a retrospective analysis of a single institution experience, but the results do indicate that delaying adjuvant therapy leads to a worse outcome in TNBC.

LOW DOSE TAMOXIFEN FOR THE PREVENTION OF RECURRENCE IN WOMEN WITH OPERATED HORMONE SENSITIVE BREAST DUCTAL OR LOBULAR CARCINOMA IN SITU

In the phase III TAM-01 trial, De Censi *et al.* randomly assigned 500 women with ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), and atypical ductal hyperplasia (ADH) who had been treated with surgery and, if needed, radiotherapy, to be treated with either low-dose tamoxifen (5 mg/day) or placebo. Treatment continued for 3 years, and patients were seen by the research team every 6 months and had a mammogram annually. After a median follow-up of 5.1 years, 14 (5.5%) of the 253 patients in the low-dose tamoxifen arm and 29 (11.3%) of the 247 patients in the placebo

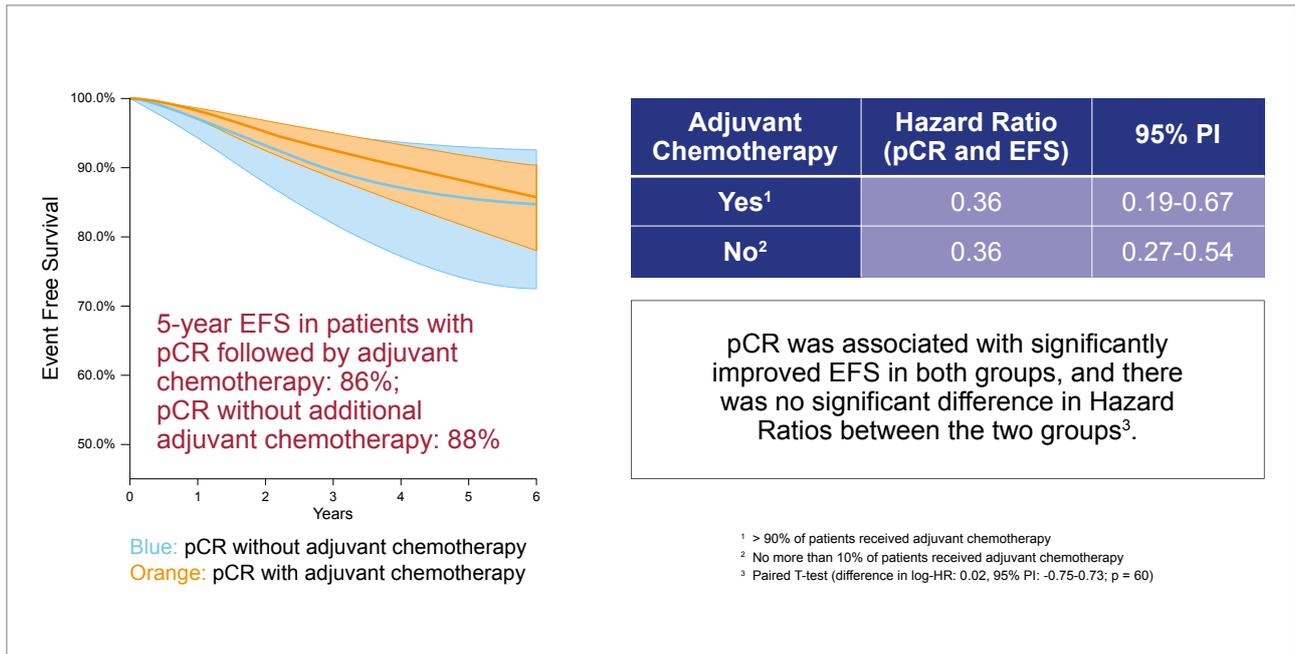


FIGURE 2. Association of pCR to neoadjuvant chemotherapy with reduced recurrence was similar among studies where patients did or did not receive subsequent adjuvant chemotherapy.³

arm had disease recurrence or new disease, corresponding to a risk reduction of 52% in favour of low-dose tamoxifen (HR[95%CI]: 0.48[0.25-0.89]; p= 0.02).⁵ Among the patients who had a recurrence or new disease in the opposite breast, 3 of the 14 in the low-dose tamoxifen arm had invasive breast cancer and 11 had breast intraepithelial neoplasia. In the placebo arm, 10 had invasive breast cancer and 18 had breast intraepithelial neoplasia. There were 12 serious AEs among the patients in the low-dose tamoxifen arm and 16 among those in the placebo arm. There was one case of endometrial cancer among the patients in the low-dose tamoxifen arm and none among those in the placebo arm. There was one venous thromboembolism in the tamoxifen arm and one pulmonary embolism in the placebo arm. There were no significant differences between the two arms in reporting of menopausal symptoms such as hot flashes, vaginal dryness, and pain during intercourse.⁵

CLINICAL UTILITY OF CIRCULATING TUMOUR CELL COUNT AS A TOOL TO CHOOSE BETWEEN FIRST LINE HORMONE THERAPY AND CHEMOTHERAPY FOR ER+ HER2-METASTATIC BREAST CANCER

In ER+ HER2- metastatic breast cancer patients, the choice between 1st line hormone therapy (HT, the recommended option) or chemotherapy (CT) is based on the absence of visceral crisis or adverse prognostic fac-

tors, without any proven/objective criteria. The phase III STIC CTC trial was set up to test whether circulating tumour cells (CTC) could help to customize the 1st line treatment choice in this setting.⁶ The multicentre, phase 3, non-inferiority STIC CTC trial enrolled 778 patients with hormone receptor-positive, HER2-negative metastatic breast cancer to receive first-line treatment with chemotherapy or endocrine therapy. The choice of treatment was by random assignment, selected by clinically-driven choice or CTC-driven choice (CTC count not disclosed, HT or CT administered as decided a priori). In the CTC count arm, patients with low CTC levels (as defined as < 5 CTC/7.5 mL) received endocrine therapy, whereas patients with high CTC levels (as defined as ≥ 5 CTC/7.5 mL) received chemotherapy. The CTC count was non-inferior to the clinician's choice arms for the primary endpoint of PFS, with a median of 15.6 months (95%CI: 12.8-17.3) compared with 14.0 months (95%CI: 12.2-16.0) in the clinician's choice arm (HR[95%CI]: 0.92[0.80-1.06]), based on the pre-specified non-inferiority margin of 1.25. Also the OS was similar between arms, with a 2-year rate of 82.1% in the CTC count arm compared with 81.4% in the clinician's choice arm. The CTC count confirmed the clinician's choice in 67% of patients who received endocrine therapy and in 48% of patients who received chemotherapy. For discordant cases, CTC count that differed from clinician's choice resulted in a switch in therapy. In these cases, patients

who were switched to chemotherapy demonstrated a significantly prolonged PFS compared with endocrine therapy (median PFS: 15.5 vs 10.5 months). There was also a trend towards an improved OS with chemotherapy vs. endocrine therapy based on CTC count (median OS: 42.0 vs. 37.1 months). Patients who were switched to endocrine therapy based on low CTC count demonstrated no difference in PFS between arms.⁶

The authors concluded that high CTC count favours chemotherapy compared with endocrine therapy. As such, they argue that CTC count should be included in the decision algorithm for HR-positive, HER2-negative metastatic breast cancer patients.

RADIOTHERAPY OR SURGERY OF THE AXILLA AFTER A POSITIVE SENTINEL NODE IN BREAST CANCER PATIENTS: 10 YEAR FOLLOW UP RESULTS OF THE EORTC AMAROS TRIAL

Traditionally, patients early-stage invasive breast cancer who had cancer detected in a sentinel lymph node biopsy underwent axillary lymph node dissection, which is an effective but invasive surgical procedure that is associated with adverse side effects such as lymphedema and difficulties moving the arm. The phase III AMAROS clinical trial tested whether axillary radiotherapy could yield comparable outcomes to axillary lymph node dissection with fewer adverse side effects. Previously reported data with five-years of follow-up showed that lymphedema occurred significantly more often after axillary lymph node dissection than after axillary radiotherapy. During SABCS 2018 10-year follow-up data of this trial were reported.⁷ Of the 4,806 patients with early-stage, clinically node-negative breast cancer who enrolled in the trial, 1,425 went on to have a positive sentinel lymph node biopsy. In total, 744 of these patients had been randomly assigned to axillary lymph node dissection and 681 to axillary radiotherapy. After 10 years, 1.82% (11 out of 681 patients) of those assigned to axillary radiotherapy had axillary recurrence, compared with 0.93% (7 out of 744 patients) of those assigned to axillary lymph node dissection. In addition, neither distant metastasis-free survival (DMFS, 78.2% vs. 81.7%) nor OS (81.4% vs. 84.6%) were significantly different between the two treatment arms. A significantly greater proportion of patients assigned to axillary radiotherapy went on to develop a second primary cancer than did patients assigned to axillary lymph node dissection: 11.0% vs. 7.7% (mainly due to a higher incidence of contralateral breast cancer in the patients treated with axillary radiotherapy). The main limitation of

the study is that the size of the radiation field was greater than what is currently deemed necessary, which caused some morbidity that may now be avoided. There was also an imbalance in the number of patients who had a sentinel lymph node biopsy in the two arms and the number of recurrences was by far lower than expected, reducing the statistical power of the study. However, the researchers noted that these limitations do not adversely affect the conclusion from the trial data that axillary radiotherapy is not inferior to axillary lymph node dissections in terms of locoregional control.⁷

CONVENTIONAL WHOLE BREAST IRRADIATION VS. PARTIAL BREAST IRRADIATION FOR WOMEN WITH STAGE 0, I, OR II BREAST CANCER

Whole breast irradiation (WBI) following lumpectomy has comparable ipsilateral recurrence rates as mastectomy. Accelerated partial breast irradiation (PBI) treats the tumour bed area instead of the entire breast and as such reduces the radiation treatment time from 3-6 weeks to 5-8 days. The main purpose of the presented phase III study was to determine if accelerated PBI is equivalent to WBI in controlling for ipsilateral breast cancer recurrence in women who desire breast-conservation surgery.⁸ In total, 4216 breast cancer patients who had recently received a lumpectomy with 0-3 positive axillary nodes were randomly assigned to treatment with WBI or PBI. Of these breast cancer patients, 25% had DCIS, 65% had stage I breast cancer, and 10% had stage II disease. Overall 81% of patients had HR-positive cancer, and 61% of patients were postmenopausal. In total 2,109 patients received WBI and 2,107 received PBI. Treatment with WBI was defined as daily treatment with 2 grays (Gy) of radiation totalling 50 Gy with a sequential boost to the surgical site; treatment with PBI was defined as twice daily treatment with 3.4-3.85 Gy totalling 10 treatments delivered via 3D external beam radiation or brachytherapy. The primary endpoint of the trial was evidence of ipsilateral breast tumour recurrence (IBTR).

There were 161 IBTRs as first events: 90 in the PBI arm and 71 with WBI (HR[90%CI]: 1.22[.94-1.58]). While the risk of recurrence was not statistically different between the two treatment arms, the hazard ratio did not meet the statistical criteria for treatment equivalence (the per protocol-defined margin to declare PBI and WBI equivalent regarding IBTR risk, the 90% CI for the observed HR had to lie entirely between 0.667 and 1.5). The proportion of patients who were IBTR-free 10 years after treatment was 95.2% among those who received PBI and 95.9% among those who received WBI. The difference in the 10-year relapse free interval (RFI) be-

tween the two treatment arms was statistically significant, favouring WBI (91.9% vs. 93.4%; HR[95%CI]: 1.32[1.04-1.68]; p=0.02). No statistical difference was seen with respect to OS, DFS and distant disease-free interval. Grade 3 toxicity was modestly higher in patients who received PBI vs. WBI (9.6% vs. 7.1%). Likewise, grade 4-5 toxicity was slightly higher in the PBI arm compared to WBI (0.5% vs. 0.3%).

Despite only small differences in IBTR (<1%) and RFI (1.5%) between the two treatment arms at 10 years, the researchers could not declare that WBI and PBI were equivalent in controlling local in-breast tumour recurrence because the HR between arms fell short of meeting statistical equivalence. However, these findings do suggest that the less burdensome radiation method of accelerated PBI may be an acceptable choice for many women. Additional analyses are underway to determine if specific cohorts may have advantages in local and regional relapse control between the two treatment arms.

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BACR Awards for Best Talks and Posters

2019 BACR Annual Meeting, Antwerp University

NOVEL COMBINATION STRATEGIES FOR CANCER TREATMENT: CURRENT CHALLENGES AND FUTURE DIRECTIONS

FIRST TALK AWARD

ACIDOSIS DRIVES BOTH METABOLIC REPROGRAMMING AND EPITHELIAL- MESENCHYMAL TRANSITION IN CANCER CELLS

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During cancer progression, tumor cells must adapt to survive and proliferate under low pO₂ but also low pH. Indeed, extracellular pH in tumors is about 10-fold more acidic than in healthy tissues, with mean values ranging from 6.2 to 6.8. We previously reported that cancer cells chronically exposed to acidosis (pH 6.5) exhibit a dysregulated fatty acid (FA) metabolism with the concomitance of mitochondrial FA oxidation (FAO) and cytosolic glutamine-fueled FA synthesis. In the course of these experiments, we observed that pH6.5-adapted cancer cells consistently exhibited an elongated and flat, mesenchymal-like appearance (vs parental cells). This led us to suspect that acidosis, besides a well-known activation of proteases, could promote cancer cell invasiveness by inducing an epithelial-mesenchymal transition (EMT).

Using modified (Matrigel-coated) Boyden chambers, we first documented that pH6.5-adapted cancer cells exhibited an increased motility and invasiveness potential. Interestingly, the aggressive phenotype of acidosis-adapted cancer cells

was also obtained when using neutral-pH conditions during the time of the assay. We next confirmed the expression of mesenchymal markers (together with the loss of various epithelial markers) in acidosis-adapted cancer cells of different tissue origins.

Furthermore, we observed an accumulation of lipid droplets (LDs) in acidosis-adapted cancer cells, as detected by electron microscopy, Oil Red O staining and BODIPY 493/503 immunofluorescence. A CD36-dependent increase in FA uptake was found to support both FAO and neutral lipid storage into LDs. Perilipin 2 (a coat protein for LDs) and DGAT1 (an enzyme that supports triglyceride (TG) formation) were found to be highly expressed in acidosis-adapted. Importantly, we also showed that LDs not only act as energy stores but also support anoikis resistance, via the action of the ATGL enzyme that hydrolyzes TG to produce FA. Pharmacological inhibition or genetic silencing of any player of the signaling cascade (i.e. CD36, DGAT1, perilipin 2, ATGL) inhibited invasion capacities of acidosis-adapted cancer cells.

Our work provides new insights on the link between microenvironmental acidosis, fatty acid metabolism and tumor progression.

This study also opens new therapeutic perspectives to oppose metastatic dissemination either by directly modulating tumor acidosis or by targeting associated metabolic changes.

SECOND TALK AWARD

IMMUNE STIMULATION WITH IL-15 AND ANTI-CD40: A NOVEL COMBINATION IMMUNOTHERAPY FOR PANCREATIC CANCER

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(2), Elly Marcq (1), Amanda Oliver (2), Jorrit De Waele (1), Jinthe Van Loenhout (1), Geert Roeyen (3), Clare Y Slaney (2), Phillip K Darcy (2), Marc Peeters (1,4), Michael H Kershaw (2), Evelien LJ Smits (1,5)
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BACKGROUND:

Pancreatic Ductal Adenocarcinoma (PDAC) is the third deadliest cancer worldwide with the lowest 5-year survival of all cancers. Therapeutic improvements have barely been made over the last decade. Within the tumour microenvironment, tackling the stromal shield is needed to overcome treatment resistance. CD40 stimulation – in a single agent treatment regimen – has already demonstrated moderate anti-tumour responses in PDAC, including some anti-stroma effects. We have shown that interleukin (IL)-15 stimulated NK cells are capable of tackling both tumour as well as the surrounding desmoplastic stroma. Therefore, we explored a novel combination immunotherapy consisting of an agonistic anti-CD40 monoclonal antibody and IL-15 in two mouse models of PDAC.

METHODS:

C57BL/6 mice bearing Panc02 or KPC tumours were treated over a two-week period with IL-15 and/or anti-CD40. Tumour kinetics and survival were monitored. Tumour infiltrating lymphocytes (TIL) were characterised using multicolour flow cytometry and immunohistochemistry. Experiments depleting different immune cell populations were performed. Re-challenge experiments were executed to check immune memory induction.

RESULTS:

Combination treatment of IL-15 and anti-CD40 caused distinct reduction of tumour growth rates in comparison with single agent treatments. Mice receiving the combination treat-

ment showed significantly increased survival, with 60-80% of the mice becoming completely tumour free. Characterisation of TIL revealed that the combination caused increased amounts of infiltrating CD8+ T cells, NK cells and neutrophils while T regulatory cells were decreased. Depletion of CD8+ T cells and NK cells confirmed that both immune cells are mechanistically involved. Re-challenge experiments showed induction of immune memory by IL-15 but not by anti-CD40.

CONCLUSION:

To our knowledge, this is the first study demonstrating that combination of IL-15 and anti-CD40 exhibits a profound anti-tumour response in two mouse models of PDAC resulting in prolonged survival and even total eradication of >60% of PDAC. These data provide a solid proof of principle to advance with this combination strategy to an early phase clinical trial.

THIRD TALK AWARD

HUMAN PD-L1 SPECIFIC SINGLE-DOMAIN ANTIBODY AS A THERANOSTIC FOR CANCER IMMUNOTHERAPY

Quentin Lecocq (1*), Katrijn Broos (1*), Jessica Bridoux (2), Geert Raes (3,4), Catarina Xavier (2), Nick Devoogdt (2), Marleen Keyaerts (2,5), Karine Breckpot (1)
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Programmed cell death-ligand 1 (PD-L1) is one of most intensively studied immune checkpoints with the widest clinical applications. The rise of interest was initially driven by the

observation that PD-L1 is intrinsically expressed on a variety of tumor cells, while other tumor cells upregulate PD-L1 expression as a result of adaptive resistance. Moreover, immune cells with anticancer functions express high levels of PD-1, an inhibitory receptor that upon binding to PD-L1 induces anergy and even cell death. Antibodies that bind PD-L1 or its receptor PD-1 evoke durable responses in advanced stage cancer patients. However, only a subset of patients and cancer types react to the therapy. We developed a single domain antibody (sdAb) that targets human PD-L1, referred to as K2. Unlike antibodies, sdAbs are small and can therefore penetrate more efficiently into tumors. Therefore, K2 is an excellent candidate theranostic. We studied K2 for non-invasive imaging of PD-L1 in xenograft cancer models. SPECT/CT imaging showed that K2 labeled with ^{99m}Tc has several properties that make K2 an interesting diagnostic, incl. 1) low kidney retention, which is unique for this particular sdAb, as typically sdAbs show high kidney retention at the tubuli, 2) high signal to noise ratio's, 3) accumulation in PD-L1 positive tumors, and 4) binding to the same epitope on PDL1 as the FDA-approved antibody Avelumab. Furthermore, we studied the therapeutic value of K2 in vitro, showing that sdAb K2 is able to restore T-cell receptor triggering of T cells when co-cultured with PD-L1 positive tumor cells. Moreover, we used sdAb in the context of dendritic cell (DC) vaccination, showing that sdAb K2 leads to enhanced activation of primary, tumor specific T-cells when using weakly activated DCs. These preliminary data suggest that K2 is a novel immune checkpoint drug with a strong potential for direct translation from bench to bedside, and warrant further research into K2 and its value as a theranostic.

FIRST POSTER AWARD

THE SPATIAL LOCALIZATION OF IMMUNE CELLS PREDICTS PROGNOSIS AND RESPONSE TO THERAPY IN INFLAMMATORY BREAST CANCER

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BACKGROUND

The mechanisms contributing to the aggressive biology of inflammatory breast cancer (IBC) are still under investigation. Our lab reported a 79-gene signature that is shaped by specific immune response programs and discriminates between IBC and non-IBC (nIBC). In this study we assessed the spatial associations between immune cells in IBC.

METHODOLOGY

Affymetrix gene expression data of 105 IBC patients were analyzed using the CIBERSORT module to narrow down the number of stainings. Slides were stained according to a validated protocol, scanned and evaluated using VISIOPHARM® software that allows virtual multiplexing. We used five validated antibodies: PD-L1 (SP142 AB), CD79 α (B cell lineage), CD8 (cytotoxic T cells), FOXP3 (Tregs) and CD163 (TAMs, Tumor-associated macrophages). Using specific image analysis algorithms for every staining, we quantified the relative marker area (RMA) and located each positive cell using XY coordinates. Spatial co-localization was examined using point pattern (effector index, EI) and quadrant analysis (Morisita-Horn index, MHI), developed for ecological studies. The EI is based on the number of cells within a circle around a CD8+ cell and the MHI measures the dissimilarity in species between two quadrants.

RESULTS

A total of 51 patients (= 104 tissue samples) were analysed and 23.5% achieved complete pathological response (pCR) after neo-adjuvant chemotherapy. Only a negative HR-status ($P=0.01$) and a high CD8-RMA ($P=0.04$) predicted pCR. Interestingly, the presence of CD79 α + ($P=0.005$) or FOXP3+ cells ($P=0.02$) in close distance of CD8+ T cells was associated with pCR (using both EI and MHI), while the number of CD79 α + or FOXP3+ cells did not predict prognosis nor pCR. PD-L1 positivity and CD8-RMA were not associated with OS, but patients with more PD-L1+ cells (>0.7 cells/30 μm) in close contact with the CD8+ cells had a worse survival outcome (5y OS: 50% vs 68%, $P=0.03$). TAMs near CD8+ cells also seem to inhibit a good cytotoxic immune response

as the EI for CD163+ TAMs was also prognostic ($P=0.02$).

CONCLUSION

In this study we show that not only the presence but also the spatial localization plays a role in the functional immune response.

SECOND POSTER AWARD

IDENTIFICATION OF A NEW TARGET TO TACKLE THE IMMUNE SUPPRESSIVE TUMOR MICROENVIRONMENT IN COLORECTAL CANCER

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Cancer cells are embedded in stroma, the connective tissue framework of solid tumors. In colorectal cancer (CRC), cancer associated fibroblasts (CAFs) are the main cellular components of the tumor reactive stroma and support tumor progression and invasiveness. However, CAFs represent a heterogeneous population with both cancer-promoting and -restraining actions, lacking specific markers to target them. Expression of immune checkpoint ligand CD70 is normally tightly regulated and limited to cells of the lymphoid lineage. Instead, expression of CD70 on tumor cells has been shown, enabling immune evasion by increasing the amount of suppressive regulatory T cells (Tregs). In this study, we aimed at investigating the role of CD70 in CRC.

Expression of CD70 was analyzed by immunohistochemistry on 51 CRC specimens. Primary CAF cell lines were divided into a CD70^{low} and CD70^{high} CAF subpopulation by cell-sorting (FACSARIA II) and used in migration assays (IncuCyte Zoom system). Co-cultures with CD4+ T-cells were set-up to investigate the effect of CD70-positive CAFs on Tregs by flow cytometry. Supernatants were collected for cytokine analysis. Finally, whole transcriptome-sequencing was performed using the mRNA-Seq Library Prep kit (Lexogen).

We have revealed the expression of CD70, not on the cancer cells, but highly expressed on a subset of CAFs in invasive CRC specimens. Moreover, CD70-positive CAFs were strongly associated with poor clinicopathological parameters and inferior prognosis. CD70^{high} CAFs significantly stimulated migration and increased the production of IL-6. We also revealed a significant increase in the amount of Tregs and production of interleukin-2 upon co-culture of CD4+ T-cells with CD70^{high} CAFs, as opposed to CD70^{low} CAFs. Finally, experiments aimed at unravelling the underlying mechanism of CD70-positive CAFs are currently being analysed. In conclusion, we have identified a targetable CAF subpopulation, marked by the expression of CD70 and equipped with strong migratory capabilities. Thereby, we found evidence of a cross talk between CD70+ CAFs and Tregs, paving the way towards immune escape. As such, this study provides a strong rationale for our ongoing exploration of CD70-targeting therapy in CRC, especially in light of the limited immunotherapeutic options available in CRC.

THIRD POSTER AWARD

HUMAN COLON CANCER CELLS OVEREXPRESS MYOFERLIN TO MAINTAIN A FIT MITOCHONDRIAL NETWORK AND ESCAPE P53-DRIVEN APOPTOSIS

Rademaker Gilles (1), Costanza Brunella (1), Bellier Justine (1), Agirman Ferman (1), Maloujahmoum Naima (1), Bellahcène Akeila (1), Castronovo Vincenzo (1), Olivier Peulen (1)
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Colon cancer is the second most common cancer and leading cause of cancer-related death. Although the cancer mortality has decreased during the last decade, some tumors remain resistant to therapy. Myoferlin, a membrane protein involved in membrane fusion, was recently shown by our laboratory as a key player in the mitochondrial dynamics of pancreatic ductal adenocarcinoma. Its presence in the cell is required to maintain an adequate mitochondrial structure and an efficient energy metabolism. In the present study, we discovered that myoferlin is overexpressed in colon cancer and, as in pancreas, controls mitochondrial structure and metabolism. Indeed, myoferlin silencing induces a decrease in mitochondrial respiration and an increase of mitochondrial fission in colon cancer cell lines HCT116 and SW480. This mitochondrial disorganization is concomitant to a nuclear DNA damage response in both cell lines. An activation of the p53-p21 cascade is triggered in the p53 wild-type HCT116 cell line

leading to a cell cycle arrest, an apoptosis induction and a resulting strong decrease of cell growth. In the p53-mutant SW480 colon cell line, the DNA damage response leads neither to apoptosis nor cell cycle blockage. In that case, a low reduction of cell proliferation was observed, confirming the major role of the p53 cascade in the strong effects of myoferlin silencing. We confirmed *in ovo* the decrease of HCT116 proliferation when myoferlin was silenced.

To confirm the clinical importance of myoferlin in colon cancer, we showed that low myoferlin expression was significantly correlated to high overall survival.

Induced-apoptosis escape is one of the most frequent resistance mechanisms in colon cancer. As an apoptosis inducer in p53 wild-type cells or in combination with a p53 restoration treatment in p53-mutant cell line, myoferlin silencing could open-up new perspectives in the development of new therapeutic strategies.

Congress Calendar

2019

MARCH

1 MARCH

5th Symposium on Primary Breast Cancer in Older Women

Nottingham, United Kingdom

Website: <http://siog.org/content/5th-symposium-primary-breast-cancer-older-women>

1-2 MARCH

9th Innovation in Breast Cancer

Madrid, Spain

Website: <http://www.innovationinbreastcancer.com/>

2 MARCH

15th Annual Symposium on Pancreatic Cancer

Los Angeles, California, United States

Website: <http://pancreatic.org/event/symposium/>

3-6 MARCH

Childhood Cancer: Research Challenges and the Future of Therapy

San Antonio, Texas, United States

Website: <http://www.gccrisymposium.org/>

6-8 MARCH

16th Annual ENETS Conference

Barcelona, Spain

Website: <https://enetsconference.org>

7-10 MARCH

36th Annual Miami Breast Cancer Conference

Miami Beach, Florida, United States

Website: <http://bit.ly/AnnualMiamiBreastCancerConference2019>

9-11 MARCH

9th European Multidisciplinary Colorectal Cancer Congress (EMCCC-9)

Lisbon, Portugal

Website: <https://www.emccc2019.org/>

11-13 MARCH

Defence is the Best Attack: Immuno-Oncology Breakthroughs

Barcelona, Spain

Website: <https://www.eacr.org/content/meetings>

13-14 MARCH

4th International Conference on Pancreatic Cancer and Liver Diseases

London, United Kingdom

Website: <https://pancreas.cmesociety.com/>

14-15 MARCH

EORTC Groups Annual meeting (EGAM) Brussels, Belgium

Website: <http://www.eortc.org/event/eortc-groups-annual-meeting-egam-3/>

14-16 MARCH

Multidisciplinary Thoracic Cancers Symposium

San Diego, California, United States

Website: <http://www.thoracicsymposium.org/index.aspx>

14-16 MARCH

7th ICHNO: International Conference on Innovative Approaches in Head & Neck Oncology

Barcelona, Spain

Website: <https://www.esmo.org/Conferences/>

15 MARCH

25th NVPO Congress

Utrecht, The Netherlands

Website: <https://nvpo.nl/congres/25e-nvpo-congres/>

15-17 MARCH

19th Multidisciplinary Management of Cancers: A case-based approach

Napa, California, United States

Website: <http://www.multicancers.org/>

15-19 MARCH

34th Annual EAU Congress

Barcelona, Spain

Website: <https://eau18.uroweb.org/eau19/>

15-20 MARCH

The 29th Annual Interdisciplinary Breast Center Conference (NCoBC 2019)

Las Vegas, Nevada, United States

Website: <https://www2.breastcare.org/asbd-and-ncbc/>

16 MARCH

12th Annual Interdisciplinary Prostate Cancer Congress and other Genitourinary Malignancies

New York, United States

Website: <http://bit.ly/AnnualInterdisciplinaryProstateCancerCongressGenitourinaryMalignancies19>

16-19 MARCH

Society of Gynaecologic Oncology's 2019 Annual Meeting on Women's Cancer

Honolulu, Hawaii, United States

Website: <https://www.sgo.org/>

20-23 MARCH

St. Gallen International Breast Cancer Conference

Vienna, Austria

Website: <http://www.oncoconferences.ch/+>

21-23 MARCH

NCCN Annual Conference: Improving the Quality, Effectiveness, and Efficiency of Cancer Care

Orlando, Florida, United States

Website: https://www.nccn.org/professionals/meetings/annual_conference.aspx

22-23 MARCH

CSCO-AACR Joint Conference on Immunotherapy

Shanghai, China

Website: <http://bit.ly/CSCO-AACRJointConferenceImmunotherapy19>

23-26 MARCH

ENDO 2019 - The Endocrine Society's Annual Meeting

New Orleans, Los Angeles, United States

Website: <https://www.endocrine.org/endo2019>

Congress Calendar

2019

23-28 MARCH

SIR 2019 - Annual Scientific Meeting

Austin, Texas, United States
Website: <https://www.sirmeeting.org/>

23-28 MARCH

18th ESO-ESMO Masterclass in Clinical Oncology

Nauen OT Gross Bernitz, Berlin Area, Germany
Website: <http://bit.ly/18ESO-ESMOMasterclassClinicalOncology>

27-30 MARCH

72nd SSO Annual Cancer Symposia

San Diego, California, United States
Website: <https://events.jspargo.com/SSO19>

29 MARCH - 3 APRIL

AACR Annual Meeting 2019

Atlanta, Georgia, United States
Website: <https://www.aacr.org/Meetings/>

APRIL

3-6 APRIL

HOPA's 15th Annual Conference

Fort Worth, Texas, United States
Website: <http://www.hoparx.org/conference-events>

8-11 APRIL

ECIO 2019

Amsterdam, The Netherlands
Website: <http://www.ecio.org/index.php>

10 -13 APRIL

ELCC 2019 - European Lung Cancer Congress

Geneva, Switzerland
Website: <https://www.esmo.org/Conferences/>

11-13 APRIL

ITOC - Immunotherapy of Cancer Conference

Vienna, Austria
Website: <http://itoc-conference.eu/>

19-20 APRIL

Cancer Research & Therapy

Dubai, United Arab Emirates
Website: <https://scientificfederation.com/wscrt-2019/index.php#about>

24-27 APRIL

15th EADO Congress

Paris, France
Website: <https://www.eadoparis2019.com/>

24-28 APRIL

AACE 28th Annual Scientific & Clinical Congress

Los Angeles, California, United States
Website: <http://am.aace.com/>

25-26 APRIL

9th World Congress on Breast Cancer

London, United Kingdom
Website: <https://breastcancer.conferenceseries.com/>

26-30 APRIL

38th Annual ESTRO

Milan, Italy
Website: <https://www.estro.org/congresses-meetings/items/estro-38>

MAY

1-4 MAY

2019 ASPHO Conference

New Orleans, Los Angeles, United States
Website: <http://aspho.org/>

1-5 MAY

2019 AHNS Annual Meeting

Austin, Texas, United States
Website: <https://www.ahns.info/meetings/>

2 MAY

6th Symposium on Gynaecologic Oncology

Luzern, Switzerland
Website: <https://gyn-onko-luzern.ch/>

2-4 MAY

ESMO Breast Cancer

Berlin, Germany
Website: <https://www.esmo.org/Conferences/>

3-6 MAY

AUA Annual Meeting

Chicago, Illinois, United States
Website: <http://www.aula2019.org/>

15-17 MAY

32nd annual Meeting of the EMSOS

Florence, Italy
Website: <https://www.emsos.org/>

16-17 MAY

5th EORTC Quality of Life: Cancer Clinical trials conference

Brussels, Belgium
Website: <http://events.eortc.org/wpmulti/qol-conference-2019/>

20-25 MAY

SIOE Europe: 1st Annual Meeting of the European Society for Paediatric Oncology

Prague, Czech Republic
Website: <http://sioeurope.eu/>

30-31 MAY

3rd International Conference on Women Health and Breast Cancer

Nice, France
Website: <https://scientificfederation.com/womens-health-2019/>

JUNE

31 MAY - 4 JUNE

ASCO 2019

Chicago, Illinois, United States
Website: <https://am.asco.org/>

5-8 JUNE

30th European Society of Gastrointestinal and Abdominal Radiology 2019: Annual Meeting

Rome, Italy
Website: <https://www.esgar.org/>

8-11 JUNE

SIO 2019: World Conference on Interventional Oncology

Boston, Massachusetts, United States
Website: <http://www.sio-central.org/page/sio-2019-conference-program>