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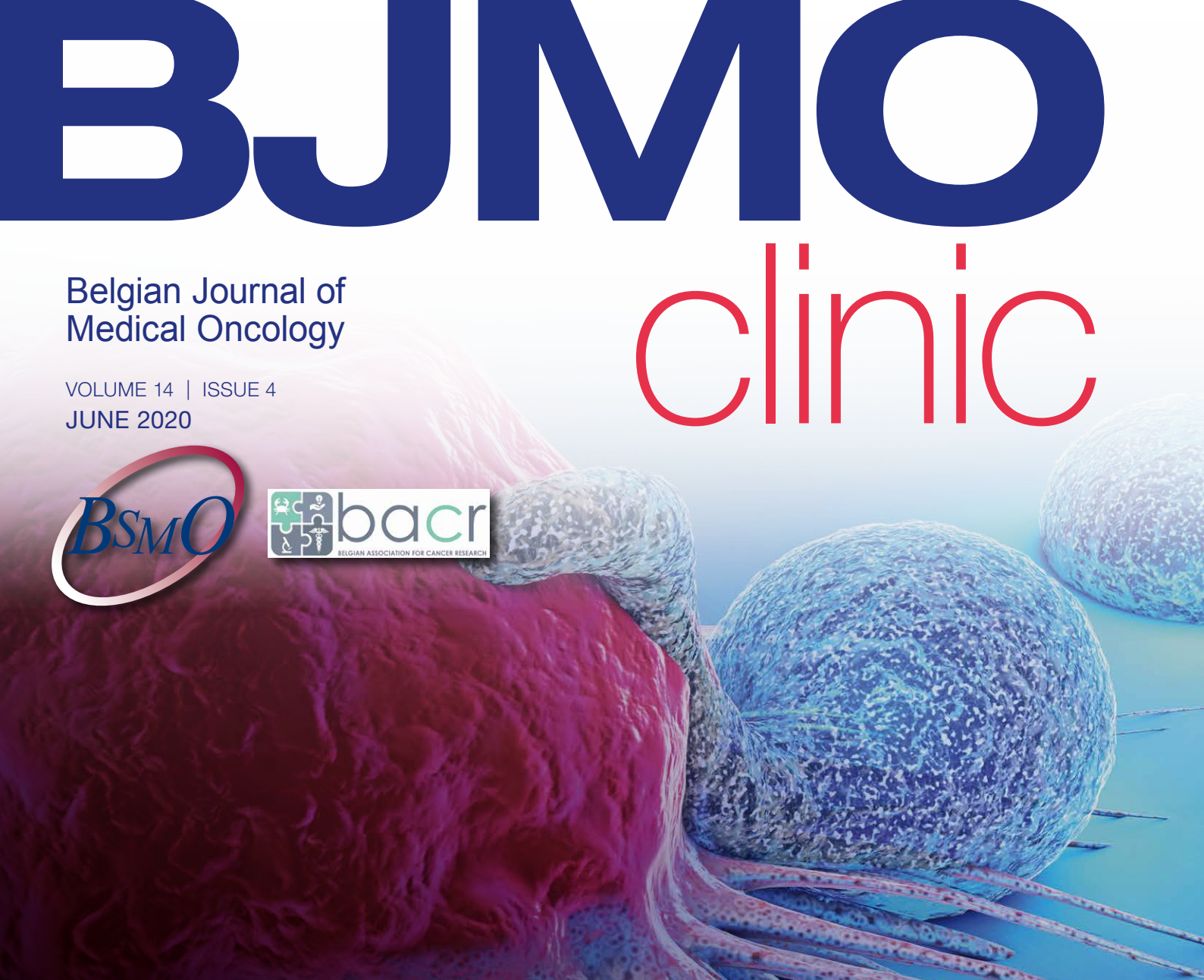

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Ariez International B.V.
Ms. E. van Zanten, MSc
c/o Oude Houtlei 118-120, 9000 Gent, Belgium
Tel: 0031-75-642 94 20
E-mail: editor@bjmo.be

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Partial breast irradiation of early-stage breast cancer

M. Machiels, MD, D. Nevens, MD, PhD, K. Erven, MD, PhD, G. Buelens, MD, C. Billiet, MD, PhD, Y. Geussens, MD, P. Janssens, MD, S. Vanderkam, MD, R. Weytjens, MD

SUMMARY

Whole-breast irradiation, as part of breast-conservation therapy (BCT), has been well-established the last decades. Nonetheless, most local recurrences found after BCT are within or close to the tumour bed. This led to the concept of partial breast irradiation (PBI), delivering the radiation dose to a decreased target volume, thereby lowering exposure to the organs at risk and hence potentially minimizing late adverse effects. This became increasingly important with growing survivorship of patients with early-stage breast cancer over the past decades and the consideration of late adverse effects is gaining more importance. In this review, we will present an overview of the current literature, techniques to deliver PBI and we try to establish whether there is a place for PBI in early-stage breast cancer treatment.

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INTRODUCTION

The past few decades, the successful treatment of early-stage breast cancer with breast-conserving therapy (BCT) - consisting of breast-conserving surgery (BCS) followed by adjuvant whole-breast irradiation (WBI) - has been well established by numerous randomised trials. These trials demonstrated similar survival rates for patients treated with BCT compared with patients undergoing mastectomy.[1,2] By tradition, the radiation regimen - nowadays referred to as standard fractionation - consisted of 25-33 daily fractions delivered in five to seven weeks, to the breast with or without regional lymph nodes. The aim of this standard regimen is to obtain a good tumour control, while sparing the normal tissues as much as possible. Even so, a radiation course of five to seven weeks can be challenging for patients in terms of time and money.[3] In the UK Standardization of Breast Radiotherapy (START) trials and the Canadian hypofractionation trial, different hypofractionation schedules were compared to the standard fractionation schedule.[4–6] It was demonstrated that the shorter treatment schedules were not worse for local recurrence or survival compared to the control group, with similar cosmetic outcome and lower rates of acute toxicity.[7] Furthermore, the reduced resource use in terms of personnel and machine time is advantageous for radiotherapy (RT) departments.[3] In Belgium, the hypofractionated treatment schedules are mostly used as standard of care.[8]

The observation that most local recurrences after BCT are within or close to the tumour bed, led to the concept of partial breast irradiation (PBI) and the hypothesis that this technique might reduce side-effects while maintaining a high rate of local tumour control.[9–11] This article aimed to review the role of PBI after BCS for breast cancer in the modern era.

Department of Radiation Oncology, Iridium Kankernetwerk, Antwerp, University of Antwerp, Belgium.

Please send all correspondence to: M. Machiels, MD, Department of Radiation Oncology, Iridium Kankernetwerk, Wilrijkstraat 10, 2650 Edegem, Belgium, tel: +32 3 443 37 37, email: melanie.machiels@gza.be.

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Keywords: brachytherapy, breast cancer, IORT, partial breast irradiation, radiotherapy, toxicity.

PARTIAL BREAST IRRADIATION

Most of the local recurrences found after BCT are within or close to the tumour bed.[9–11] This pattern of recurrence was confirmed by studies of BCS without adjuvant irradiation[12] and by the update of the NSABP B-06 trial.[1] A review of multiple BCT trials showed that the site of local recurrences after BCT was mostly in the tumour bed, with less than 10% of LR elsewhere in the breast.[13] This led to the concept of PBI, delivering dose to a decreased target volume thereby lowering exposure to the organs at risk (*e.g.*, contralateral breast tissue, heart, lung, skin, *etc.*), and hence potentially minimising late adverse effects. With growing survivorship of patients with early-stage breast cancer patients over the past decades, this consideration of late adverse effects is gaining more importance.

The role of conventionally (*i.e.*, 40 Gy in three weeks) fractionated PBI has been established by the IMPORT LOW trial.[14] In this study, women aged ≥50 years, who had undergone BCS for unifocal invasive ductal carcinoma ≤3 cm in size with a 2 mm non-cancerous excision margin, were randomly assigned (1:1:1) to receive daily over three weeks, one of the following three regimens: (a) 40 Gy WBI; (b) 36 Gy WBI with 40 Gy PBI; or (c) 40 Gy PBI targeted to the tumour bed. The primary endpoint was ipsilateral local recurrence with a non-inferiority margin of 2.5% at five years. RT toxicity was assessed by photographs and clinicians while quality of life, was analysed using 72 different patient-reported outcome measures (PROM).

This study was the first PBI study using standard EBRT to demonstrate a five-year non-inferiority local recurrence rate for PBI patients compared to standard external beam (EB) WBI (0.5% *vs.* 1.1%; p= 0.420). Additionally, patients treated with PBI reported fewer and less severe breast appearance changes. Albeit, this was only one of the 72 assessed PROMs that significantly reduced and no difference in late RT toxicity was seen. Included patients were mostly early-stage luminal disease; node negative (98%), grade 1-2 (91%), oestrogen receptor (ER) positive (95%) and human epidermal growth factor receptor 2 (HER2) negative tumours (94%). This is in agreement with the recommendations of the 'Groupe Europeen de Curietherapie - European Society for Therapeutic Radiology and Oncology' (GEC-ESTRO) and the updated 'American Society for Radiation Oncology' (ASTRO), considering these patients 'suitable' for PBI.[8]

For patients and health-care systems, the three-week daily treatment schedule has very limited advantages over conventional WBI, especially since toxicity was not significantly reduced. Nevertheless, since only a limited volume of breast tissue is irradiated in PBI, it offers the possibility of delivering a higher dose per fraction compared to WBI, which is called *accelerated partial breast irradiation* (APBI).

Findings suggest a different radiobiology and fractionation sensitivity for adenocarcinomas and subsequently of breast cancer, proposing a low α/β ratio.[15,16] Considering this low α/β ratio, and thus higher sensitivity to high dose per fraction, there is no reason to prefer 2.0 or even 2.67 Gy fractions over larger fractions for most women who need RT after BCS. Moreover, at this low α/β ratio there is a maximal sensitivity for changes in fractionation and the relative effectiveness becomes proportional with the dose per fraction. When overall treatment time could be safely reduced when using APBI, it may fruitfully minimise treatment burden for patients and health-care systems.

ACCELERATED PARTIAL BREAST IRRADIATION

A variety of techniques can be used to deliver APBI, and because of the advantage of delivering radiation directly to the target volume (*i.e.*, the tumour bed) more invasive methods are frequently used. Available techniques include; (a) brachytherapy, (b) intraoperative RT (IORT), and (c) external beam RT (EBRT).

BRACHYTHERAPY

Currently, there are two types of brachytherapy available for APBI; multicatheter interstitial brachytherapy and intracavitary balloon brachytherapy.

The most mature date exists in the setting of ***multicatheter brachytherapy***. Insertion of the interstitial catheters can be performed either at the time of surgery or at a later time after wound healing. A trial from the Hungarian National Institute of Oncology randomised 258 patients with early-stage breast cancer to WBI or interstitial high-dose-rate (HDR) APBI.[17] After a median follow up of 10.2 years, they demonstrated a ten-year local recurrence of 5.9% *vs.* 5.1%, and excellent-good cosmetic outcome in 81% *vs.* 63% of patients, in the APBI and WBI group, respectively. These findings were strengthened by a more recent GEC-ESTRO phase III trial randomising 1,184 patients to WBI (50 Gy in 25 fractions) or APBI (using HDR or pulsed-dose rate (PDR) multicatheter brachytherapy 32/30 Gy in 2.5 to 4 days).[18] They reported APBI to be non-inferior with respect to five-year local control and disease-free survival, and with low rates of skin toxicity seen in both groups. Multiple other phase II studies have reported the same favourable local control and cosmetic outcome when using multicatheter brachytherapy.[19–21]

Intracavitary balloon catheter brachytherapy is a more user-friendly approach, using a single brachytherapy catheter instead of numerous needles (MammoSite, Hologic) inserted in the lumpectomy cavity. No randomised trials have

TABLE 1. ASTRO 2017 guidelines for accelerated partial breast irradiation.

Characteristic	Suitable	Cautionary	Unsuitable
Age	≥50 years	40-49 years and meeting all other 'suitable' criteria or ≥50 years with one or more other cautionary features	<40 years or 40-49 years and not meeting all other criteria
Margins	≥ 0.2 cm	< 0.2 cm	positive
DCIS	≤ 2.5 cm, screen-detected, low/intermediate grade, margins ≥ 3 mm	≤ 3 cm not meeting criteria for 'suitable'	> 3 cm
Size	≤ 2.5 cm	2 – 3 cm	> 3 cm
LVSI	None	Limited/focal	Extensive
Hormone-receptor status	ER positive	ER negative	-
Histology	Invasive ductal	Invasive lobular	-
Extensive intraductal component	None	≤ 3 cm	> 3 cm
Focality	Clinically unifocal	-	Clinically multifocal or microscopically multifocal with total size > 3 cm
Centricity	Unicentric	-	Multicentric
Lymph node status	pN0	-	pN+
Neoadjuvant therapy	None	-	Any

DCIS= ductal carcinoma in situ; LVSI= lymphovascular space invasion; pN0= pathologically node-negative; ER= oestrogen receptor; pN+= pathologically node-positive.

investigated this technique, only a large registry trial was published. This registry trial included 1,449 patients with early-stage breast cancer patients after BCS. Patients received brachytherapy to a dose of 34 Gy in 10 fractions delivered twice daily. At five years, the in-breast recurrence rate was 3.8%, subgroup analysis from these patients suggested that lack of ER positivity as well as tumour size were associated with increased risks of ipsilateral breast recurrence. Further, in this series a good or excellent cosmetic outcome was achieved in over 90% of patients.[22]

In general, brachytherapy APBI has the most robust and mature APBI data showing favourable local control rates. Further, reported cosmetic outcome is often better when using brachytherapy APBI.[21–23] Nonetheless, the invasive nature of these techniques induces some extra impediments. First, practitioner experience is required for an optimal outcome using these technically challenging procedures. This limits its broad availability. Secondly, it requires a hospital stay of three to five days and it may deter patients from choosing this technique over alternative forms of APBI. Lastly, strict quality assurance procedures are necessary and followed; all increasing the cost and widespread use of brachytherapy APBI.

INTRAOPERATIVE APBI

Intraoperative APBI (IORT-APBI) delivers electrons or low-energy photons during surgery in one session after lumpectomy. Because this technique is developed more recently, mature long-term data are currently lacking.

In the prospective ***TARGIT-A trial***, women aged 45 years or older with invasive ductal breast carcinoma undergoing BCT were randomised to receive either IORT-APBI (1 x 20 Gy) using 50-kV x-rays or WBI (40-56 Gy with or without a lumpectomy boost).[24] The primary endpoint was ipsilateral local recurrence with a non-inferiority margin of 2.5% at five years. After a median follow-up of two years and five months, the actuarial five-year local recurrence rates in the ipsilateral breast were 3.3% in the IORT-APBI and 1.3% in the EBRT group, respectively (p= 0.04), not exceeding the pre-set non-inferiority margin. Criticism on this publication was the inappropriate statistical methodology used for such short follow-up.[25] When using survival analysis for local recurrence estimation, a calculated local recurrence rate

of as high as 7.1% could be found using the TARGIT-A data, a great deal above their pre-set non-inferiority margin of 2.5%. The frequency of any complications and major toxicity was similar in the two groups.

The ***ELIOT trial*** randomised 1,305 patients with unicentric primary breast cancer measuring ≤ 2.5 cm, to WBI (50 Gy in 25 fractions with a 10 Gy lumpectomy boost) or IORT-APBI receiving 21 Gy of IORT with electrons.[26] With a mean follow-up of 5.8 years, the rate of local recurrence and development of a new ipsilateral primary lesion at five years were 4.4% and 0.4%, respectively (p= 0.0001). Interestingly, published five-year rates of in-breast tumour recurrences in the ELIOT study for 'suitable group, cautionary group and unsuitable group', as defined by ASTRO recommendations (*Table 1*), were 1.5%, 4.4%, and 8.8 %, respectively.[27] This highlights the importance of a meticulous patient selection for this technique. The toxicity associated with IORT-APBI was low, but significantly more fat necrosis was noted in patients treated with IORT compared to WBI (15% *vs.* 7%). No information on cosmetic outcome or quality of life was given.

In general, these trials included more patients with high-grade disease and with lymph node involvement (26.6% in the ELIOT study and 16.1% in TARGIT-A) when compared to other phase III trials comparing APBI to WBI, often even including patients with more than three involved lymph nodes. The worse prognostic features of the patients included in these studies could account for the encountered high local recurrence rate seen at five years. This explanation is supported by a recent meta-analysis showing in meta-regression a significantly higher magnitude of effect on local recurrence in patients with lymph node involvement and a significantly greater magnitude of effect on local recurrence with high-grade disease.[28]

Both trials reported less skin toxicity in patients treated with IORT compared to WBI, but more fat necrosis was observed in patients treated with IORT APBI.

EXTERNAL BEAM APBI

The advantages of postoperative EBRT APBI are the availability of pathological information at time of treatment and the possibility to optimise tumour bed delineation in function of this pathological information. This might result in better coverage of the target volume when compared to intraoperative methods. Nonetheless, several small phase III trials showed mixed results with regard to local control.[29,30] Recently, some highly anticipated, large randomised trials were published.

The ***Canadian Randomized Trial of Accelerated Partial Breast Irradiation (RAPID)*** included 2,135 women aged 40 years or older with node-negative invasive ductal carcinoma or ductal carcinoma in-situ <3 cm.[31] Patients were randomised to WBI (42.56 Gy in 16 fractions or 50 Gy in 25 fractions with or without a boost) or EBRT APBI (38 Gy in 10 fractions delivered twice daily). The 8-year cumulative incidence of ipsilateral breast-tumour recurrence was 3.0% (95% CI 1.9–4.0) and 2.8% (1.8–3.9) in the APBI group and WBI group, respectively (hazard ratio [HR] 1.27, 90% CI 0.84–1.91), after a median follow-up of 8.6 years. Hence, the pre-set non-inferiority was not exceeded. Worse cosmetic outcome was reported in patients treated with APBI compared to WBI as scored by trained nurses (29 *vs.* 17%; p< 0.001), patients (26 *vs.* 18%; p= 0.0022) and physicians (35 *vs.* 17%; p< 0.001), and cosmetic results declined over time. Toxicity rates at three years were significantly worse in patients treated with PBI (66%) when compared to patients treated with WBI (46%) (p<0.001).

The ***National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/RTOG 0413 trial*** randomised 4,216 patients to APBI (brachytherapy or 3D-CRT, 34 Gy with brachytherapy or 38.5 Gy with 3D-CRT in ten fractions, given twice daily, on five treatment days within an eight-day period) or WBI (50 Gy in 25 fractions with or without a boost).[32] While the ten-year cumulative incidence of ipsilateral breast-tumour recurrence rates were very low in both arms (4.6% (95% CI 3.7–5.7) for APBI and 3.9% (3.1–5.0) for WBI), with an absolute difference of <1%, APBI did not meet pre-set criteria for equivalence to WBI. In contrast with the RAPID trial, toxicity rates were similar between both groups.

More recently, the updated long-term results of the ***Florence trial*** were presented (SABCS 2019). The ten-year incidence of ipsilateral breast-tumour recurrence was 3.3% and 2.6% in the APBI group (30 Gy in five daily non-consecutive fractions) and WBI group (50 Gy in 25 fractions with a 10 Gy lumpectomy boost), respectively (p= 0.39). Patients treated with APBI had significantly less grade 1-2 fibrosis and better cosmetic outcome than patients treated with WBI. Cosmetic outcome as rated by the physician was excellent in 95% of patients treated with APBI.

In general, EBRT APBI is a more accessible treatment technique, as its use is not limited to centres with brachytherapy or IORT capabilities. Despite the discrepant primary endpoint conclusions of the NSABP B-39/ RTOG 0413 and the RAPID trial, differences in interpretation are mainly the result of statistical design. NSABP B-39/ RTOG 0413 defined a smaller tolerated rise in relative risk than the RAPID trial. From a clinical perspective, the HRs and associated CIs show that no fundamental difference exist between the two studies. Discrepant differences in reported toxicity results were also demonstrated. The RAPID trial investigators pointed at the twice-daily schedule resulting in incomplete repair and

KEY MESSAGES FOR CLINICAL PRACTICE

1. **PBI is gaining acceptance for well-selected patients, as recommended 'suitable' by the current ASTRO guidelines.**
2. **PBI can be used with confidence in clinical practice, with low ipsilateral breast recurrence rates seen in mature PBI trials.**
3. **Consider offering PBI to postmenopausal patients with ER+, node negative, pT1 tumours, where the balance between benefit and risk appears optimal.**
4. **In other patients, it is important to consider age, likely survival, and the implications of any later increase in locoregional relapse on long-term survival.**
5. **The most appropriate technique depends on capabilities of individual centres, with most mature evidence existing for interstitial brachytherapy.**
6. **Twice-daily EBRT APBI should be used with caution, with a once-daily or even less frequent schedule, as was used in the IMPORT LOW or Florence trials, being a more opportune alternative for EBRT APBI.**

a higher biological dose toxicity. However, the first results of the NSABP B-39 trial using the same fractionation schedule, did not confirm this. Of note, in this trial, 27% patients received brachytherapy APBI, which might attribute to the more favourable toxicity results. Nevertheless, as demonstrated by the Florence trial; when using 30 Gy in five daily non-consecutive fractions, excellent late toxicity and cosmetic outcome are seen, which makes this schedule the most opportune for EBRT APBI, but the full publication has to be awaited. Noteworthy, there are currently multiple ongoing trials investigating EBRT APBI delivered in a neoadjuvant setting which are beyond the scope of this current paper but may represent another avenue of APBI utilization in the near future.[33,34]

CONCLUSION

PBI is gaining acceptance for well-selected patients, as recommended 'suitable' by the current ASTRO guidelines. PBI can be used with confidence in clinical practice, since ipsilateral breast recurrence rates are reassuringly low in all mature PBI trials. Consider offering PBI to postmenopausal patients with ER+, node negative, pT1 tumours, where the balance between benefit and risk appears optimal. In other patients, it is important to consider age, likely survival, and the implications of any later increase in locoregional relapse on long-term survival. The most appropriate technique depends on capabilities of individual centres, with most mature evidence existing for interstitial brachytherapy. Twice-daily EBRT APBI should be used with caution, with a once-daily or even less frequent schedule, as was used in the IMPORT LOW or Florence trials, being a more opportune alternative for EBRT APBI.

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Optimal treatment of metastatic gastric and gastro-oesophageal junction adenocarcinoma

J. Siplet, MD[1,2], A. De Cuyper, MD[1], M. Van den Eynde, MD, PhD[1,2]

SUMMARY

Standard of care for advanced and metastatic gastric and gastro-oesophageal junction adenocarcinoma relies on palliative systemic therapy that can improve both survival and quality of life of patients. In first-line, platinum – fluoropyrimidine-based doublet (combined with trastuzumab for HER2/neu positive tumours) or triplet chemotherapy regimen (mainly combining a taxane) is now standard option. For fit patients, a second-line with taxane and/or ramucirumab or irinotecan monotherapy, is an option. Latest studies showed interest for new treatments such as immune checkpoint inhibitors (anti-PD-1) or trifluridine/tipiracil in some situations.
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INTRODUCTION

In 2018, 1,577 new diagnoses of gastric cancer and 788 related deaths were registered in Belgium.[1] At the time of diagnosis, approximately one-third of patients have metastatic spreading. The current treatment approach for these patients with metastatic disease relies on several systemic therapies that can be administered sequentially, leading to improve both their survival and quality of life. There is now a clear trend towards personalised medicine considering the patient's age and comorbidities, clinical features, molecular tumour characteristics and recent advance in the field of targeted therapy and immuno-oncology.[2]

Treatments for metastatic gastro-oesophageal junction (GEJ) adenocarcinoma have been developed as a type of metastatic gastric (G) cancer, and many clinical trials were conducted targeting both advanced (inoperable) and metastatic G and GEJ adenocarcinoma (mG/GEJ). In this section, we discuss the current available options to treat mG/GEJ adenocarcinoma in Western countries.

AVAILABLE THERAPIES IN METASTATIC GASTRIC AND GASTRO-OESOPHAGEAL CANCER

CHEMOTHERAPY REGIMENS

Fluoropyrimidines (5-fluorouracile or capecitabine) with **platinum salts** (cisplatine or oxaliplatine) doublet chemotherapy is recommended in first-line for fit patients with mGEJ/G adenocarcinoma. In some situations (fit and young patients, need for a rapid tumour response), a **taxane** (docetaxel) or more rarely an **anthracycline** (epirubicine) can be added (triplet regimen).[2] Common use of the triplet remains controversial because of its toxicity. A recent Dutch nationwide study[3] including 2,204 real-life treated patients reported similar overall survival (OS) and treatment failure rate with doublet or triplet chemotherapy but a better toxicity profile in favour of the doublet regimen (grade 3–5 toxicity 21% *vs.* 33%). Additionally, a network meta-analysis (>50 analysed studies, >10,000 patients) evaluating safety and OS after first-line treatment reported that doublets containing

[1]Department of Medical Oncology, Institut Roi Albert II, Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium, [2]Department of Hepatogastroenterology, Institut Roi Albert II, Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium.

Please send all correspondence to: M. Van den Eynde, MD, PhD, Cliniques Universitaires Saint-Luc, 10 Avenue Hippocrate, 1200 Woluwe-Saint-Lambert, Belgium, tel: +32 2 764 11 11, email: marc.vandeneynde@uclouvain.be.

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fluoropyrimidines were the preferred option compared to triplet containing cisplatin or anthracycline.[4] Nevertheless, the association of fluoropyrimidine, oxaliplatin and docetaxel remains a promising treatment and is currently evaluated in several phase III trials. Conversely to Asian trials, the FLAGS study did not show any OS benefit with S-1 (fluoropyrimidine) compared to 5-fluorouracil despite a better toxicity profile (decrease of neutropenia, stomatitis and treatment-related deaths) for S-1.[5]

In second- and later lines, **docetaxel** or **irinotecan** provided survival benefit (median OS gain: 1.6 – 2.4 months) compared to best supportive care (BSC).[6,7] A randomised phase III trial directly comparing weekly **paclitaxel** with irinotecan reported similar efficacy for both regimens.[8]

For fit patients, previously treated with at least two prior systemic therapies, **trifluridine/tipiracil** provided a significant OS benefit *vs.* placebo (5.7 *vs.* 3.6 months; HR 0.69, p= 0.0006).[9]. This treatment was recently approved (July 2019) by the European Medicine Agency (EMA) and should be available soon.

TARGETED AND ANTIANGIOGENIC THERAPIES

Trastuzumab is a monoclonal antibody targeting the HER2/neu receptor: its use in combination with first-line cisplatin-fluoropyrimidines (CF) is indicated for HER2-overexpressing tumours, defined by either IHC score 3+ or ISH+. The TOGA trial demonstrated improved OS for patients treated with trastuzumab combined with CF compared to CF alone (16 *vs.* 11.8 months respectively, HR: 0.65).[10]

Ramucirumab is a human monoclonal antibody which directly binds to VEGFR2 and inhibits angiogenesis. Ramucirumab is approved in second-line treatment (monotherapy or combined with paclitaxel). The REGARD study (N= 355) comparing ramucirumab to BSC reported a median OS benefit (5.2 *vs.* 3.8 months respectively).[11] In the RAINBOW study (N= 665), the addition of ramucirumab to paclitaxel improved OS and quality of life compared to paclitaxel monotherapy (mOS: 9.6 *vs.* 7.3 months, respectively) [12].

IMMUNOTHERAPY

Nivolumab and **pembrolizumab** are human monoclonal antibodies targeting PD-1, and thus allowing cancer cells destruction through immune system stimulation.

In the KEYNOTE 062 study[13], **pembrolizumab** was not inferior to CF and had a better tolerability profile in patients with CPS >1 tumours treated in the first-line metastatic setting (HR: 0.91, 95%CI: 0.69-1.18). No additional benefit was observed when pembrolizumab was combined with CF.

The KEYNOTE 181 study[14], including only patients with metastatic oesophageal cancers (adenocarcinoma and squamous cell carcinoma) showed that **pembrolizumab** was superior to second-line chemotherapy (taxane or irinotecan) for tumour response rate (21.5% *vs.* 6.1%) and OS (HR[95%-CI]: 0.69[0.52-0.93], p= 0.007) in the subgroup of tumours with CPS ≥10. This benefit was mainly observed in squamous cell carcinoma (which often expressed PD-L1). This survival benefit was not observed in the KEYNOTE-061 trial[15] including CPS ≥1, mG/GEJ adenocarcinoma treated with pembrolizumab *vs.* paclitaxel.

In chemo-refractory disease, the Asian ATTRACTION 2 study (nivolumab *vs.* placebo)[16] reported an OS benefit of 2.1 months (HR:0.69, p= 0.0003) for **nivolumab**. A similar benefit seems to be observed with pembrolizumab in Western patients (KEYNOTE 059: non-randomised, phase II, single-arm) for tumour with CPS ≥ 1, but need to be confirmed in randomised trials.[17] So far, none of these treatments have been approved by the EMA even though pembrolizumab and nivolumab were granted accelerated approval in the United States and in some Asian countries.

For MSI-high mG/GEJ adenocarcinoma, **pembrolizumab** provides significant and durable tumour responses with OS benefit compared to chemotherapy.[13,15,18] EMA approval is still awaited. Epstein–Barr virus (EBV) positive tumours seem also to benefit significantly from these drugs, while the role and threshold of PD-L1 expression remain not completely defined.

Considering the results available so far, anti-PD-1 monoclonal antibodies (mainly pembrolizumab in Western countries) are efficacious for the treatment of MSI-high mG/GEJ cancers and in second-line of metastatic oesophageal cancers with strong PD-L1 expression (CPS>10, mainly squamous cell carcinoma).

TREATMENT OPTIONS FOR mG/GEJ ADENOCARCINOMA

The sequential treatment options are summarised in *Figure 1*.

FIRST-LINE TREATMENT

Use of doublet (platinum-fluoropyrimidine) or triplet regimen (containing taxane) should be decided according to the efficacy/safety balance in each patient. A triplet regimen comprising platinum/fluoropyrimidine/taxane (preferred to anthracycline) is an option for fit and young patients with advanced and bulky disease. CF + trastuzumab is the treatment of choice for HER2-overexpressing tumours (IHC score 3+ or ISH+). Patients unfit for treatment should be considered for BSC.

SECOND- AND LATER LINE TREATMENT

Compared with BSC, second-line therapy improved OS and quality of life for patients with an ECOG PS ≤ 2. Paclitaxel-ra-

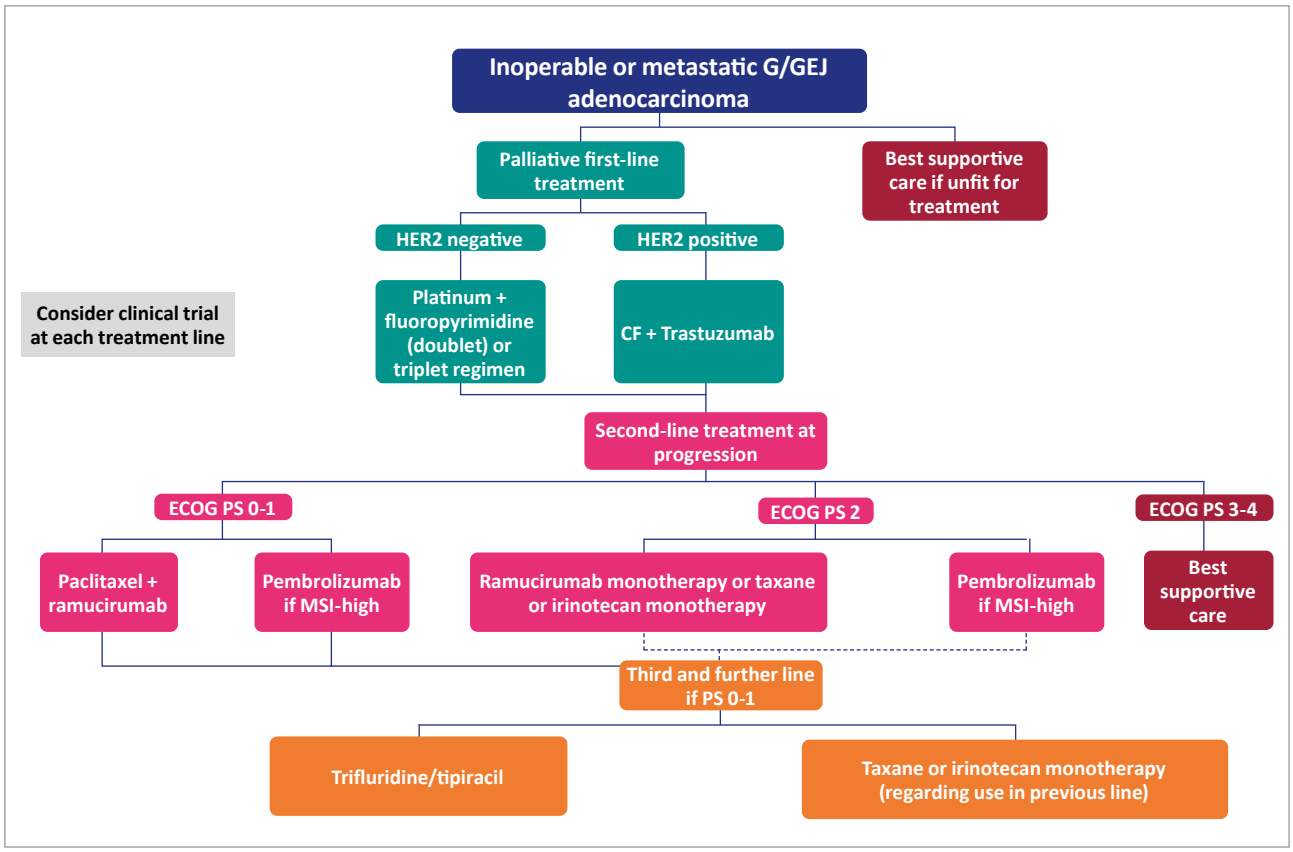

FIGURE 1. Sequential treatment options for patients with mG/GEJ adenocarcinoma.[2]
G/GEJ: gastric and gastro-oesophageal junction; BSC: best supportive care; CF: cisplatin and fluoropyrimidine; ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; MSI: microsatellite instability; PS: performance status.

mucirumab is the treatment of choice for fit patients. Taxanes (paclitaxel or docetaxel), irinotecan and ramucirumab monotherapy are alternative treatment options.

MSI-high tumours are more likely to benefit from anti-PD-1 treatments. We eagerly expect pembrolizumab could be available soon, depending EMA approval. For fit patients, previously treated with at least two prior systemic therapies, trifluridine/tipiracil is now a treatment option.

Unfit patients (ECOG PS 3-4) should receive BSC only.

ABOUT FRAIL AND ELDERLY PATIENTS

Elderly and frail patients with gastric cancer are under-represented in clinical trials. The most evaluated chemotherapy regimens include oxaliplatin and fluoropyrimidine. A phase III trial recently reported that low-dose capecitabine-oxaliplatin (until 40% of dose reduction) may be offered to these patients without compromising quality of life, cancer control or OS.[19]

Decisions regarding chemotherapy in these patients have to take into account ECOG PS, functional age of the patient, comorbidities, and the patient's preference for treatment. Geriatric assessment is helpful.

MOLECULAR APPROACH

The Cancer Genome Atlas (TCGA) described four molecular subtypes of mG/GEJ cancers: (i) tumours positive for EBV; (ii) MSI-high tumours; (iii) genomically stable (GS) tumours and (iv) tumours with chromosomal instability (CIN). EBV and MSI-high tumours generally exhibit extreme DNA methylation and mutation burden and are good candidates for immune therapies.[20] GS tumours are enriched for the diffuse histological variant and mutations of *CDH1* and *RHOA* or CLDN18–ARHGAP fusion. CIN tumours (mainly GEJ cancers) harbour frequently recurrent *TP53* mutation and numerous amplifications of Receptor Tyrosine Kinases (RTKs) genes (such as *HER2, EGFR, MET, FGFR2*). Remarkable advances in elucidating molecular profiles have facilitated the development of novel agents such as RTKs inhibitors, immune therapies and IMAB362 (anti-Claudin 18.2).[21] Developing appropriate biomarkers for patient selection in early clinical trials could lead to successful results of pivotal clinical trials with new drugs.

CONCLUSION

Available sequential treatments are indicated for fit patients

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Chemotherapy combining platinum/fluoropyrimidine (doublet) is recommended for fit patients. In some situations (fit and young patients, need for rapid tumour response), docetaxel (preferentially) or epirubicine can be added (triplet combinations).**

2. **Trastuzumab combined with cisplatinum-fluoropyrimidine -based chemotherapy is recommended for HER2-positive tumours.**

3. **Elderly and frail patients with mG/GEJ adenocarcinoma may benefit from chemotherapy but treatment decision must consider geriatric assessment and the patient's preference.**

4. **Second-line treatment with ramucirumab +/- paclitaxel, taxane, or irinotecan provides OS benefit for fit patients.**

5. **Trifluridine/tipiracil is now a treatment option for fit patients with refractory disease.**

6. **Despite a lack of accessibility in our country, the current evidence supports the treatment of MSI-high tumours with anti-PD-1 monoclonal antibodies.**

with mG/GEJ adenocarcinoma as studies showed improvement in both OS rate and quality of life. At least a platinum-fluoropyrimidine-containing regimen (combined with trastuzumab for HER2/neu + tumours) is recommended for fit patients in first-line treatment. Ramucirumab +/- paclitaxel is the preferred option in second-line. Administration of trifluridine/tipiracil is a valid and well-tolerated treatment for refractory diseases. Literature supports the use of anti-PD-1 monoclonal antibodies (pembrolizumab in Western countries) for MSI-high tumours. This treatment is currently not accessible in Europe.

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A case of a life-threatening toxicity following capecitabine treatment: advocacy for dihydropyrimidine dehydrogenase deficiency screening

H. Houssiau, MD[1], L. Duck, MD[1], S. Carlier, MD[1], R. Poncin, MD[1], N. Whenham, MD[1], V. Haufroid, PharmD, PhD[2,3]

SUMMARY

We discuss a life-threatening case of capecitabine toxicity due to the presence of a heterozygous variant on exon 14 (c.1905+1G>A, rs3918290) of the dihydropyrimidine dehydrogenase gene (*DPYD*). We advocate the need for dihydropyrimidine dehydrogenase deficit screening, which could become mandatory in Belgium, as in France, before any fluoropyrimidine administration to avoid cases of foreseeable toxicity.

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INTRODUCTION

Severe (grade ≥3) fluoropyrimidine (*e.g.* 5-fluorouracil and capecitabine) toxicity is common (20-25%) and potentially lethal in 0.2-0.8%.[1,2] It is characterised by myelosuppression, mucocutaneous manifestations (alopecia, dermatitis, palmo-plantar erythrodermia, oro-pharyngeal ulcers) and gastrointestinal involvement (nausea, vomiting and intractable diarrhoea). The vast majority of these adverse events are due to partial (or complete) dihydropyrimidine dehydrogenase (DPD) deficiency, which can be unmasked either by genotyping the corresponding gene (*DPYD*) or phenotyping the DPD enzyme by functional tests.[3,4] The primary objective of the screening is to detect the few completely deficient individuals (0.01-0.5% of the population), who will die after a first course of fluoropyrimidine, and the more common partially deficient individuals (3-8%), who may experience life-threatening toxicity.

In France, since 2019, screening for DPD deficiency has been made mandatory before fluoropyrimidine administration. In Belgium, screening tests are also available and are now officially recommended by the European Medicine Agency (EMA).

Here, we briefly discuss the different DPD deficiency screening strategies, in light of a recently observed real-world case.

CASE REPORT

A 42-year old woman was admitted to the hospital on October 21, 2019 for fever and intractable diarrhoea (up to 15 stools/day; grade 3 after Common Terminology Criteria Adverse Events) after a first cycle of capecitabine (1 g/m^2 twice daily for 14 days every 21 days) prescribed for metastatic triple negative breast cancer with lymph node and bone involvement. The initial cancer was diagnosed in December 2016. As adjuvant chemotherapy she received dose-dense epirubicine/cyclophosphamide and weekly paclitaxel without any complications. Two years later, she relapsed and was

[1]Oncology Department, Clinique St-Pierre, Ottignies-Louvain-la-Neuve, Belgium, [2]Clinical Chemistry Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium, [3]Louvain centre for Toxicology and Applied Pharmacology (LTAP), Université catholique de Louvain, Brussels, Belgium.

Please send all correspondence to: H. Houssiau, Clinique Saint-Pierre, Avenue Reine Fabiola 9, 1340 Ottignies-Louvain-la Neuve, Belgium, tel: +32 10 43 72 41, email: helene.houssiau@student.uclouvain.be.

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Keywords: dihydropyrimidine dehydrogenase deficiency, fluoropyrimidine toxicity, genotyping, phenotyping, screening, uracil.

TABLE 1. *DPYD* variants and hetero- and homozygous carrier rates in Caucasians.

Variants	Percentage of heterozygous carriers	Percentage of homozygous carriers	Loss of enzymatic activity
DPYD*2A (IVS14+1G>A,c.1905+1G>A, rs3918290)	1.5%	0.01%	Complete
DYPD*13 (c.1679T>G,p.I560S, rs55886062)	0.2%	0.0001%	Complete
c.2846A>T (p.D949V, rs67376798)	1%	0.004%	Partial
HapB3 (3 SNPs) (c.1129-5923C>G, rs75017182, c.1236G>A, p.E412E, rs56038477 and c.483+18G>A, rs56276561	4.6%	0.06%	Partial

After INCa, HAS.[7]

treated within the frame of a clinical trial aimed at testing the combination of carboplatine, paclitaxel, anti-PDL-1 durvalumab, with or without anti-CD73 (adenosine-generating enzyme) oleclumab (*Synergy* trial). Due to disease progression, the patient was withdrawn from the trial and oral chemotherapy with capecitabine was started on October 7, 2019, given the lack of any other trial at that time. At day fourteen of the first cycle, she was admitted through the emergency room, for febrile neutropenia. Her ECOG performance status was three. Severe ulcerated, necrotic oral and genital lesions were observed. Clinical examination was otherwise normal. Grade 4 neutropenia was diagnosed (90 neutrophils/µl), together with Grade 2 anaemia (Hb: 9.2 g/dl) and Grade 1 thrombocytopenia (77,000/µl). CRP (38.5 mg/L; normal values <5 mg/L) and LDH (494 U/L; normal values < 243 U/L) levels were marginally elevated. Despite immediate treatment with piperacillin/tazobactam (4x4g/500 mg) and filgrastim (30 MU/day), patient's condition did not improve, with persistence of fever and Grade 4 neutropenia (nadir: 0/µl), thereby leading to the addition of vancomycin (1,800 mg/day) and fluconazole (200 mg/day), shift from piperacillin/tazobactam to meropenem (3x1 g) and doubling of filgrastim dose (30 MU twice daily). Parenteral nutrition was required as well as administration of RBC packs, platelets and fresh plasma. Two weeks after admission, neutrophils started to rise (89/µl) and were normalised on day 16 (2,850/µl). Oral and genital ulcers healed but hand and feet desquamation occurred. Patient left the hospital on day 17 after complete recovery.

Subsequent genotyping of the dihydropyrimidine dehydrogenase gene (*DPYD*) revealed the presence of a heterozygous variant on *DPYD* exon 14 (c.1905+1G>A, rs3918290) predisposing to toxicity of fluoropyrimidine-based chemotherapy. This led to a review of current and foregoing recommendations for DPD deficiency screening.

DISCUSSION

This case illustrates a severe capecitabine toxicity, with an unusual fourteen day-lasting period of myelosuppression, due to the presence of a *DPYD* variant. Capecitabine is an orally administered fluoropyrimidine drug which is metabolised *in vivo* in 5-flurouracil (5-FU), the latter being further transformed in active cytotoxic nucleotides.[5] Inactivation of 5-FU is mainly controlled by an enzyme, called dihydropyrimidine dehydrogenase (DPD). If the corresponding *DPYD* gene bears a least one loss-of-function variant, 5-FU accumulates and more active metabolites are produced. The *DPYD* gene is located on chromosome 1 and contains 23 exons. More than 100 variants have been described but, so far, only four variants have been clinically associated with increased toxicity of fluoropyrimidines, mainly in Caucasians, and are recommended with a "strong evidence level" by the *Clinical Pharmacogenetics Implementation Consortium* (CPIC) for DPD deficiency screening strategies.[6] Homozygous variant carriers usually do not survive after standard fluoropyrimidine exposure, while heterozygous carriers may experience severe life-threatening adverse events.[1,2] *Table 1* summarises the four

KEY MESSAGES FOR CLINICAL PRACTICE

1. Severe (Grade ≥3) fluoropyrimidine toxicity is common (20-25%) and potentially lethal in 0.2-0.8%.
2. Toxicity is often related to partial or complete dihydropyrimidine dehydrogenase deficiency, which can be unmasked either by genotyping (only validated in Caucasian patients) of the corresponding gene (DPYD) or phenotyping of the enzyme by functional tests.
3. Dose adjustments are recommended, based on the results of the screening tests.
4. Assessment of partial or complete dihydropyrimidine dehydrogenase deficiency is now officially recommended by EMA.

most common *DPYD* variants, the estimated percentages of hetero- and homozygous variants carriers and the partial or total loss of enzymatic activity due to the variant.

The CPIC has computed a fluoropyrimidine metabolizer score based on the results on *DPYD* genotyping, which should be used to adapt the drug doses.[6] Each of the two *DPYD* genes is given a score of 1 if none of the four variants are detected, a score of 0.5 if one of the two variants associated with partial loss (*vide supra*) is present and a score of 0 if one of the two variants associated with complete loss is present. The total score (in a wild-type patient) is two. Based on the score calculated in a patient elected for treatment with fluoropyrimidines, the following dose reductions should apply: normal dose if score = 2; 50% dose reduction if score = 1 or 1.5 (at least for the first two doses; doses may be increased later in the absence of adverse effects according to patient tolerance); no treatment with fluoropyrimidines if score = 0 or 0.5. Of note, these recommendations apply only to a Caucasian population. The patient whose clinical case is described here was genotyped *DPYD*1/*2A* (activity score 1) and, according to the CPIC recommendations, should therefore have received an initial dose reduced by 50% compared to the standard dose during the first cycles of treatment. It should be stressed that targeted genotyping of only four *DPYD* variants does not exclude the presence of other rare variants that could induce a DPD poor-metabolizer status. Full sequencing of the *DPYD* gene would allow the detection of such rare variants but the genotype/phenotype relation could still be uncertain in these cases. Moreover, the turn-around time (TAT) of the full *DPYD* sequencing should remain compatible with its use in pre-emptive DPD deficiency screening [maximum ten days according to *Haute Autorité de Santé* (HAS) recommendations].[7]

Another approach to diagnose DPD deficiency is to measure the *in vivo* functional activity of the enzyme by determining the plasma level of uracil (U) and the dihydrouracil (UH2)/uracil ratio. Uracil is a pyrimidine base which is metabolised in dihydrouracil by DPD. A lower DPD activity will result in higher levels of plasma uracil and lower UH2/U ratios. According to recent HAS recommendations, it is considered that a U plasma level <16 ng/ml is suggestive of a normal DPD activity. At the opposite, a full DPD deficient patient would have an uracil plasma level >150 ng/ml, thereby contra-indicating the use of fluoropyrimidines. Values between 16 and 150 ng/ml would suggest partial DPD deficiency and should lead to fluoropyrimidines dose reduction after a "clinical-biological dialogue".[7] These uracilaemia cut-offs, proposed by HAS, still need further validation in the real-world practice. This phenotyping test was also applied to our patient with the following results: uracilaemia measured at 16.4 ng/ml, UH2 at 78,0 ng/ml and UH2/U ratio at 4.8. Although the uracilaemia value is higher than 16 ng/ml, the measured value is still quite low in relation to the genotype status of the patient (heterozygous with a complete loss of function gene) and to the clinical situation. This therefore raises the question of the relevance and validation of the currently HAS recommended cut-offs. From this point of view, it is interesting to emphasise that the value of 16 ng/ml was proposed on the basis of a paper where fluoropyrimidine toxicities were still significantly increased at uracilaemia levels between 14 and 16 ng/ml.[8] Therefore, a 14 ng/ml threshold for uracilaemia would certainly be more appropriate not only in view of the current case report but also in relation to the experience acquired in the determination of plasma uracil with more than 90% of the population below 14 ng/ml. Anyway, even with an uracilaemia value very close to the proposed cut-off, the UH2/U ratio left no doubt about the presence of a DPD deficiency in our patient. Indeed, UH2/U ratios are always greater than ten

in patients with normal DPD activity. This clinical case therefore illustrates the importance of taking into account not only the value of uracilaemia but also the value of the UH2/U ratio for a correct interpretation of the results. Compared to the genotyping approach, it must be stressed that the main limitation of the phenotyping test is the very strict pre-analytical requirements. Indeed, U level rapidly increases in whole blood mainly when the sample is kept at room temperature and the maximum delay for centrifugation and plasma freezing is 90 minutes after blood collection. Furthermore, precise recommendation regarding dose reduction for patients with U values between low (14 ng/ml) and high cut-off must always be validated in prospective studies.

CONCLUSION

Fluoropyrimidines have been used for decades without performing tests aimed at detecting individual susceptibility towards severe adverse events. Recent unravelling of the genetic control of fluoropyrimidine metabolism lead to wide availability of screening tests. From an ethical perspective, it would be – in our view – unfair not to offer this screening to cancer patients who could therefore escape major treatment-related side effects. From an economical viewpoint, it should be stressed that the cost linked to life-threatening adverse events may well exceed the cost of systematic screening. Of note, genotyping of *DPYD* is currently reimbursed in Belgium, which is not yet the case for phenotyping of the DPD enzyme by functional tests. The Pharmacovigilance Risk Assessment Committee of the EMA has very recently (March 13, 2020) edited the following recommendation: "*Testing of patients for DPD deficiency is recommended before starting treatment with fluorouracil injection or infusion, capecitabine and tegafur. This can be done by measuring the level of uracil (a substance broken down by DPD) in the blood, or by checking for the presence of certain mutations (changes) in the gene for DPD which are associated with an increased risk of severe side effects*".[9]

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Overcoming intrinsic and acquired resistance to EGFR-targeting agents in cancer treatment: focus on identification of predictive biomarkers and novel therapeutic strategies

I. De Pauw, PhD[1], JB. Vermorken, MD, PhD[1,2], M. Peeters, MD, PhD[2], F. Lardon, PhD[1*], A. Wouters, PhD[1*]

SUMMARY

Targeted therapies that inhibit oncogenic signalling pathways are the key for precision medicine in cancer treatment. Research over the past decades has revealed that deregulated or increased signalling of the epidermal growth factor receptor (EGFR) plays an integral role in the development of various cancer types, including colorectal cancer (CRC) and head and neck squamous cell carcinoma (HNSCC). After initially promising results of EGFR-targeted therapies, it became clear that therapeutic resistance is a major clinical problem. Moreover, as an increasing number of patients are currently considered as candidates for treatment with EGFR-targeted therapy, identification of predictive biomarkers is extremely important. The objective of this PhD project was to unravel and overcome resistance to the EGFR-targeting agent cetuximab in CRC and HNSCC. Hereby, we focused on the identification of drug resistance mechanisms, novel drug targets and therapeutic strategies as well as predictive biomarkers.

The present study demonstrated that afatinib, a second-generation irreversible inhibitor of EGFR, HER2 and HER4, has the potential to overcome cetuximab resistance in CRC and HNSCC cell lines. Therefore, these data support the hypothesis that afatinib may be a promising therapeutic agent to treat CRC and HNSCC patients experiencing intrinsic or acquired cetuximab resistance. Furthermore, we found that increased phosphorylation of Akt seems to be characteristic for acquired cetuximab resistance in HNSCC. Although further confirmation in tumour samples of HNSCC patients is imperative, Akt appears a novel drug target to improve outcome after cetuximab treatment as well as a potential predictive biomarker for EGFR-targeted therapies in HNSCC patients. In this view, we encourage further studies that focus on targeting Akt in combination with cetuximab, as this may be a promising strategy to overcome drug resistance in HNSCC patients. These findings can form a solid basis for further experiments with advanced *in vitro* and *in vivo* models.

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[1]Centre for Oncological Research Antwerp, Antwerp, Belgium, [2]Antwerp University Hospital, Antwerp, Belgium.

*These authors share senior authorship.

Please send all correspondence to: I. De Pauw, PhD, Centre for Oncological Research Antwerp, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium, tel: +32 32652533, email: ines.depauw@uantwerpen.be.

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INTRODUCTION

During the past decades, important advances have been made in the understanding of the molecular biology of cancer. This has led to the development of targeted therapies and a shift towards precision medicine for cancer patients. Deregulated or increased signalling of the epidermal growth factor receptor (EGFR) plays an integral role in the development of various cancer types, including colorectal cancer (CRC) and head and neck squamous cell carcinoma (HNSCC), making it a compelling drug target.[1] After initially promising results of EGFR-targeted therapies, it became clear that both intrinsic and acquired therapeutic resistance are major roadblocks in the field of cancer medicine that compromise the efficacy of available treatment regimens in the clinic.[2] Therefore, understanding these resistance mechanisms is an area of extreme importance and novel therapeutic strategies are needed to overcome this drug resistance. Moreover, as an increasing number of patients are currently considered as candidates for treatment with EGFR-targeted therapy, identification of predictive biomarkers is extremely important. In an effort to identify therapeutic resistance mechanisms and predictive biomarkers towards the EGFR-targeting agent cetuximab, we conducted several studies investigating cetuximab resistance as well as novel therapeutic strategies effective in overcoming drug resistance in CRC and HNSCC.

EVALUATION OF THE POTENTIAL OF IRREVERSIBLE AND MULTIPLE HER RECEPTOR INHIBITION TO OVERCOME DRUG RESISTANCE

To start with, we evaluated the potential of irreversible and multiple HER receptor inhibition to overcome resistance towards the EGFR inhibitor cetuximab in CRC and HNSCC cell lines. Due to the particular mode of activation of the HER receptor network, involving ligand-induced homo- and heterodimerisation of the four HER receptors, an increased inhibition scope of HER receptors most likely results in a more potent blockade of the HER network, preventing premature emergence of resistance and leading to a more pronounced therapeutic benefit.[3-5]

In this regard, we first determined the expression of HER receptors in a panel of CRC cell lines and HNSCC cell lines with different sensitivity to cetuximab and compared these results with RNA sequencing data from the Cancer Genome Atlas (TCGA) dataset of CRC and HNSCC patients. We found that *RAS* wild type CRC cell lines used in this study and CRC patients show rather low EGFR expression but high HER2 and HER3 expression.[6] Concerning HNSCC, the cell lines used in this study and patients from the TCGA dataset demonstrated considerable expression of EGFR, HER2 and HER3. Importantly, cetuximab resistance had no influence on the expression levels of HER receptors in both CRC and HNSCC cell lines.[7] However, kinase activity of these receptors could still be strongly induced, provoking resistance to EGFR-targeting agents.[8]

Given this, we evaluated the *in vitro* potential of MEHD7945A (duligotuzumab), a monoclonal antibody with dual EGFR/HER3 specificity, and afatinib, an irreversible tyrosine kinase inhibitor of multiple HER receptors, to overcome intrinsic and acquired cetuximab resistance in *RAS* wild type CRC cell lines and in HNSCC cell lines with different HPV status. Our results showed that the extended inhibition scope of HER receptors by afatinib leads to a more robust blockade of the HER network compared to MEHD7945A treatment.[6,7,9] Neither cetuximab resistance nor HPV status had a significant impact on the efficacy of afatinib. Nevertheless, our results suggested the possibility of cross-resistance between cetuximab and afatinib. Importantly, exposure to hypoxia did not provoke therapeutic resistance to afatinib in CRC and HNSCC cell lines. Overall, these data support the hypothesis that afatinib may be a promising therapeutic strategy to treat CRC and HNSCC patients experiencing intrinsic or acquired cetuximab resistance. However, *Hickish et al.* reported no survival benefit in CRC patients after treatment with afatinib.[10] Clinical studies also demonstrated that afatinib has a comparable antitumour activity as cetuximab in HNSCC patients.[11] Furthermore, clinical data suggest that afatinib might be more effective in untreated and cetuximab-naïve HNSCC patients.[12,13] These clinical findings underlie the need for the identification of predictive biomarkers to select those patients that would benefit most from treatment with afatinib.

IDENTIFICATION OF DRUG RESISTANCE MECHANISMS AND PREDICTIVE BIOMARKERS TO RATIONALLY DESIGN NOVEL DRUG COMBINATION STRATEGIES TO OVERCOME RESISTANCE TO THE EGFR INHIBITOR CETUXIMAB IN HNSCC

Another way to improve patient response to EGFR-targeting therapy is the identification of the molecular mechanisms responsible for treatment resistance. In this PhD project, we applied whole-exome sequencing and phospho-kinase profiling to establish, respectively, a genetic and protein phosphorylation profile from acquired cetuximab resistant HNSCC cell lines.

The genetic profile of cetuximab sensitive and acquired cetuximab resistant HNSCC cell lines provided additional insights in the potential role of genetic alterations in the development of acquired cetuximab resistance. Sever-

KEY MESSAGES FOR CLINICAL PRACTICE

1. ***In vitro*** **observations indicate that irreversible inhibition of multiple HER receptors with afatinib has the potential to overcome cetuximab resistance in CRC and HNSCC. Importantly, the identification of predictive biomarkers in order to select those patients that would benefit most from afatinib treatment, is highly necessary.**

2. **Increased phosphorylation of Akt might be characteristic for acquired cetuximab resistance in HNSCC cell lines. These findings need to be further investigated in tumour samples of HNSCC patients.**

3. **Our preclinical data suggest that Akt represents a potential drug target to improve the response of cetuximab-based treatment in HNSCC patients.**

al single-nucleotide variants were found and based on gene function, these identified alterations my lead to acquired cetuximab resistance.[14] Importantly, validation of this genetic profile characteristic for acquired cetuximab resistance is currently being performed.

What's more, phospho-kinase profiling showed that there is a differential response between cetuximab sensitive and acquired cetuximab resistant HNSCC cell lines to EGFR inhibition by cetuximab.[14] Our results strongly suggested that increased phosphorylation of Akt and its downstream substrates following cetuximab treatment is characteristic for acquired cetuximab resistant HNSCC cell lines. Although further confirmation in tumour samples of HNSCC patients is imperative, Akt appears a novel drug target to improve outcome after cetuximab treatment as well as a potential predictive biomarker for EGFR-targeted therapies in HNSCC patients. Additional studies are crucial to precisely define the role of the PI3K/Akt signalling pathway in resistance towards EGFR-targeting agents.

CONCLUSIONS

In conclusion, the preclinical results presented in this doctoral project, provide better insights in the underlying mechanisms of resistance towards EGFR-targeting agents in CRC and HNSCC. In general, new therapeutic approaches were evaluated and evidence for novel mechanisms of therapeutic resistance were generated in these *in vitro* studies. First, we demonstrated that irreversible inhibition of multiple HER receptors with afatinib has the potential to overcome cetuximab resistance in CRC and HNSCC.[6,7] Second, we found that increased phosphorylation of Akt seems to be characteristic for acquired cetuximab resistance in HNSCC.[14] In this view, we encourage further studies that focus on targeting Akt in combination with cetuximab, as this may be a promising strategy to overcome drug resistance in HNSCC patients. As such, these findings can form a solid basis for further experiments with advanced *in vitro* and *in vivo* models using patient-derived tumour material. We are hopeful that additional research will lead to the start-up of clinical studies and ultimately an improved treatment of CRC and HNSCC patients.

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Journal Scan

J. Blokken, PharmD, PhD, T. Feys, MSc, MBA

SUMMARY

In this section of the BJMO, we aim to provide a snapshot of pivotal studies published in recent issues of the most important international journals focusing on oncology. Importantly, the selection of the studies discussed here is the sole responsibility of the publisher and was not influenced by third parties. Do you miss an important study, or did you read a hidden jewel that deserves to be shared with your colleagues? Please, let us know (editor@bjmo.be) and we will make sure to include it in the journal scan section of the next BJMO issue.

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LURBINECTEDIN AS SECOND-LINE TREATMENT FOR PATIENTS WITH SMALL-CELL LUNG CANCER

Patients with small-cell lung cancer (SCLC) have limited treatment options after failure of first-line therapy. *Trigo et al.* assessed the safety and efficacy of lurbinectedin, a selective inhibitor of oncogenic transcription, in SCLC patients after failure of platinum-based chemotherapy. Their single-arm, open-label phase II trial enrolled 105 patients who received 3.2 mg/m^2 of lurbinectedin, administered as a one-hour intravenous infusion every three weeks until disease progression or unacceptable toxicity. After a median follow-up of 17.1 months, an overall response rate (ORR, investigator assessed according to RECIST 1.1) of 35.2% was obtained. Haematological abnormalities such as anaemia (9%), leukopenia (29%), neutropenia (46%) and thrombocytopenia (7%) were the most common grade 3-4 adverse events (AEs). Serious treatment-related AEs occurred in 10% of the patients, of which neutropenia (5%) and febrile neutropenia (5%) were the most common. No treatment-related deaths were observed.[1] Given the high ORR and the acceptable and manageable safety profile, lurbinectedin is now under investigation in combination with doxorubicin as a second-line treatment option for advanced SCLC patients in a randomised phase III trial.[2]

PEMIGATINIB FOR PREVIOUSLY TREATED, LOCALLY ADVANCED OR METASTATIC CHOLANGIOCARCINOMA

The phase II FIGHT-202 trial enrolled 146 patients aged eighteen years or older with disease progression following at least one previous treatment and an ECOG PS of 0-2. Of these patients, 107 patients had *FGFR2* fusions or rearrangements. In addition, 20 patients had other *FGF/FGFR* alterations, eighteen patients did not have an alteration in *FGF/ FGFR* and one patient had an undetermined *FGF/ FGFR* status. All patients received a starting dose of 13.5 mg oral pemigatinib once daily (two weeks on, one week off) until disease progression, unacceptable toxicity, withdrawal of consent, or physician decision. After a median follow-up of 17.8 months, 38 patients with *FGFR2* fusions or rearrangements (35.5%) achieved an ORR, including three complete and 35 partial responses. Hyperphosphataemia was observed in 60% of the patients and was the most common all-grade AE. In to-

Ariez International BV, Ghent, Belgium.

Please send all correspondence to: T. Feys, Msc, MBA, Ariez International BV, Oude Houtlei 108A, 9000 Ghent, Belgium, tel: +32 479 567890, e-mail: t.feys@ariez.com.

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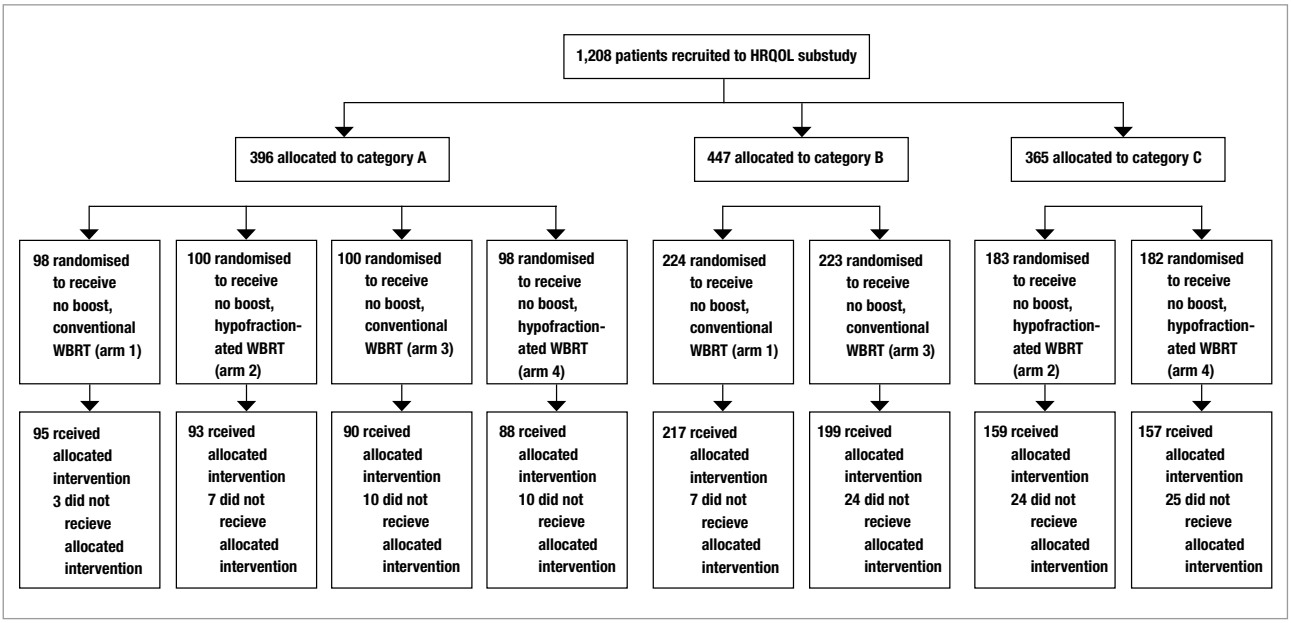

FIGURE 1. Randomisation of enrolled patients in the BIG 3-07/TROG 07.01 trial.[4]

tal, 64% of the patients had grade 3 or worse AEs and 45% of the patients experienced a serious adverse event, of which abdominal pain (5%), pyrexia (5%), cholangitis (3%) and pleural effusion (3%) were the most common. Overall, 49% of the patients died during the study, mostly because of disease progression (42%). None of the deaths were considered to be treatment related. In conclusion, pemigatinib might have therapeutic potential in previously treated patients with cholangiocarcinoma who harbour *FGFR2* fusions or rearrangements.[3]

QUALITY OF LIFE AFTER BREAST-CONSERVING THERAPY AND ADJUVANT RADIOTHERAPY FOR NON-LOW-RISK DUCTAL CARCINOMA *IN SITU*

The phase III BIG 3-07/TROG 07.01 trial is a randomised trial that is being conducted in more than 118 hospitals from eleven countries. A total number of 1,208 patients were enrolled in the study, which evaluated tumour bed boost and hypofractionation in patients with non-low-risk ductal carcinoma *in situ* following breast-conserving surgery and whole breast radiotherapy (WBRT). The Lancet Oncology recently reported the effects of diagnosis and treatment on health-related quality of life (HRQoL) at two years. Women were randomly assigned, by use of a minimisation algorithm, to tumour bed boost or no tumour bed boost, following conventional WBRT or hypofractionated WBRT using one of three randomisation categories. Category A was a four-arm randomisation of tumour bed boost *versus* no boost following conventional WBRT (50 Gy in 25 fractions over five weeks) *versus* hypofractionated WBRT (42.5 Gy in sixteen fractions over 3.5 weeks). Category B was a two-arm randomisation between tumour bed boost *versus* no boost following conventional WBRT, and category C was a two-arm randomisation between tumour bed boost *versus* no boost following hypofractionated WBRT (*Figure 1*). By means of four questionnaires at baseline, end of treatment, and at six, twelve and twenty-four months after radiotherapy, patients were questioned about fatigue and physical functioning, cosmetic status, breast-specific symptoms, arm and shoulder functional status, body image and sexuality and perceived risk of invasive breast cancer. In total, 91% of the patients received their allocated treatment (*Figure 1*) and most patients completed their scheduled HRQoL assessments (95% at baseline and 87% at two years). Tumour bed boost was associated with persistent adverse effects on cosmetic status (difference 0.10, global p= 0.00014, Hochberg-adjusted p= 0.0016 across all time points, an estimated difference of 0.13, p= 0.00021 at the end of treatment and persisting at 24 months; 0.13, p= 0.00021). Also the arm and shoulder function was adversely affected by tumour bed boost across all time points (0.08, global p= 0.0033, Hochberg adjusted p= 0.045); the difference between tumour bed boost and no boost at the end of treatment was 0.08 (p= 0.021), and did not persist at 24 months (0.04, p= 0.29). None of the other prespecified aspects of HRQoL significantly differed after adjustment for multiple testing. Patient reported outcomes between conventional WBRT compared with hypofractionated WBRT only differed significantly when assessing body image. In this case, conventional WBRT was associated with worse body image than hypofractionated

WBRT at the end of treatment (-1.10; p= 0.0016). The primary endpoint of this trial, time to local recurrence, will be reported when participants have completed five years of follow-up.[4]

BEVACIZUMAB AND PLATINUM-BASED COMBINATIONS FOR RECURRENT OVARIAN CANCER

Professor Pfisterer and colleagues investigated the combination of carboplatin, pegylated liposomal doxorubicin and bevacizumab (experimental group) to carboplatin, gemcitabine and bevacizumab (standard group) in patients with histologically confirmed epithelial ovarian, primary peritoneal or fallopian tube carcinoma with first disease recurrence more than six months after first-line platinum-based chemotherapy. A total number of 682 eligible patients were randomised (1:1) to an experimental arm in which patients received six cycles of bevacizumab (10 mg/kg, days 1 and 15) plus carboplatin (AUC 5, day 1) plus pegylated liposomal doxorubicin (30 mg/m^2, day 1) every four weeks, or a control arm where the treatment consisted of six intravenous cycles of bevacizumab (15 mg/kg, day 1) plus carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2, days 1 and 8) every three weeks. Both regimens were followed by maintenance bevacizumab (15 mg/kg every three weeks in both groups) until disease progression or unacceptable toxicity. The median follow-up for progression-free survival (PFS) at data cut-off of this open-label phase III trial was 12.4 months in the experimental group and 11.3 months in the standard group. The median PFS was 13.3 months in the experimental arm, as compared to 11.6 months in the standard arm (HR[95%CI]: 0.81[0.68-0.96], p= 0.012). The most common grade 3-4 AEs were hypertension (27% *vs.* 20%) and neutropenia (12% *vs.* 22%) in the experimental and standard group, respectively. Comparable numbers of serious adverse events occurred in both study arms (10% *vs.* 9%, respectively). One patient in the experimental group and two patients in the standard group died because of a treatment-related event. The authors conclude that carboplatin–pegylated liposomal doxorubicin–bevacizumab is a new standard treatment option for platinum-eligible recurrent ovarian cancer.[5]

RUCAPARIB FOR PATIENTS WITH PLATINUM-SENSITIVE, RECURRENT OVARIAN CARCINOMA (ARIEL3)

The ARIEL3 trial included 564 patients with platinum-sensitive, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma and an ECOG PS of 0-1 who had received at least two previous platinum-based chemotherapy regimens and responded to their last platinum-based regimen. Patients were randomly assigned (2:1) to oral rucaparib (600 mg, twice daily) or placebo in 28-day cycles. After a median follow-up of 28.1 months, in the intention-to-treat population, the median chemotherapy-free interval (CFI) was 14.3 months in the rucaparib group and 8.8 months in the placebo group (HR[95%CI]: 0.43[0.35-0.53], p< 0.0001). The median time to start of second subsequent therapy (TFST) was 12.4 months *versus* 7.2 months (HR[95%CI]: 0.43[0.35-0.52], p< 0.0001) and the median time to disease progression on subsequent therapy or death (PFS2) was 21.0 months *versus* 16.5 months (HR[95%CI]: 0.66[0.53-0.82], p= 0.0002). Finally, median time to start of second subsequent therapy (TSST) was 22.4 months *versus* 17.3 months (HR[95%CI]: 0.68[0.54-0.85], p= 0.0007) for the rucaparib and placebo group respectively. Of note, the CFI, TFST, PFS2, and TSST were also significantly longer with rucaparib than placebo in the *BRCA*-mutant and homologous recombination-deficient cohorts. Updated safety data were consistent with previous reports. The most common grade ≥3 TRAEs were anaemia or decreased haemoglobin (22% in the rucaparib group as compared to 1% in the placebo group) while serious TRAEs were reported in 22% of the patients in the rucaparib group and 11% in the placebo group. As such, rucaparib maintenance led to a clinically meaningful delay in starting subsequent therapy and provided lasting clinical benefits as compared to placebo in all three analysis cohorts.[6]

OLAPARIB VERSUS NONPLATINUM CHEMOTHERAPY IN PATIENTS WITH PLATINUM-SENSITIVE RELAPSED OVARIAN CANCER AND A GERMLINE *BRCA1/2* MUTATION

In the phase III randomised, open-label SOLO3 trial, patients with germline *BRCA*-mutated platinum-sensitive, relapsed ovarian cancer who had received at least two prior lines of platinum-based chemotherapy were randomised (2:1) to olaparib 300 mg twice a day or physician's choice single-agent nonplatinum chemotherapy (pegylated liposomal doxorubicin, paclitaxel, gemcitabine or topotecan). In total, 178 patients were assigned to olaparib and 88 to chemotherapy. In patients with measurable disease (olaparib, N = 151; chemotherapy, N = 72), the blinded independent central review (BICR)-assessed objective response rate was significantly higher with olaparib as compared to chemotherapy (72.2% *vs.* 51.4%; odds ratio [OR][95%CI]: 2.53 [1.40- 4.58]; p = 0.002). The median PFS was 13.4 months with olaparib and 9.2 months with chemotherapy and thus also favoured olaparib (HR[95%CI]: 0.62[0.43-0.91], p= 0.013). OS data are currently still immature. Adverse events were consistent with the established safety profiles of olaparib and chemotherapy. The authors conclude that olaparib tablets resulted in statis-

tically significant and clinically meaningful improvements in ORR and PFS as compared to nonplatinum chemotherapy in patients with germline *BRCA*-mutated platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum-based chemotherapy. Olaparib can thus provide a chemotherapy-free treatment alternative in this patient population.[7]

APIXABAN FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM ASSOCIATED WITH CANCER

The New England Journal of Medicine published the results of a multinational, randomised, open-label non-inferiority trial of apixaban and dalteparin. In total, 576 cancer patients with symptomatic or incidental acute proximal deep-vein thrombosis or pulmonary embolism were randomised to oral apixaban (10 mg, twice daily for the first seven days, followed by 5 mg twice daily) or subcutaneous dalteparin (200 IU/ kg bodyweight once daily for the first month, followed by 150 IU/kg bodyweight thereafter). In both groups, treatment was administered for six months. Objectively confirmed recurrent venous thromboembolism during the trial period occurred in 5.6% of the patients in the apixaban group and in 7.9% of the patients in the dalteparin group (HR[95%-CI]: 0.63[0.37-1.07], p< 0.001 for non-inferiority). A major bleeding was observed in 3.8% of the patients in the apixaban group and in 4.0% in the dalteparin group (HR[95%CI]: 0.82[0.40-1.69], p= 0.60). In summary, oral apixaban was non-inferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism without an increased risk of major bleedings.[8]

PATIENT-REPORTED OUTCOMES FROM THE PHASE III IMPASSION130 TRIAL OF ATEZOLIZUMAB PLUS NAB-PACLITAXEL IN METASTATIC TRIPLE-NEGATIVE BREAST CANCER

As metastatic triple negative breast cancer (mTNBC) is still incurable, providing palliation while maintaining the patients' health-related quality of life (HRQoL) is of utmost importance. In the IMpassion130 trial, patients with untreated advanced or mTNBC received atezolizumab (840 mg) or placebo every two weeks in combination with nab-paclitaxel (100 mg/m^2) on days one, eight and fifteen of each 28-day cycle until disease progression or intolerance. A recently published paper in Annals of Oncology reported patient-reported outcomes (PROs) as assessed by the 'European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire' (QLQ-C30) and its 'Breast Cancer Module' (QLQ-BR23) on day one of each cycle, at the end of treatment, and every four weeks during one year of follow-up. At baseline, 92% of the patients completed QLQ-C30 and 89% QLQ-BR23 and the completion rate remained more than 80% through cycle 20 in both the intent-to-treat (ITT) and PD-L1 positive population. In PD-L1 positive patients, no differences in median time-to-deterioration (TTD) for HRQoL (HR[95%CI]: 0.94[0.69-1.28]) or physical (HR[95%CI]: 1.02[0.76-1.37]) or role functioning (HR[95%CI]: 0.77[0.57-1.04]) were observed. Mean baseline scores for HRQoL (67.5 *vs.* 65.0), physical (82.8 *vs.* 79.4) and role functioning (73.7 *vs.* 71.7) were comparable between the atezolizumab and placebo arm, respectively, throughout the course of treatment. No clinically meaningful changes, defined as at least ten-point changes, from baseline until treatment discontinuation occurred. In addition, no clinically meaningful worsening of fatigue, diarrhoea or nausea and vomiting were observed upon the addition of atezolizumab. Of note, results in the ITT population were similar.[9] Previously, the combination of atezolizumab and nab-paclitaxel demonstrated a PFS benefit over placebo plus nab-paclitaxel as a first-line treatment for patients with PD-L1 positive mTNBC.[10] these new data underline that this delay in disease progression does not come at the cost of a compromised HRQoL.

ARCTIC: DURVALUMAB WITH OR WITHOUT TREMELIMUMAB AS THIRD-LINE OR LATER TREATMENT IN PATIENTS WITH METASTATIC NON-SMALL-CELL LUNG CANCER

The phase III, randomised, open-label ARTIC trial, assessed durvalumab with or without tremelimumab *versus* standard of care (SoC, erlotinib, gemcitabine or vinorelbine) as a third-line treatment option for patients with metastatic non-small cell lung cancer (mNSCLC). In sub-study A of the ARTIC trial, 126 patients with at least 25% of tumour cells expressing PD-L1 were randomly assigned (1:1) to durvalumab (up to twelve months 10 mg/kg every two weeks) or SoC. Study B randomised 469 patients with PD-L1 expression < 25% on tumour cells to durvalumab plus tremelimumab (twelve weeks durvalumab 20 mg/kg plus tremelimumab 1 mg/kg q4w then 34 weeks durvalumab 10 mg/kg q2w), SoC, durvalumab (up to twelve months 10 mg/kg q2w), or tremelimumab (24 weeks 10 mg/kg q4w then 24 weeks q12w) in a (3:2:2:1) ratio. In study A, durvalumab demonstrated clinically meaningful improvements in OS (11.7 *vs.* 6.8 months, HR[95%CI]: 0.63[0.42-0.93]) and PFS (3.8 *vs.* 2.2 months, HR[95%CI]: 0.71[0.49-1.04]) as compared to SoC. In study B, a median OS of 11.5 months was obtained with durvalumab plus tremelimumab *versus* 8.7 months in the SoC arm (HR[95%CI]: 0.80[0.61-1.05], p= 0.109), 10.0

months in the durvalumab arm (HR[95%CI] as compared to SoC: 0.80[0.59-1.08]) and 6.9 months (HR[95%CI] as compared to SoC: 1.02[0.71-1.46]) in the tremelimumab arm. In both the combination arm and the SoC arm, a median PFS of 3.5 months was obtained (HR[95%CI]: 0.77[0.59-1.01], p= 0.056) while this was 3.1 months in the durvalumab arm and 2.1 months in the tremelimumab arm. Treatment-related grade 3-4 adverse events occurred in 9.7% of the patients in the durvalumab arm and in 44.4% of the patients in the SoC arm of study A, and in 22.0% of the patients in the durvalumab plus tremelimumab arm and 36.4% of the patients in the SoC arm of study B. In heavily pre-treated patients with mNSCLC, durvalumab thus demonstrated clinically meaningful improvements in OS and PFS as compared to SoC in patients with PD-L1 expression levels of at least 25% on tumours cells. In patients with PL-L1 levels of less than 25%, numerical improvements in OS and PFS were observed for patients treated with durvalumab in combination with tremelimumab.[11]

EXTENDED INDUCTION CHEMOTHERAPY DOES NOT IMPROVE THE OUTCOME FOR HIGH-RISK NEUROBLASTOMA PATIENTS

The randomised open-label GPOH trial NB2004-HR was carried out in 58 hospitals in Germany and Switzerland. Eligible patients had stage 4 neuroblastoma and were aged between 1-21 years or had *MYCN*-amplified tumours and were aged between six months and 21 years. All 422 patients were randomly assigned (1:1) to standard induction therapy with six chemotherapy courses or to experimental induction chemotherapy starting with two additional courses of topotecan, cyclophosphamide and etoposide, followed by standard induction chemotherapy (eight courses in total). All of the enrolled patients also received high-dose chemotherapy with autologous haematopoietic stem cell rescue and isotretinoin for consolidation, after induction chemotherapy. Radiotherapy was applied to those patients who had active tumours at the end of induction chemotherapy. Median follow-up time of the trial was 3.32 years. At the data lock, the three-year event-free survival was 34% in the experimental arm and 32% in the control arm (p= 0.258). Similarly, the three-year overall survival of the patients did not differ between both arms (54% and 48% respectively, p= 0.558). In addition, neither the early response rates assessed after the first two courses of induction chemotherapy nor those at the completion of induction chemotherapy were different between the groups. In contrast, the median number of non-fatal toxicities per patient was higher in the experimental group as compared to the standard group (31 *vs.* 22, p< 0.001) while the median number of toxicities per treatment course was four in both arms. The authors thus conclude that their data strongly suggest that extended induction chemotherapy with topotecan, cyclophosphamide, and etoposide cannot be recommended for high-risk neuroblastoma patients.[12]

STANDARD ANTHRACYCLINE BASED VERSUS DOCETAXEL-CAPECITABINE IN EARLY HIGH CLINICAL AND/OR GENOMIC RISK BREAST CANCER

A second randomisation in the MINDACT trial compared docetaxel-capecitabine with an anthracycline-based regimen in patients with early breast cancer at high clinical but low genome risk. In total, 649 patients received anthracycline-based regimens, with or without taxanes (control) and 652 patients in the experimental arm were treated with docetaxel 75 mg/m^2 intravenously plus oral capecitabine 825 mg/m^2 two times per day for fourteen days every three weeks for six cycles. Due to a lower-than-expected accrual and event rate, DFS events (N= 148) were much less than required (N= 422). At a median follow-up of five years, DFS was not different between the experimental arm and the control arm (90.7% *vs.* 88.8%, HR[95%CI]: 0.83[0.60-1.15], p= 0.26). Overall survival (HR[95%CI]: 0.91[0.54-1.53] and DFS in the clinical high and genomic high-risk subgroup (HR[95%CI]: 0.83[0.58-1.21]) were also similar in both arms. In contrast, more grade 1 neuropathy (27.1% *vs.* 11.2%) and more grade 2 hand/foot syndrome (28.5% *vs.* 3.3%) and diarrhoea (13.7% *vs.* 5.8%) were observed in the docetaxel-capecitabine arm as compared to the control arm. Four patients in the control arm and five patients in the experimental arm had a serious cardiac event while two patients in the control arm and three in the experimental arm died due to a treatment-related event. Finally, 53 patients developed second cancers (32 in the control arm *vs.* 21 in the experimental arm). Although one has to keep in mind that the study was underpowered, this second randomisation of the MINDACT trial failed to demonstrate improved outcomes or safety benefits with the use of docetaxel-capecitabine as compared to anthracycline-based chemotherapy.[13]

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Masterclass On Site Neuroendocrine Tumours 2020

J. Blokken, PharmD, PhD[1], T. Feys, MSc, MBA[1], W. Lybaert, MD, PhD[2]

SUMMARY

On January 30-31th, 2020 the Masterclass on neuroendocrine tumours (NETs) took place in Antwerp, Belgium. This meeting was organised by NETwerk Antwerpen-Waasland (ENETS Centre of Excellence) with support from IPSEN. A broad plethora of presentations on molecular aspects, lung NETs, digestive NETs and neuroendocrine carcinomas (NECs), immunotherapy, Merkel cell carcinoma and patient-centred care were presented. This report will highlight the key messages of the symposium.

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THE CURRENT LANDSCAPE OF NEUROENDOCRINE TUMOURS

Neuroendocrine tumours (NETs) are a subgroup of endocrine tumours formed by cells of epithelial origin, presenting with structural and functional characteristics similar to those of the normal endocrine cells specialised in the production of peptide hormones and amines. All NETs have a malignant potential but, in general, they grow at a slower pace than adenocarcinomas of the gastro-intestinal tract. Most NETs are functionally inactive and thus present without a clinical syndrome. NETs usually appear in the gastro-intestinal tract, the pancreas or the lungs.[1] The incidence of NETs is increasing and is currently estimated at 6-7 per 100,000 people. As such, they represent 1-2% of all malignant cancers, making them the second most common type of GI tumours.[2] Based on mitotic count and Ki-67 index, NETs can be further classified as grade 1, 2 or 3 NETs, neuroendocrine carcinoma's (NECs) and mixed neuroendocrine–non-neuroendocrine neoplasm (MiNENs) (*Table 1*).[3] In order to select the appropriate treatment, accurate staging of the disease is of utmost importance. In this respect, ^{68}Ga-DOTATATE PET/CT imaging provides important information for accurate staging, even in the absence of biochemical evidence of disease in symptomatic patients.[4] As depicted in *Figure 1,* significant therapeutic progress has been made for patients with NETs in recent years. For example, peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-octreotate proved to be an effective treatment for patients with a somatostatin receptor-positive NET and can be repeated while maintaining an acceptable toxicity profile in patients with recurrent NETs.[5] Consensus guidelines from the European Neuroendocrine Tumour Society (ENETS) and ENETS Centres of Excellence are important in daily practice for diagnosis, treatment and follow-up of patients. *Prof. Dr. Marc Peeters, Head of NETwerk (ENETS Centre of Excellence Antwerpen-Waasland, Belgium)* finished his presentation by touching upon some ongoing clinical trials, underscoring that randomised phase III trials are also feasible in rarer cancer types such as NETs.

MOLECULAR ASPECTS OF NETS AND NECS: MOVING BEYOND HISTOLOGY

In the first presentation of this session, *Dr. Gitta Boons (University of Antwerp)* addressed the different techniques to look at molecular pathways. Gene expression is strictly regulat-

[1]Ariez International BV, Ghent, Belgium, [2]NETwerk Antwerpen-Waasland, Antwerp, Belgium.

Please send all correspondence to: T. Feys, MSc, MBA, Ariez International BV, Oude Houtlei 108A, 9000 Ghent, Belgium, tel: +32 479 567890, e-mail: t.feys@ariez.com.

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TABLE 1. Classification and grading criteria for neuroendocrine neoplasms of the gastro-intestinal tract and hepato-pancreatobiliary organs.[3]

Terminology	Differentiation	Grade	Mitotic rate* (mitoses/2 mm^2)	Ki-67 index*
NET, G1	Well differentiated	Low	<2	<3%
NET, G2		Intermediate	2–20	3–20%
NET, G3		High	>20	>20%
NEC, small-cell type (SCNEC)	Poorly differentiated	High†	>20	>20%
NEC, large-cell type (LCNEC)			>20	>20%
MiNEN	Well or poorly differentiated‡	Variable‡	Variable‡	Variable‡

LCNEC: Large-cell neuroendocrine carcinoma; MiNEN: Mixed neuroendocrine–non-neuroendocrine neoplasm; NEC: Neuroendocrine carcinoma; NET: Neuroendocrine tumour; SCNEC: Small-cell neuroendocrine carcinoma.
**Mitotic rates are to be expressed as the number of mitoses/2 mm^2 as determined by counting in 50 fields of 0.2 mm^2 (i.e. in a total area of 10 mm^2); the Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hot-spots), which are identified at scanning magnification; the final grade is based on whichever of the two proliferation indexes places the neoplasm in the higher-grade category.*
†Poorly differentiated NECs are not formally graded, but are considered high-grade by definition.
‡In most MiNENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indices in the same range as other NECs, but this conceptual category allows for the possibility that one or both components may be well differentiated; when feasible, each component should therefore be graded separately.

ed by the binding of transcription factors to their binding site on DNA, as well as by epigenetic regulation. Molecular alterations in cancer cells can thus occur at both the DNA level and the epigenetic level. These alterations can be monitored by studies in familial cases, by genetics of sporadic cases (next-generation sequencing) or by RNA analysis. As such, there is a broad range of molecular techniques that can be used and their application in NETs was discussed in the following presentations by *Dr. Timon Vandamme (University of Antwerp)* and *Dr. Hans Hofland (Erasmus MC, Rotterdam, the Netherlands)*. First, *Dr. Vandamme* discussed which pathways can become relevant in NETs and NECs. The somatostatin pathway seems to be important across all NET subtypes and somatostatin agonists proved to be an effective treatment option in most NET subtypes. However, a pitfall in targeting this pathway consists of receptor internalisation, which might explain low overall response rates and treatment failures. In addition, also the *MEN1* and *ATRX/DAXX* genes and elements of the PI3K-AKT-mTOR signalling pathway are commonly mutated in patients with pancreatic NETs. So far, however, only mTOR proved to be a targetable pathway.[6] Everolimus, a first-generation mTOR inhibitor, induced a significant progression-free survival benefit in advanced gastroenteropancreatic NETs, but resistance regularly occurs.[7]

In a last presentation of this session, *Dr. Hofland* addressed biomarkers in NETs. Unfortunately, the median time to a diagnosis is 24 months in patients with pancreatic NETs and even mounts to 36 months in case of small bowel NETs. In general, patients are seen seven to eight times by a general practitioner or specialist before a diagnosis is made. In NETs, histology remains the central pillar in the diagnostic work-up and there is a lack of diagnostic and predictive biochemical biomarkers.[8] In contrast, there is a plethora of poorly validated prognostic biomarkers such as chromogranin A, neurokinin A, ectopic hormones, *etc.* Excellent imaging biomarkers exist and together with modern scanning techniques these markedly expanded the options for clinicians dealing with NETs.[9] A further understanding of molecular drivers is however still needed to discover novel biomarkers for NETs.

LUNG NETS: COPYING THE DIGESTIVE NET ALGORITHM FOR DIAGNOSTICS AND THERAPEUTICS?

In lung cancer, around 75% of the tumours are classified as non-small cell lung cancer while the remaining 25% are lung neuroendocrine neoplasms (NENs). As depicted in *Figure 2*, these lung NENs can be further subdivided in tumours of low grade (with typical carcinoids and atypical carcinoids) and

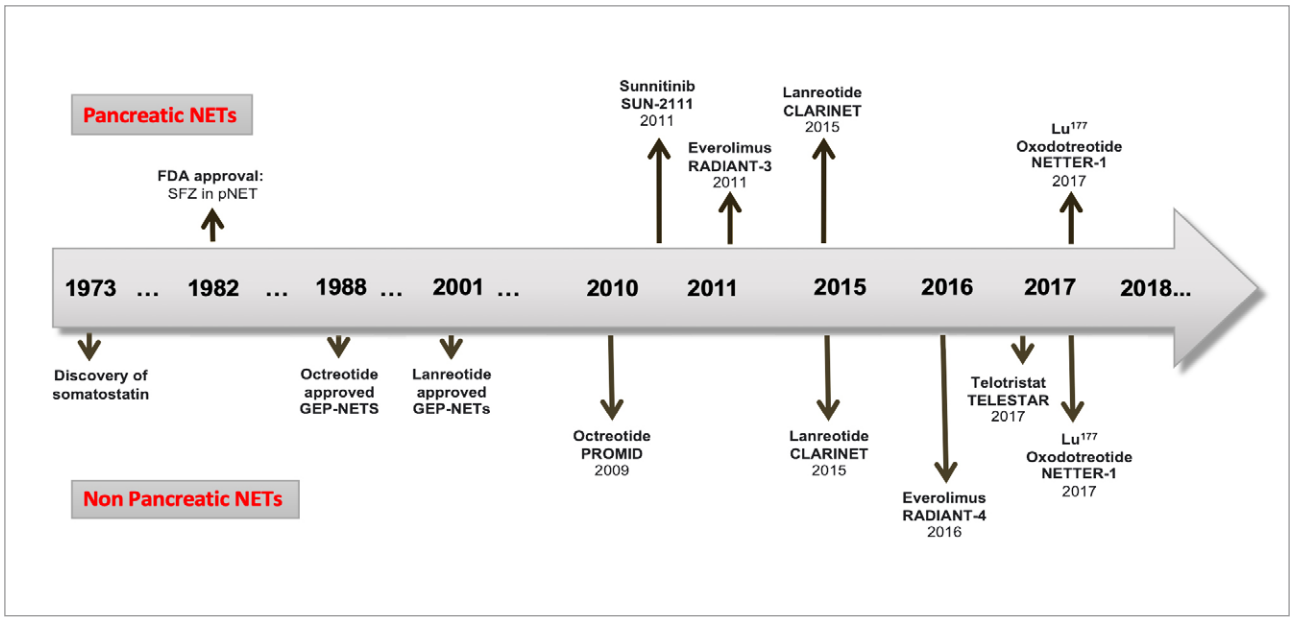

FIGURE 1. Therapeutic progress in neuroendocrine tumours.[30]

the far more prevalent high grade tumours (with large cell neuroendocrine carcinomas and small cell carcinomas).[10] As such, lung NETs make up a heterogeneous group of diseases that require a multidisciplinary treatment approach. When the disease is still resectable, complete surgery must be performed. Up till now, everolimus is the only approved drug for the treatment of neuroendocrine tumours originating in the lungs when the cancer cells are well-differentiated and the cancer is metastatic or cannot be removed by surgery.[11] This EMA-approval was based on results of the phase III RADIANT-4 trial in which treatment with everolimus was associated with a significant improvement in PFS in patients with progressive lung or gastrointestinal NETs.[12] According to *Dr. Francesca Spada (European Institute of Oncology, Milano, Italy),* in the future, chemotherapy, PRRT and other TKIs might also play a role in the treatment of lung NETs.

DIGESTIVE NETS AND NECS: WHICH TREATMENT ALGORITHM TO USE IN 2020?

Grade 3 neuroendocrine neoplasms are a heterogeneous group of diseases that can be further divided into NECs and grade 3 NETs. Although NECs can be successfully treated with a combination of platinum and etoposide in first-line, there are currently no validated second-line treatment options for these patients.[13-14] These tumours should be treated based on Ki-67 levels and also PRRT can be of use in this setting. For grade 3 NETs, no standard treatment exists. These tumours do not respond well to platinum-etoposide chemotherapy, but could be treated by targeted therapies and grade 2-type chemotherapy.[15-17] As a closure of his presentation, *Dr. Ivan Borbath (UCL Cliniques Universitaires Saint-Luc, Brussels)* encouraged everyone to add patients to the DNET registry to gather more information on digestive NETs. Next, *Dr. Francesca Spada (European Institute of Oncology, Milano, Italy)* shared her critical view on the uncertainties in the treatment of digestive NETs/NECs. She agrees with *Dr. Borbath* that there is currently no validated, universally supported therapeutic sequence for patients with NENs. An ideal therapeutic strategy depends on patients and disease factors as well as on early and late objectives. Furthermore, a multidisciplinary approach is highly recommended, and should preferably involve dedicated NET centres (particularly in the beginning).

IMMUNOTHERAPY LOOKING FOR ITS PLACE IN THE NEUROENDOCRINE FIELD

During her talk, *Prof. Evelien Smits (University Hospital Antwerp)* addressed the potential of immunotherapy with PD-(L)1 targeting to CAR T-cells in NETs. In recent years, immunotherapy has gained momentum and by now several PD-1 blocking antibodies (pembrolizumab, nivolumab) and PD-L1 blocking antibodies (atezolizumab, durvalumab, avelumab) are approved for the treatment of various cancer types. Despite the amazing responses that can be obtained with immune checkpoint inhibitors, several cancer types are resistant, and a significant percentage of patients does not respond to therapy. The question even though remains on how to overcome this resistance. On the other hand, CAR T-cell therapy with tisagenlecleucel and axicabtagene ciloleucel has been approved for some specific types of blood cancer, but

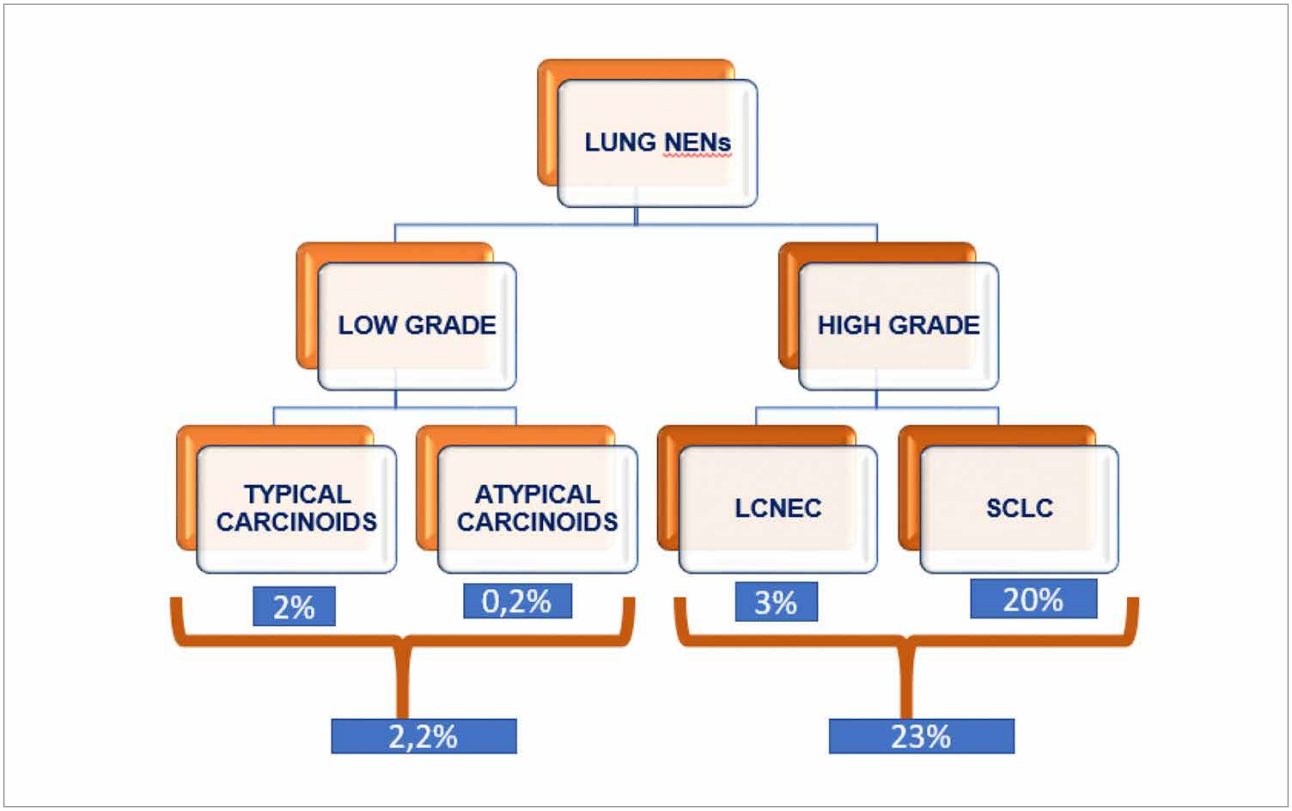

FIGURE 2. Frequency and terminology of lung NENs.

so far not in solid tumours.[18,19] Currently, CAR T-cells and CAR NK cells are also under investigation in solid tumours, but optimal target selection and immunosuppression of the microenvironment pose important challenges. In addition, possible infections, acute cytokine release syndrome, autoimmune complications and off-target toxicities also need to be considered when thinking about CAR T-cell therapy. For the future, *Prof. Smits* predicts a shift towards combination therapies (*i.e.* combining different immunotherapeutic strategies as well as combining immunotherapy with other therapeutic strategies) and highlights that we need to identify predictive biomarkers and markers to monitor treatment response. *Prof. Jeroen Dekervel (University Hospital Leuven)* further elaborated on this topic during his presentation on immunotherapy in NETs and NECs. He stressed that well-differentiated NETs are "cold" tumours with a low tumour mutational burden (TMB) and low levels of tumour infiltrating lymphocytes. Poorly-differentiated NECs on the other hand have a higher TMB and are, at least theoretically, better candidates for immune checkpoint inhibition (ICI).[3] However, so far clinical trials have shown very limited activity of ICI monotherapy in both NETs and NECs. Therefore, *Prof. Dekervel* recommends to further explore dual ICI treatment or combinations of an ICI with for example anti-angiogenic tyrosine kinase inhibitors or PRRT.

FROM OLD FRIENDS TO NEW ALLIES IN MERKEL CELL CARCINOMA TREATMENT

Merkel cell carcinoma (MCC) is a rare, aggressive and frequently recurring skin cancer that predominantly affects older males with fair skin. MCC usually appears as a single painless lump on sun-exposed skin, especially on the head and neck, arms, legs and trunk. Several factors have been associated with the development of MCC, including infection with the Merkel cell polyomavirus (MCPyV), exposure to UV radiation, other malignancies and immunosuppression.[20] *Prof. Vibeke Kruse (University Hospital Ghent)* shared a reminder with the audience to remember the features that raise the clinical suspicion of MCC: "*The acronym AEIOU stands for asymptomatic, expanding rapidly (significant growth in ≤ three months), immune suppression, older than 50 years and UV-exposed area in a fair-skinned individual. The presence of at least three of the features below increase the clinical suspicion of MCC.*" However, a biopsy with a subsequent histological examination remains necessary to establish the diagnosis and to differentiate from other malignant lesions that can closely mimic MCC (*e.g.* basal and squamous cell carcinoma).[21] There is a clear unmet need for new treatment options for metastatic MCC. Several observations predicted that immunotherapy would be effective in MCC. For example, cases of spontaneous tumour remissions were documented, there is

an increased incidence of MCC in immune-suppressed patients and both virus-induced (80%) and UV radiation-induced (20%) MCC can be immunogenic. Despite molecular differences, virus-positive and -negative MCC are almost indistinguishable in their response to immune checkpoint inhibitors.[22] Avelumab was the first EMA-approved immunotherapeutic drug for the treatment of MCC. Other immune checkpoint inhibitors are currently under evaluation.[23]

PATIENT-CENTRED CARE IN NET: UNITING ALL STAKEHOLDERS

As addressed by *Prof. Karen Geboes (University Hospital Ghent)*, a first priority in treating NETs should be to keep patients comfortable. Unfortunately, a proportion of patients with NETs present with carcinoid syndrome symptoms that are characterised by diarrhoea, frequent bowel movements, flushing and /or wheezing. As carcinoid syndrome is driven by an excessive serotonin production of functioning carcinoid NETs, telotristat etiprate (250 mg 3x daily) can relieve the patient's symptoms. Telotristat etiprate blocks the binding of tryptophan to tryptophan hydroxylase, resulting in a reduced serotonin production. Telotristat etiprate has demonstrated to be effective in reducing hormonal symptoms related to carcinoid syndrome and so far has proven to be safe. However, one has to be cautious for symptoms of depression and elevations in hepatic enzymes. In addition, telotristat etiprate may also play a role in diminishing carcinoid heart disease and mesenterial fibrosis, but more research is needed on this matter.[24]

In a next presentation, *Michaël Sels (University Hospital Antwerp)* discussed the evolving story of nutritional support for patients with NET/NEC disease. He stressed that nutritional advice in cancer prevention is not the same as nutritional advice during therapy. For cancer prevention, it is recommended to be active and eat smart (healthy weight, a diet rich in wholegrains, vegetables, fruits and beans, limited alcohol consumption, limited red and processed meat, *etc.*) However, during cancer treatment the focus should be on adequate energy and protein intake.[25] In this respect, not only weight loss, but also muscle loss should be prevented since this is associated with decreased chemotherapy efficacy, increased chemotherapy toxicity, a poor quality of life and reduced survival.[26] By focusing on nutritional interventions such as determining the nutritional needs, counselling for problems and an enrichment of oral nutrition, the addition of oral nutritional supplements to the diet and the necessity of enteral or parenteral nutrition can be avoided. Digital apps can also be used to closely monitor the patient and his dietary habits. Next, *Mieke Maesschalck (Sint-Elisabeth Hospital Zottegem)* and *Eva Pape (University Hospital Ghent)* shared their experiences on how a digestive onco-coach can help patients and physicians at diagnosis and during examinations and treatment. A clinical nurse specialist or consultant can play a key role and supports patients through a complex illness trajectory and provides a consistent single point of contact.[27]

In the final lecture of this session, *Dirk Van Genechten (VZW NET & MEN)* stated that patient advocacies can be valuable for patients, health care practitioners and the pharma industry, provided they have a vision and a mission and are managed properly. This may require professional help to run the organisation, but patient advocacies should be cautious not to lose focus: "*when and where possible, patients should be in charge*".

DIGESTING ALL THINGS DIGESTIVE BY AN EXPERT NET SURGEON

The management of NETs is a multidisciplinary effort. The European Neuroendocrine Tumour Society (ENETS) published guidelines for the diagnosis and treatment of each NET subtype.[28] Surgery, if necessary, should be performed as sparing as possible and different surgical strategies and their specific pros and cons should be evaluated carefully. As stated by *Dr. Geert Roeyen (Antwerp University Hospital): "Surgeons often face a dilemma when they have to choose between minimal invasive surgery and pancreatic preserving surgery."* In case of more advanced surgery (*e.g.* liver transplantation), adequate patient selection is crucial. Liver transplantation is generally not recommended in advanced NEN, but may be an option in carcinoid syndrome, functional NET and extended liver disease or in patients who are refractory to multiple systemic treatments.[29] Finally, it is still unclear whether PRRT or systemic therapies have a place in the neoadjuvant setting.

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The 22nd annual BSMO meeting 2020

J. Blokken, PharmD, PhD, T. Feys, MSc, MBA

SUMMARY

On the 14th and 15th of February 2020, the Belgian Society of Medical Oncology (BSMO) organised the 22nd annual BSMO meeting in Ghent. At this meeting, medical oncologists, oncologists in training and other specialists involved in the management of cancer patients again had the opportunity to gather as a community, exchange ideas and engage in cooperation.

(BELG J MED ONCOL 2020;14(4):171-7)

BREAST CANCER TASK FORCE

Optimal adjuvant endocrine treatment in premenopausal patients with HR+/HER2- breast cancer (*Francois Duhoux, UC Louvain)*

For a long time, the standard adjuvant endocrine treatment for premenopausal patients with HR+/HER2- breast cancer consisted of five years of tamoxifen. This treatment proved to be safe and significantly reduced the fifteen-year risks of breast cancer recurrence and death.[1] However, also patients who received five years of tamoxifen remain at an increased risk of breast cancer recurrence. To address this, several studies looked into the effect of an additional five years of tamoxifen treatment. The benefit of extended tamoxifen therapy was demonstrated in both the ATLAS study and the aTTOM trial.[2,3] The clinical treatment score post-five years (CTS5) can be used to make an estimation of the residual risk of distant relapse after five years of endocrine treatment. If the score is below 1% per-year risk of distant relapse, there is limited potential value of extended endocrine therapy.[4] However, it is important to note that this score was validated in datasets of ATAC and BIG 1-98, which are two postmenopausal studies. In the SOFT (suppression of ovarian function trial) and TEXT (tamoxifen and exemestane trial) trials, the combination of an aromatase inhibitor and ovarian function suppression (OFS) was evaluated in premenopausal women with breast cancer. A combined analysis of both studies revealed that the addition of OFS to either tamoxifen or exemestane resulted in a significantly higher eight-year overall (OS) and disease-free survival (DFS) rate.[5] Of note, this benefit was most pronounced in patients who were previously exposed to chemotherapy. Compared to tamoxifen alone, the combination of exemestane and OFS also resulted in a significantly higher rate of distant-metastasis-free survival at eight years (91.2% *vs.* 88.4%; HR[95%CI]: 0.73[0.55-0.96]; no significant difference between tamoxifen and tamoxifen + OFS [89.4%]).[5] A specific analysis of the SOFT trial in patients below 35 years of age revealed that the exemestane + OFS seemed to provide particular clinical benefit in this subgroup of patients. In fact, in this analysis, the eight-year breast-cancer free survival was 80% with exemestane + OFS *vs.* 74.6% and 64.9% for tamoxifen + OFS and tamoxifen alone, respectively. A similar observation was made in terms of the eight-year distant metastasis free survival (82.4%, 77.5% and 73.8% respectively).[6] As such, these findings support the recommendation to

Ariez International BV, Ghent, Belgium.

Please send all correspondence to: T. Feys, MSc, MBA, Ariez International BV, Oude Houtlei 108A, 9000 Ghent, Belgium, tel: +32 (0)479 567890, email: t.feys@ariez.com.

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Keywords: breast cancer, cancer survivorship, cardio-oncology, genomic profiling, haematology, hepato-cellular carcinoma, hereditary cancer syndromes, next-generation sequencing, onco-geriatrics, precision trials, quality, sarcoma, squamous cell carcinoma of the head and neck, supportive care, urology.

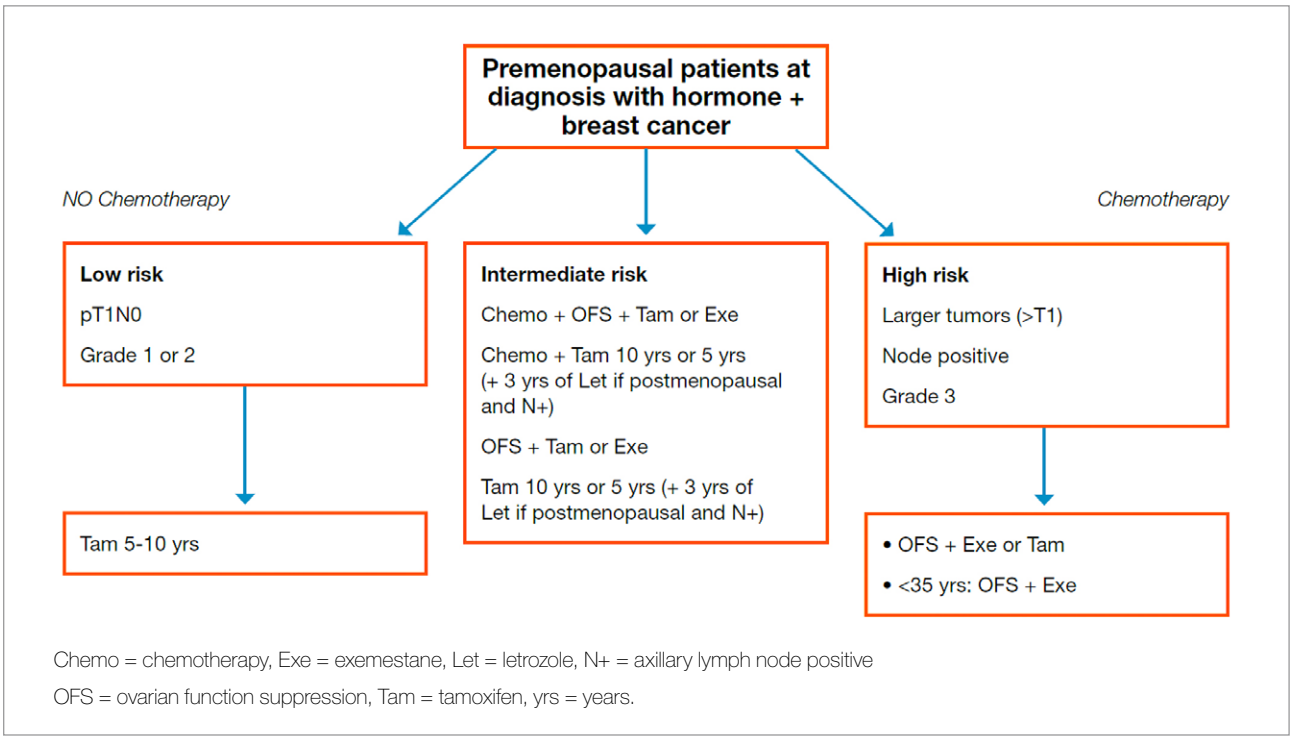

FIGURE 1. Treatment guidelines for the management of adjuvant endocrine therapy for premenopausal women.[8]

use exemestane + OFS in this setting. Of note, when opting for OFS it is important to take the additional potential side effects (*e.g.* hot flashes, sweating, reduced libido, insomnia, *etc.*) into consideration.[7]

Also when discussing the choice between endocrine therapy and chemotherapy, quality of life needs to be considered. In fact, data from the CANTO trial demonstrate that endocrine therapy had a persistent negative impact on quality of life, while this was not the case for chemotherapy. Importantly, however, this effect was only seen in postmenopausal patients. In premenopausal patients, the effect of endocrine therapy alone on quality of life was limited, while chemotherapy had a significant detrimental effect. *Prof Duhoux* ended his presentation with a schematic representation of the current treatment guidelines for the management of adjuvant endocrine therapy for premenopausal women (*Figure 1*).[8]

Neoadjuvant treatment considerations in HER2-positive breast cancer (*Evandro De Azambuja, Institut Jules Bordet*)

Neoadjuvant treatment of breast cancer can be advantageous and allows the *in vivo* assessment of response, tumour downstaging and more conservative surgeries, the early treatment of micro-metastases and tailoring of post-neoadjuvant treatment.[9] In patients with HER2-positive breast cancer, the pathological complete response rate (pCR) is very important since an incremental gain in pCR can be used as a surrogate outcome for event-free survival (EFS) and OS.[10] In HER2-positive breast cancer, continuous improvements in patient outcomes have been made over the past years with treatment escalation from chemotherapy to chemotherapy plus trastuzumab, chemotherapy plus dual HER2 targeting (trastuzumab and pertuzumab) or trastuzumab followed by neratinib and trastuzumab-emtansine for residual disease. However, there are prohibitive costs of cancer therapies and a lack of biomarkers to select patients who are most likely to benefit from a given therapy. In addition, unnecessary toxicities associated with treatment escalation can sometimes be avoided. Therefore, patient selection is crucial. However, when considering treatment de-escalation, caution is warranted since treatment outcomes and efficacy may not be compromised. There are many opportunities in de-escalating therapies but the challenge is to find the right population and the best strategy. Therefore, several de-escalation trials (PAMELA, PerELISA, TBCR006, *etc.*) in HR+/HER2 negative early breast cancer are initiated. Also a response-adapted de-escalation (PHERGain) trial and imaged-guided de-escalation of neoadjuvant chemotherapy (TRAIN-3) study are ongoing. In addition, there is an urgent need for biomarkers to identify those patients that require more or less treatment.[9]

Gene expression profiling in early breast cancer in the context of the Belgian pilot project (*Donatienne Taylor, CHU UCL Namur*)

The Belgian gene expression profiling pilot study by the

RIZIV/INAMI was written in the spirit of the Mindact trial where genomic expression profiling (GEP) aims at determining the patients in whom adjuvant chemotherapy can be safely avoided. Results of the trial demonstrated that GEP could predict a poor benefit of chemotherapy in 46% of high-risk patients.[11] As the Mindact results are not strictly applicable to the Belgian population, there is a need for more information and therefore, the Belgian pilot study was initiated. Over a time-period of three years, each year 1,442 tests (Oncotype DX or Mammaprint) will be reimbursed by RIZIV/INAMI and the number of tests that will be allocated to each breast clinic is based on the number of breast cancers that were registered in the last three years. The target population of the pilot study consists of patients with early breast cancer at first diagnosis with a maximum of three affected lymph nodes and a tumour size of no more than 5 cm. Importantly, Mammaprint and Oncotype differ in their characteristics and in the trials that validated them. In fact, Mammaprint is a Negative Predictive Test in high clinical risk patients and cannot be used as a positive predictive test in low clinical risk patients while Oncotype has prognostic and predictive value in node negative patients. The main goal of the project is to gather more information on what criteria are used by the multidisciplinary oncological consult (MOC) to decide for adjuvant chemotherapy. In addition, the project will address practical aspects of using GEP in the daily routine and will likely answer many other questions (*e.g.* how often is the MOC decision modified by GEP results?; how does the GEP changes the patient's decision to undergo chemotherapy?; What are the potential cost reductions linked to the reduction of chemotherapy use?) In order to get an answer to these important questions, careful data registering is of utmost importance. It is also important to keep in mind that clinico-pathological factors and gene signatures have independent prognostic values and should be used in combination. Finally, the decision to receive or forgo chemotherapy (or any other treatment) lies with each patient who is properly informed about the potential side effects and the potential benefits of such treatment. For the same risk–benefit scenario, different patients may make different decisions.[12]

NEWS IN SPECIFIC AREAS

Geriatric oncology: an update *(Lore Decoster, UZ Brussel)*

Data indicate that 44% of new cancer cases are diagnosed in patients above 70 years old. Given the increasing age of our population, there is a rising incidence of older patients with cancer.[13] This older population poses several treatment challenges as this group is often excluded from clinical trials because of rigid in- and exclusion criteria or a low performance status.[14] In addition, older patients may respond differently to treatment because of differences in pharmacokinetics or –dynamics, the presence of comorbidities and interactions with concomitant medications. Moreover, there is a big heterogeneity between patients with respect to their performance status (fit *vs.* frail), life expectancy, quality of life and preferences. In order to improve the quality of care for older patients with cancer, the integration of a comprehensive geriatric assessment (CGA) in daily oncology practice can be crucial. This CGA aims to identify patients who can benefit from CGA by screening tools, to assess these patients, develop recommendations for interventions, implement these interventions in a care plan and provide follow-up and adjustments to the care plan with repeated geriatric assessments.[15] Finally, the international society of geriatric oncology (SIOG) focuses on strengthening the health care workforce for older people living with cancer. Therefore, the SIOG provides several training programs and educational activities, develops models and guidelines for the optimal treatment of older patients with cancer, establishes centres of excellence in geriatric oncology, aims to improve the relevance of clinical trials and invests in collaborations and different partnerships.

Head and neck cancer *(Willem Lybaert, AZ Nikolaas, AZ Lokeren, UZA)*

As the incidence of human papillomavirus (HPV)-positive oropharyngeal cancer is increasing, the De-ESCALaTE HPV trial assessed the safety of cetuximab as a de-escalation regimen in this setting to reduce the toxicity of standard cisplatin treatment. Unfortunately, cetuximab did not show benefit in terms of reduced toxicity but was associated with a significant decrease in two-year overall survival (p= 0.001) and two-year recurrence (p= 0.0007).[16] Also in the RTOG 1016 trial, radiotherapy plus cetuximab showed inferior OS and PFS as compared to radiotherapy plus cisplatin while the proportions of overall moderate to severe acute and late toxicity were similar between both treatment groups. Therefore, cisplatin in combination with radiotherapy remains the standard of care for patients with HPV-positive, low-risk patients.[17]

In the relapsed and metastasised setting of untreated squamous cell carcinoma of the head and neck (R/M SCCHN), the EXTREME regimen has long been a trusted and approved standard of care. The addition of cetuximab to platinum-based chemotherapy plus fluorouracil significantly improved the median OS (from 7.4 months to 10.1 months, p= 0.04) and median PFS (from 3.3 months to 5.6 months, p < 0.001).[18] However, nowadays we are witnessing a shift towards immunotherapy. In the second-line treatment of R/M SCCHN, the CheckMate 141 trial was the first to demonstrate a significant improvement in survival with the checkpoint

inhibitor nivolumab in patients who progress after platinum-based therapy in a global, phase III comparative trial. Nivolumab doubled the one-year OS rate from 17% with investigator's choice therapy to 36%. In addition, there were fewer treatment-related adverse events and nivolumab also stabilised patient-reported outcome measurements (in contrast, investigator's choice therapy resulted in meaningful declines in function and worsening of symptoms). Therefore, nivolumab is a new standard-of-care option for patients with R/M SCCHN after platinum-based therapy.[19] In addition, the Keynote-040 study supported the use of pembrolizumab as monotherapy and as part of combination therapy in earlier stages of disease.[20]

Also in the first-line treatment of R/M SCCHN, immunotherapy is gaining momentum. The Keynote-048 trial demonstrated that pembrolizumab plus platinum and 5-fluorouracil is an appropriate first-line treatment for patients with R/M SCCHN. In addition, data of the Keynote-048 trial support the use of pembrolizumab monotherapy as a new first-line standard-of-care for R/M SCCHN PD-L1 positive patients.[21]

Systemic treatment of hepatocellular carcinoma *(Ivan Borbath, UCLouvain)*

For a long time, sorafenib was the standard of care in the treatment of hepatocellular carcinoma (HCC) because it consistently increased OS in different patient populations, across geographical regions, and etiologies.[22,23] After a long list of failed first-line phase III trials with sunitinib, brivanib, erlotinib, linifanib, *etc.*, a global, randomised, open-label phase III study could demonstrate that the median OS for lenvatinib of 13.6 months was non-inferior to the 12.3 months with sorafenib in untreated advanced HCC patients (HR[95%CI]: 0.92[0.79-1.06]).[24] In the second-line setting, regorafenib is the only systemic treatment that showed an improved survival benefit in HCC patients who progressed on sorafenib treatment. The median OS was 10.6 months, as compared to 7.8 months with placebo (HR[95%CI]: 0.63[0.50-0.79], p < 0.001).[25] Other drugs (brivanib, everolimus, ramucirumab, tivantinib) could not demonstrate a significant survival benefit as compared to placebo. Among patients with previously treated advanced HCC, treatment with cabozantinib resulted in longer OS (p= 0.0049) and PFS (p < 0.0001) than placebo.[26] In addition, for patients with advanced HCC and increased α-fetoprotein levels (≥400 ng/ml) who had previously received sorafenib, the REACH-2 trial could demonstrate that ramucirumab significantly improved OS as compared to placebo (p = 0.0002).[27]

With respect to immune checkpoint inhibitors, nivolumab did not meet its predefined threshold of statistical significance for OS (median OS of 16.4 months for nivolumab as compared to 14.7 months with sorafenib), although nivolumab demonstrated a clinical benefit in the first-line treatment of patients with advanced HCC.[28] Also pembrolizumab in patients with HCC who progressed on (or were intolerant to) sorafenib failed to reach the prespecified levels of statistical significance for OS and PFS although it reached a significantly higher ORR as compared to placebo (18.3% *vs.* 4.4%, p = 0.00007).[29] Impressive results did come from a study evaluating a combination of atezolizumab and bevacizumab in the frontline treatment of patients with unresectable HCC. In this trial, the experimental combination induced a significant OS and PFS benefit compared to sorafenib.[30] When confirmed, this combination could well become a new standard in the frontline treatment of patients with advanced HCC.

In conclusion, HCC is a unique and hard to treat disease where transplantation is the only available cure. For a long time, HCC was an oncological desert but currently there are six treatment options available (sorafenib, lenvatinib and atezolizumab+bevacizumab in first-line and regorafenib, cabozantinib and ramucirumab in second-line) with potentially more to come.

Cardio-oncology *(Marie Moonen, CHU de Liège)*

Advances in cancer treatment have led to an improved survival of patients with cancer but also comes at the cost of an increased morbidity and mortality due to treatment side effects. Among cancer survivors, cardiovascular diseases (CVD) and second neoplasms are the main cause of death. Cardiac toxicity of anti-cancer agents may involve direct effects of the cancer treatment on heart function and structure or may be the result of an accelerated development of CVD, especially in the presence of traditional cardiovascular risk factors.[31] Although the field of cardio-oncology has received increasing attention in recent years, it still remains a very complex issue as there is an increasing number of anti-cancer drugs with potent, and sometimes unexpected, cardiac toxicity, diverse toxic mechanisms, the time point by which cardiotoxicity becomes clinically manifest can vary substantially and there can be irreversible damage or transient cardiac dysfunction. As published by *Armenian et al.*, several patient groups with cancer have an increased risk for developing cardiac dysfunction: those treated with high-dose anthracycline, high-dose radiation-therapy (> 30 Gy) when the heart is in the treatment field, lower-dose anthracycline in combination with lower-dose RT, lower-dose anthracycline or trastuzumab alone and the presence of additional risk factors and sequential therapy (lower-dose anthracycline followed by trastuzumab).[32] In addition, 0.27-1.14% of patients on immune checkpoint inhibitors experience cardiovascular toxicities and the burden of this complication is growing due

to the increased number of immune checkpoint inhibitors prescriptions and indications and the greater awareness.[33] In order to ensure the best cancer and cardiovascular treatment, oncologists and cardiologists should work together as a team. Therefore, the Belgian Cardio-Oncology Council, a constituent body of the Belgian Society of Cardiology, was founded to encourage research, training and education and discuss complex patient' cases.

GENERAL SESSION

Haematology for the medical oncologist *(Stef Meers, AZ Klina)*

Since 2002, the frontline treatment of diffuse large B-cell lymphoma consists of CHOP plus rituximab and limited progress was made since then. While this frontline treatment is very effective, still around 40% of patients will relapse. For these patients, platinum-based salvage treatment followed by autologous stem cell transplantation can be a curative treatment. In third line, a treatment with CAR-T cells can be considered.

For chronic lymphocytic leukaemia (CLL), the frontline treatment depends on the patient's fitness for fludarabine and the presence or absence of del(17p) and *TP53* mutations. In the relapsed/refractory setting, the treatment choice depends on the duration of response, presence of del(17p) and TP53 mutations and the treatment-free interval.

The frontline treatment for fit patients with multiple myeloma consists of remission induction with a triplet or quadruplet regimen followed by stem cell transplantation and post-transplant lenalidomide maintenance treatment. For unfit patients, bortezomib-based, lenalidomide-based or thalidomide-based regimens or an alkylator plus steroid can be used.[34] More recently, results from the POLLUX and CASTOR trials demonstrated a significant PFS benefit with daratumumab-based regimens and these regimens will likely become the new standard in first line.[35-36] In the relapsed/refractory setting, treatment depends on age, performance status, comorbidities and the previously received treatment. The incidence of haematological cancers increases with age and these cancers are often associated with recurrent somatic mutations in specific genes. In 2014, *Jaiswal et al.* could demonstrate that age-related clonal haematopoiesis is a common condition that is associated with an increased risk of hematologic cancer and all-cause mortality, with the latter possibly due to an increased risk of cardiovascular disease.[37]

Next-generation sequencing *(Kathleen Claes and Joni Van Der Meulen, UZ Ghent)*

In a first part of this presentation, *Kathleen Claes* discussed incidental findings and genetic predisposition. As there is a substantial burden of germline variants across a range of tumour histologies, patients should ideally be informed, prior to the request of genetic tumour testing, about the potentially revealing data that might be found. These data might not only be relevant for their personal lives but may also affect their relatives. Due to the clonal nature of germline alterations, they can be considered as ideal predictive biomarkers and the demand for germline testing and its subsequent clinical interpretation will most likely increase in the future. However, the interpretation of these germline variants may be complex. For example, variants may reach a threshold for clinical relevance for therapy but not for risk management. Also in case of clonal haematopoiesis and postzygotic mosaicism, caution is warranted in the interpretation of NGS assays in order to provide adequate therapeutic and genetic counselling to individual patients. Finally, multidisciplinary tumour boards are the ideal forum to discuss the management of these, sometime challenging, cases.[38]

In a second presentation, *Joni Van der Meulen* addressed the molecular profiling of solid tumours and haematological malignancies using targeted sequencing. The first step in the next-generation sequencing workflow is the DNA extraction and quality control of the DNA. Subsequently, the SeqCap library should be prepared. First, an enzymatic fragmentation of the DNA is performed, followed by the ligation of adaptors with unique dual indexes, different for each patient sample. In a next step, there will be a hybridisation of biotinylated probes for genes of interest. In solid tumours, this will be a gene panel of 69 genes while there is a panel of 64 genes in the haemato-onco tumour panel. These biotinylated probe-bound DNA fragments are then purified with streptavidin-coated beads and amplified. After the library preparation, Illumina sequencing is performed and a NGS data-analysis has to be performed. NGS can detect substitutions, deletions, insertions and copy number variants based on coverage but cannot detect gene fusions. In a final step, somatic variants will be classified into five classes: pathogenic, likely pathogenic, variant of unknown significance (VUS), likely benign and benign. Pathogenic variants, likely pathogenic variants and VUS will be reported to the clinician. In Belgium, the RIZIV/INAMI will reimburse an extra fee for NGS tests in a selection of solid tumours (350 euro) to labs and hospitals that are part of the NGS network.[39]

KEYNOTE LECTURE

Genomics to unravel tumour progression and treatment resistance *(Christine Desmedt, UZ Leuven)*

Research autopsy is a post-mortem medical procedure performed on a deceased individual with the primary goal of collecting tissue to support basic and translational research.

For patients, research autopsy is better defined as 'tissue donation'. Unfortunately, research autopsies are not always easy. In addition to obvious ethical and legal issues, it also requires a scientific infrastructure, a multidisciplinary program coordination, clinical support, *etc.* Several autopsy programs already exist for several cancer types. Also the KULeuven has its own 'UZ/KULeuven program for post-mortem tissue donation to enhance research' (UPTIDER). In addition, phylogenetics can help us to reconstruct the evolutionary trajectory of the disease. This does not mean that all genetic alterations do have a causal role in cancer development and progression, but these genomic alterations can provide a useful record of the events that occurred. One or more successful seeding events can occur from the primary tumour and monoclonal or polyclonal seedings and cross-seedings between established metastases are possible.

The MSK-IMPACT initiative is a large-scale (more than 10,000 patients with advanced cancer), prospective clinical sequencing initiative which compiled tumour and matched normal sequence data. By using these data, clinically relevant somatic mutations, novel noncoding alterations and mutational signatures of common and rare tumour types were identified.[40] The 'count me in' initiative is a patient-partnered research form that is changing the future of cancer. In this project, patients can fill in an online form to tell about themselves and their cancer and can give permission to researchers to collect stored tumour tissue and the patient's medical records. Throughout the project, patients will be given updates about the status of the project and the discoveries that have been made.[41] Although autopsies and tissue donation programs have the potential to answer specific questions on tumour evolution, treatment resistance mechanisms, *etc.* genomics are only one piece of the puzzle to understand cancer progression and treatment resistance.

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