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BELGIAN JOURNAL OF MEDICAL ONCOLOGY

J. DE GRÈVE

DEAR COLLEAGUES,

In this issue, the management of **malignant bowel obstruction** is reviewed. Bowel (sub)obstruction severely downgrades the quality of life and should be managed and relieved as much as possible, even in end-stage disease. Surgery remains one of the options to be considered, also for patients with annoying sub-obstructive symptoms.

The Pharmacotherapy section reports on the drastic effects of three newer anti-androgen drugs on the metastasis-free survival of **locoregional castration-resistant prostate cancer**, with one of them having less toxicity and survival improvement.

The Oncocase provides yet another example of the erratic metastatic behavior of **lobular breast cancer.**

The Oncothesis examines **HER2-positive gastro-oesophageal cancer**, trastuzumab treatment, and secondary resistance.

The Highlights of the **Gastrointestinal Cancers Symposium 2019** (San Francisco) focusses on the progress in immunotherapy and genomic profiling.

Durvalumab in NSCLC and **liposomal irinotecan** in pancreatic cancer are the most recent reimbursed drugs.

Finally, I would like to call upon you to continue lobbying for broader use of **genomics** in cancer, both somatic and germline. **Somatic NGS** is introduced with the upcoming convention but should be broadened in scope, become agnostic and also include genes that identify patients for clinical trials running in Belgium or off-label access. One of the ways to go is to centralise the sophisticated diagnostics needed in platforms that are capable of implementing the various technologies in high quality and most cost-effective way. Today Belgium is lagging severely behind other countries in the reimbursement level of NGS. The broad professional co-operation very well co-ordinated by Sciensano is there while the allocated budget is insufficient.

For the **germline testing,** the time has arrived to turn genetic testing predictive for high cancer risk from a diagnostic into a life-saving preventive tool. For example, to prevent 250-500 breast cancer deaths per year. Belgium could be the global front runner showing the way to go. Why not? The citizens at least support the idea, what about the professionals?

We wish you an enjoyable read,

Jacques De Grève, MD, PhD

Management of end-stage malignant bowel obstruction: an evidence-based review for clinical practice

Q. Binet, MD, L. Duck, MD

SUMMARY

Malignant bowel obstruction is the clinical and imaging evidence of bowel obstruction beyond the ligament of Treitz in the setting of an incurable cancer with intraperitoneal spread. A multi-detector computed tomography scan with multiplanar reconstructions is the gold standard for diagnosis confirmation and treatment orientation. Treatment is challenging and can either be surgical, endoscopic or most likely medical. In the following manuscript, we discuss the current place of each treatment modality in end-stage malignant bowel obstruction management.

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INTRODUCTION

Malignant bowel obstruction (MBO) is described as the clinical and imaging evidence of bowel obstruction beyond the ligament of Treitz in the setting of an incurable cancer with intraperitoneal spread.[1] Peritoneal carcinomatosis is usually the result of metastasis from an intra-abdominal primary cancer (typically ovarian 20-50%, colorectal 10-28%, stomach 6-19%, pancreatic 6-13%, bladder 3-10% or endometrial 3-11%), but extra-abdominal cancers are also reported (e.g., breast cancer or melanoma).[2]

MBO can either be mechanical or functional. Mechanical aetiologies include intrinsic or extrinsic mass effect. Radiation-induced fibrosis and post-surgical adhesions are different entities and harbour different prognosis. Functional aetiologies include tumour infiltration of nerves responsible for intestinal mobility, secondary paralytic ileus (intra-abdominal infection, ascites or pain) and drug-induced neuropathy (opioids and anticholinergic drugs).[3] In reality, however, a mixed picture with mechanical and functional elements is most frequently encountered.[2]

MBO is of utmost importance in clinical practice since it is estimated to occur in 3-15% of all patients with advanced malignancy.[4] Hereunder, we synthesize the latest guidelines in end-stage MBO management, which is known to be challenging (*Figure 1*). We will not address upfront MBO, which treatment may involve chemotherapy, extensive surgery and more recently hyperthermic intraperitoneal chemotherapy (HIPEC). Because the prognosis of end-stage MBO is extremely limited, the goal is highly patient-specific and can either be obstruction relief, if possible, or symptom management alone.

CLINICAL MANAGEMENT

CLINICAL SUSPICION

Common clinical signs include (1) abdominal pain and distension, (2) nausea and vomiting and (3) the absence of gas

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Keywords: malignant bowel obstruction, nasogastric tube, palliative care, somatostatin analogues, supportive care

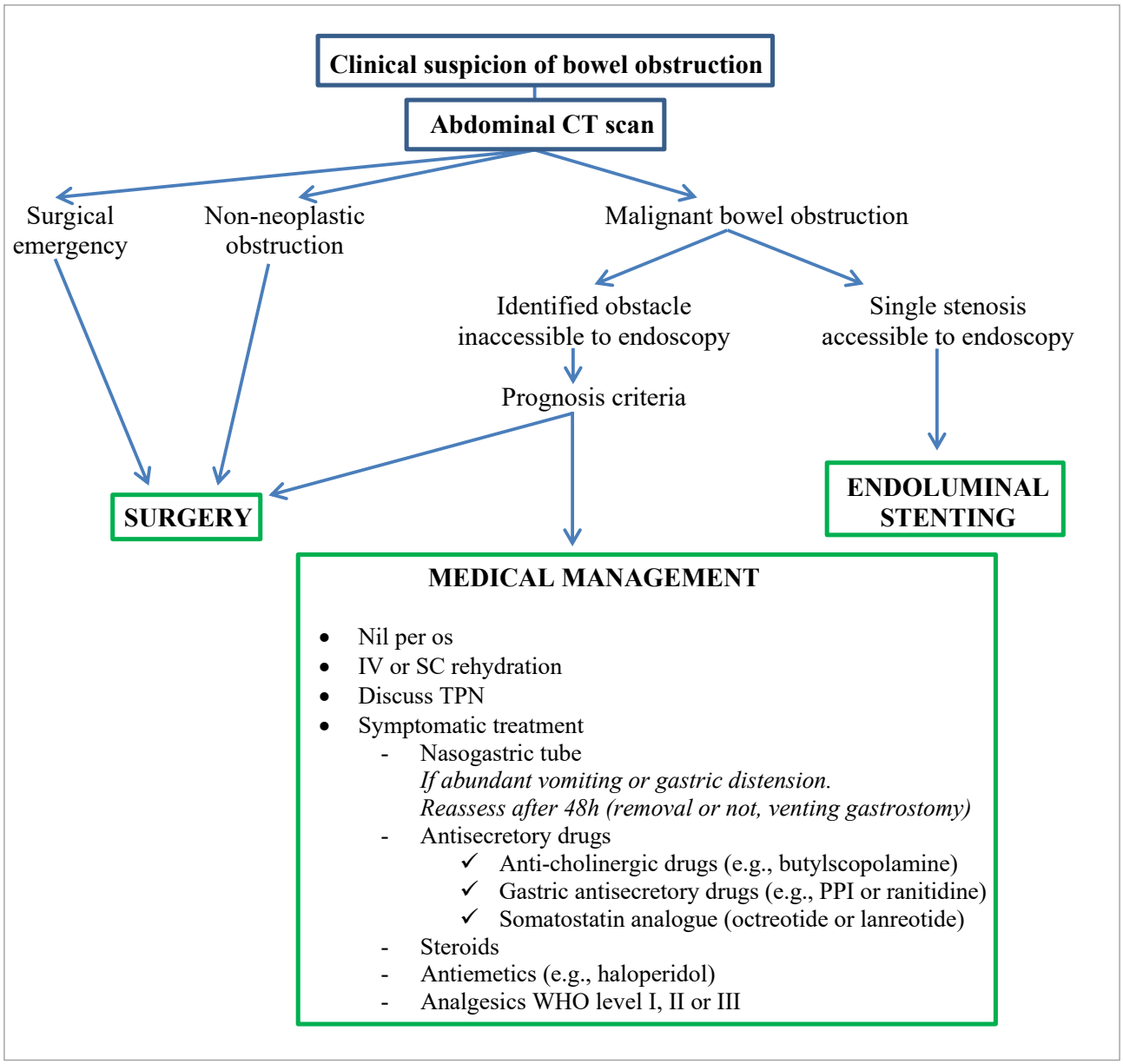

FIGURE 1. Management strategy for malignant bowel obstruction.
IV: intravenous, SC: subcutaneous, TPN: total parenteral nutrition, PPI: proton pump inhibitor, WHO: World Health Organization.

or stools. Symptoms can orientate on the level of obstruction. Small bowel obstruction will present with large volume aqueous or bilious vomiting, early periumbilical pain and anorexia, whereas large bowel obstruction is responsible for small volume foul-smelling faecaloid vomiting, with late localised colicky pain and major abdominal distension.[3] In patients with end-stage oncological disease, MBO is usually insidious, evolving over several weeks in a relapsing-remitting pattern.[5]

COMPLEMENTARY EXAMS

A multi-detector computed tomography (MDCT) scan with multiplanar reconstructions is the gold standard for diagnosis confirmation as it has a sensitivity and specificity of >90%.[6] A first acquisition is realised without contrast to identify pneumoperitoneum, haematomas or gastrointestinal bleeding. A second acquisition with intravenous contrast media at portal time will allow precise analysis of the gastrointestinal wall in conjunction with the fluid-filled intestinal loops. High opacification with oral ingestion of contrast agents is useless because of fluid stasis. Rectum-induced colonic opacification with water-soluble agents is not systematic but can be used to exclude an obstacle in the colon.

The four main goals of MDCT-scanning are (1) carcinomatosis diagnosis, (2) mechanical obstruction confirmation, (3) identification of surgical emergencies such as perforation, volvulus or strangulation, and (4) searching for a non-malig-

nant cause for the obstruction such as adhesions, hernias and eventration resulting from a previous surgery.[3]

Other imaging studies are often superfluous. A plain abdominal X-ray is fast, inexpensive and widely available. It can differentiate upper gastrointestinal, small or large bowel obstruction but is unable to accurately identify its location, cause and complications and is therefore rather futile. An ultrasound is intrinsically restrained for the evaluation of gas-containing structures and is highly operator-dependent. An MRI is accurate in diagnosing MBO but limited by high costs and an increased acquisition time and has therefore few indications such as rectal cancer local staging.[7] Enteroclysis and especially CT and MR enteroclysis enable an improved evaluation of the small bowel by challenging wall distensibility. They can help drive the management of intermittent low-grade small bowel obstructions by determining their number and location. However, the technique is time and labour intensive and uncomfortable for the patient (preparation, sedation).[8] A FDG-PET scan is expensive and relatively unavailable but proved useful in refuting the presence of intra-abdominal malignancy in patients with bowel obstruction and a prior history of cancer.[9]

TREATMENT OPTIONS

SURGICAL PALLIATION

After the above described surgical emergencies have been ruled out, patients should be selected appropriately for surgery depending on the cancer type (carcinomatosis associated with ovarian cancer is of better immediate prognosis than with gastrointestinal cancer, which supports surgical intervention) and individual prognosis factors for post-operative morbi-mortality (surgery should be avoided in case of advanced age, comorbidities, poor nutritional state, poor performance status, ascites, massive infiltration of the mesentery or mesocolon and history of radiotherapy)[3,10]. The benefit of surgery may be limited to an increase in quality of life at the cost of high operative risks of morbi-mortality.[11] Indications are therefore very rare and should be discussed in multidisciplinary collaborative meetings. For obvious obstacles with localised peritoneal infiltration, resection plus anastomosis is preferable to stoma formation or bypass as it has the greatest operative survival (7.2 months compared to 3.4 and 2.7 months respectively; Level II of evidence, grade B recommendation).[12]

INTERVENTIONAL PALLIATION

When feasible, endoscopic prosthesis procedures should be preferred to surgery as they carry a good clinical success rate and a lower morbi-mortality rate (Level III of evidence, grade C recommendation).[3] The indication is a single stenosis on a CT scan within reach of either a gastroscope or colonoscope. Complications rarely occur and consist of migration, obstruction or perforation.[3] Important risk factors for perforation are current radiotherapy and the use of anti-angiogenic drugs (e.g., bevacizumab).[13,14]

MEDICAL PALLIATION

A vicious cycle is entered wherein hypersecretion generates gut dilatation and vomiting, followed by further secretion and vomiting, quickly resulting in dehydration and electrolyte disturbances, which may prove lethal in absence of a medical intervention.

1. Nasogastric tube and venting gastrostomy

The placement of a nasogastric tube (NGT) relieves intractable vomiting and gastric distension and thereby decreases the risk of inhalation. It also enables the patient to drink. It allows time to determine if medical treatment will work. After 48 hours and only if secretions do no exceed 1L/24h, the removal of the NGT should be discussed to minimise the patient's discomfort (nostril ulceration, oesophageal erosion, pharyngitis and sinusitis; expert consensus).[3] Otherwise, a venting gastrostomy could be discussed as a long-term alternative, allowing the patient to eat small amounts of food for pleasure. Percutaneous endoscopic interventions should be preferred but there are contra-indications, principally ascites. Radiological interventions do not require general anaesthesia. Surgical indications remain rare but should be evaluated during surgical exploration of an obstruction.[3]

2. Steroids

Steroids may contribute to the treatment of MBO by (1) decreasing the oedema around the tumour, (2) their central antiemetic effect and (3) their indirect analgesic effects by reducing bowel distension and inflammation. Even though evidence is lacking, a short course of 5-10 days of 0.5-1 mg/kg/24h of intravenous methylprednisolone (or equivalent) at the time of diagnosis may help manage the symptoms and/or resolve the obstruction (Level II of evidence, grade C recommendation).[3,15] In order to reduce psychotropic effects and insomnia, total doses should be divided and administered at breakfast and lunchtime (expert consensus). Even though side effects for this posology are minimal, it is also worth bearing in mind the risks of gastrointestinal ulcerations and immunosuppression.[2]

3. Antisecretory drugs

Anticholinergic drugs. Scopolamine, butylscopolamine and glycopyrronium bromide have antispasmodic, antiemetic and antisecretory effects and reduce the volume of gastrointesti-

nal secretions. Scopolamine induces central adverse effects and butylscopolamine or glycopyrronium are therefore preferred as they hardly cross the blood-brain barrier (expert consensus).[2,3] The mean butylscopolamine dose is 60 to 120 mg/24h administered intravenously (IV) or subcutaneously (SC). Contra-indications (glaucoma and urinary retention) and undesirable effects (dry mouth, tachycardia, etc.) are those of atropinic drugs.

Gastric antisecretory drugs. Proton-pump inhibitors (PPIs) seem relevant to reduce gastric secretion or bile reflux and relieve upper digestive symptoms (Level II of evidence, grade B recommendation). Because oral administration is not feasible in MBO and half-life in blood is 60 minutes, PPIs should either be administered IV continuously over 24h or SC (validated for omeprazole).[16] Anti-histamine drugs such as ranitidine induce a greater antisecretory effect than PPIs (Level I of evidence) but conclusions on long-term use cannot be drawn, especially because H2 antagonists have been associated with rapid tolerance (within hours).[3,17]

Somatostatin analogues. Peripheral actions of somatostatin include decreasing splanchnic and portal blood flow, small intestine secretions and gastrointestinal motility, and increasing the gastrointestinal reabsorption of water and electrolytes. Synthetic analogues of somatostatin such as octreotide and lanreotide have a longer lasting effect and are effective in decreasing pain, treating nausea and vomiting, successfully removing NGT and most importantly increasing the quality of life (Level I of evidence, grade B recommendation).[3,18] Both drugs are well tolerated. Possible side effects include diarrhoea, abdominal pain, change in blood sugar levels and risk of gallstones.

Recommended posology for octreotide immediate release (IR) is 600 µg/day SC (continuous or discontinuous) or IV (continuous) with a reassessment on day 3. Octreotide long-acting-release (LAR) 30 mg administered intramuscularly (IM) every month can be considered, but effective concentration is attended on day 7 and therefore requires octreotide IR for the first six days after IM injection. Posology for lanreotide in this indication is only validated in its prolonged release (PR) form at 30 mg IM every ten days with a reassessment before the second injection. If the treatment does not prove effective on the reassessment day, it should be discontinued.[3]

Some randomised controlled trials proved somatostatin analogues to be superior to anticholinergic drugs regarding symptomatic relief, but they are much more expensive and therefore reserved for patients who responded well to these drugs previously or after failure of standard treatment (expert consensus).[3,17,19,20] In clinical practice, anticholinergic drugs and somatostatin analogues can be associated.

4. Antiemetics

Antiemetic drugs ensure a decrease in nausea and vomiting, especially when associated with antisecretory drugs. In patients with incomplete obstruction, metoclopramide is usually the first-line treatment. It is contra-indicated in complete obstructions because of its prokinetic effect that could worsen abdominal pain and the risk of perforation (Level III of evidence, grade D recommendation). In patients with complete obstruction, butyrophenones such as haloperidol (administered SC every 8-12 hours or in a continuous infusion) are therefore considered first-line treatment. Second-line treatments include phenothiazines (e.g., chlorpromazine), since they have serious sedative and anticholinergic side effects, and 5-HT3 receptor antagonists (e.g., ondansetron) because they are expensive and only have a marketing license for chemotherapy- or radiotherapy-induced emesis.[3]

5. General measures

Parenteral rehydration and electrolyte replacement should be promptly initiated and adapted to clinical and biological evolution (Level I of evidence, grade A recommendation). Biochemical imbalance, most commonly hypokalaemia and hypocalcaemia, may indeed contribute to intestinal dysmotility.

Parenteral nutrition should be discussed depending on the life expectancy and the expected risk (e.g., thrombosis, infections) -benefit ratio (Level III of evidence, grade C recommendation). Even though cachexia is a known indicator of poor prognosis in cancer patients, there is no evidence supporting parenteral nutrition in MBO in order to improve either survival or quality of life.[21,22] Its only true indication is to enable adjuvant chemotherapy in patients who are operated for MBO and have a post-surgical survival likely to be more than three months.[2] Home parenteral nutrition could be considered in end-stage MBO patients if they have an acceptable performance status and are expected to die from starvation prior to tumour spread.[21]

In terminally ill patients, treatments that prove not reasonable should be discontinued or never initiated, particularly venting gastrostomy and artificial nutrition. If obstruction resolves (36% of inoperable cases, mostly by Day 7), all treatments described above should gradually been discontinued and a laxative treatment may be discussed to limit the high risk of recurrence (72% of cases; Level III of evidence, grade C recommendation).[3,23]

CONCLUSION

Malignant bowel obstruction is a frequent and severe condition. Its management requires prompt collaboration between radiologists, surgeons and medical oncologists. After abdominal CT

KEY MESSAGES FOR CLINICAL PRACTICE

1. Malignant bowel obstruction is a frequent and challenging situation.
2. Multi-detector computed tomography is the gold standard for (1) carcinomatosis diagnosis, (2) mechanical obstruction confirmation, (3) identification of surgical emergencies and (4) searching for a non-malignant cause for obstruction.
3. In the treatment of malignant bowel obstruction, surgical indications are rare and will depend on the cancer type and prognosis factors.
4. When feasible, endoscopic prosthesis procedures should be preferred to surgery.
5. The placement of a nasogastric tube is not systematic and is reserved for intractable vomiting and gastric distension.
6. Medical symptomatic treatment includes steroids, antisecretory drugs and antiemetics.
7. Somatostatin analogues have shown better symptomatic relief than anticholinergic drugs but are second line in clinical practice because of their price and the lack of marketing license.
8. Treatments should be re-evaluated on a regular basis. Unreasonable treatments should be discontinued or never initiated in end-stage patients and if obstruction resolves, all treatments should gradually be discontinued.

scan evaluation, patients should be selected for endoscopic, surgical or most likely symptomatic medical management. The combination of a NGT for intractable vomiting or gastric distension with steroids, antisecretory drugs and antiemetics is important to relieve patient distress and proves in most cases capable of achieving acceptable patient comfort.

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Interventions in non-metastatic castration-resistant prostate cancer: earlier seems better

D. Schrijvers, MD, PhD

SUMMARY

Patients with non-metastatic castration-resistant prostate cancer benefit from an early treatment in terms of metastasis-free survival. Three drugs were compared with placebo in large randomised trials (SPARTAN, PROSPER, ARAMIS) and all showed an improvement in median metastasis-free survival. They differ in some of the secondary endpoints and side effects. This article discusses the results and the impact for patients with non-metastatic castration-resistant prostate cancer.

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INTRODUCTION

Patients with a localised prostate cancer are candidates for a local treatment. This consists of radical surgery or radiotherapy with or without androgen deprivation treatment (ADT).

Unfortunately, a proportion of patients will develop recurrent disease and the recurrence rate can be as high as 53% of patients, depending on prognostic characteristics of the primary tumour.

In case of overt metastatic disease with lymph node, bone or visceral metastases, several treatments in patients progressing after ADT defined as metastatic castration-resistant prostate cancer (mCRPC) have proven to prolong overall survival.[1]

In case of prostate-specific antigen (PSA) progression only – without demonstrable disease on a bone scan, an MRI or a computed tomography (CT) scan – defined as biochemical recurrence (BCR), the accepted treatment approach in Europe was to wait until overt clinical disease developed. However, a number of patients with BCR will be treated by ADT and may develop non-metastatic castration-resistant prostate cancer (nmCRPC).

The treatment of these nmCRPC patients presented a dilemma since many of the newer drugs (e.g., abiraterone acetate, enzalutamide, radium-223, cabazitaxel) were registered only for metastatic disease.

Now, data of three randomised trials are available in this patient population, showing that treatment with newer anti-androgens can postpone the development of overt metastatic disease.

RANDOMISED TRIALS WITH NEWER ANTI-ANDROGENS

Three randomised trials including patients with nmCRPC and a high risk of developing metastatic disease have now been published (*Table 1*).[2-4]

High risk for developing metastatic disease was defined based on the PSA values and its evolution (SPARTAN trial: PSA doubling time of ≤10 months or less during continuous ADT; PROSPER trial: minimum of three rising PSA val-

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Keywords: apalutamide, darolutamide, enzalutamide, non-metastatic castration-resistant prostate cancer.

TABLE 1. Results of randomised trials in patients with nm-CRPC.

Trial	N° patients	Exp drug	Median metastasis-free survival (months)	Overall survival (months)
SPARTAN	1207	Apalutamide	40.5 vs 16.2 HR: 0.28 (95% CI 0.23-0.35) p<0.001	NR vs 39.0 HR: 0.70 (95% CI 0.47-1.04) p=0.07
PROSPER	2874	Enzalutamide	36.6 vs 14.7 HR: 0.29 (95% CI 0.24-0.35) p<0.001	NR vs NR HR: 0.80 (95% CI 0.58-1.09) p=0.15
ARAMIS	1509	Darolutamide	40.4 vs 18.4 HR: 0.41 (95% CI 0.34-0.50) p<0.001	NR vs NR HR: 0.71 (95% CI 0.50-0.99) p=0.045

N°: number, Exp: experimental, HR: hazard ratio, CI: confidence interval, NR: not reached.

ues at an interval of at least one week apart, a baseline PSA level of ≥2 ng/ml, and a PSA doubling time of ≤10 months; ARAMIS: baseline PSA ≥2 ng/ml and a PSA doubling time of ≤10 months).[2-4]

All studies had as primary endpoint the metastasis-free survival, while secondary endpoints included progression-free survival, overall survival, pain and time to the initiation of cytotoxic chemotherapy.

In the SPARTAN trial, patients were treated with apalutamide (240 mg/day). In this study, a significant increase in median metastasis-free survival was seen from 16.2 months in the placebo arm to 40.5 months in the apalutamide arm. Although there was an improvement in progression-free survival (40.5 *vs* 14.7 months, hazard ratio [HR] 0.29 [95% confidence interval (CI) 0.24-0.36], p<0.001), there was no overall survival benefit.

Side effects considered to be related to apalutamide were fatigue (30.4% *vs* 21.1%), rash (23.8% *vs* 5.5%), falls (15.6% *vs* 9%), fractures (11.7% *vs* 6.5%), hypothyroidism (8.1% *vs* 2%) and seizures (0.2% *vs* 0%).[2]

In the PROSPER study, patients in the experimental arm were treated with enzalutamide (160 mg/day). Also in this study, there was an improvement in median metastasis-free survival (36.6 *vs* 14.7 months, HR 0.29 [95% CI 0.24-0.35], p<0.001) and PSA-progression-free survival (37.2 *vs* 3.9 months, HR 0.07 [95% CI 0.05-0.08], p<0.001), but again no improvement in overall survival was observed. Side effects more frequently reported in the enzalutamide group than the placebo group were hypertension (12% *vs* 5%), major adverse cardiovascular events (5% *vs* 3%) and mental impairment disorders (5% *vs* 2%).[3]

The third study, ARAMIS, using darolutamide (2 x 600 mg/day), was also positive in terms of median metastasis-free survival (40.4 *vs* 18.4 months, HR 0.41 [95% CI 0.34-0.50], p<0.001). This trial showed also a benefit in progression-free (36.8 *vs* 14.8 months, HR 0.38 [95% CI 0.32-0.45], p<0.001) and overall survival (HR 0.71 [95% CI 0.50-0.99], p=0.045). The most frequent side effect was fatigue, but its rate was similar to the placebo arm. No neurological symptoms were reported.[4]

DISCUSSION AND CONCLUSION

Three randomised trials showed a beneficial effect in patients with nmCRPC on median metastatic-free survival with the use of newer anti-androgens. This shows that early treatment of this patient population may improve the quality of life and progression-free survival, while the impact on overall survival is limited.

Several questions remain to be answered.

The definition of nmCRPC included an evaluation with classical imaging methods such as a bone scan, an MRI and a CT scan. The diagnostic yield of these examinations is low in asymptomatic men and low in PSA levels.

Other more sensitive examinations are introduced into clinical practice such as a choline positron emission tomography (PET)/CT with sensitivities and specificities of 86-89% and 89-93% or a prostate-specific membrane antigen-based PET/CT, which seems more sensitive than choline PET/CT.[5,6]

Both examinations may upgrade patients classified as nmCRPC to mCRPC.

We now have three new anti-androgens that all have a ben-

KEY MESSAGES FOR CLINICAL PRACTICE

1. **Apalutamide, enzalutamide and darolutamide improve median metastasis-free survival compared to placebo in patients with non-metastatic castration-resistant prostate cancer.**

2. **Darolutamide also increases the overall survival, which was studied as secondary endpoint for all three drugs.**

3. **The toxicity profile among the three drugs differs.**

eficial effect on the median metastatic-free survival. As in the past for mCRPC, the problem of choosing a treatment drug remains a challenge for the clinician since no randomised trial comparing all three drugs will be done. In the end, the clinician will have to choose, and the criteria to help him/her in this choice will be the side effect pattern and secondary endpoints, which are of limited value. Darolutamide does not penetrate the blood-brain barrier and seems to have less neurological complications than both apalutamide and enzalutamide and is the only drug with an overall survival benefit, although the remark on secondary endpoints stands.

In any case, it has been shown that patients with nmCRPC, benefit from a treatment of these new anti-androgens, and they should be discussed with them.

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Renal mass in a patient with invasive lobular adenocarcinoma

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SUMMARY

Breast cancer often metastasises to bone, lymph nodes, liver and lung. In this case report, we present a 75-year-old woman with a suspicious mammography and ultrasound of the breast who had a synchronous painless renal lesion. On computed tomography, the renal mass was suspected of being a primary lesion of the renal pelvis, but anatomopathological examination of the nephro-ureterectomy specimen revealed that it was a metastatic deposit of invasive lobular adenocarcinoma of the breast.

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INTRODUCTION

Breast cancer is the most frequent cancer in women, with worldwide an estimated two million new cases each year, and is currently the second most frequent cause of cancer death.[1,2] This type of cancer has a five-year overall relative survival rate of 90.4%.[3] The Belgian screening program with mammography has increased the number of patients with breast cancers being diagnosed in an early setting. A minority of patients with breast cancer is diagnosed with upfront metastatic disease.[4] Renal metastasis of breast cancer is uncommon, as Lee described an incidence of 15%.[5] Metastases of invasive lobular adenocarcinoma to the kidney have only been described once in medical literature.[6] We report a case of a 75-year-old woman with a painless lump in the right breast, diagnosed as an invasive lobular adenocarcinoma with an asymptomatic suspicious lesion in the left kidney during staging examinations.

MAIN SECTION

DESCRIPTION OF THE CASE

The 75-year-old woman consulted her family doctor because of retraction of both nipples and 'peau d'orange' of her right breast. A mammography and ultrasound were performed and showed a retroareolar lobulated and dense, though not well delineated, structure with a spicular appearance, multiple pathological vessels and enlarged axillary lymph nodes. A biopsy of the lesion in the right breast showed the presence of an invasive lobular adenocarcinoma, moderately differentiated (E-Cadherin negative, oestrogen receptor [ER]-positive, progesterone receptor [PR]-negative, human epidermal growth factor receptor 2 [HER2 negative]). A computed tomography of the thorax and abdomen and a PET scan were performed and showed a suspicious tumoral mass in the left kidney (*Figure 1*), originating from the renal hilus, causing hydronephrosis. The patient did not show any abdominal symptoms. After completing urine cytology, this lesion was suspected of being a second primary tumour originating from the renal pelvis.

The patient underwent a mastectomy of the right breast with axillary lymph node dissection that confirmed an invasive lobular adenocarcinoma (pT4bN3a, ER positive, PR negative, HER2 negative).

Twenty days later, after recovery of the previous surgery, a left nephro-ureterectomy was done and anatomopatho-

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Keywords: breast cancer, invasive lobular adenocarcinoma, renal metastasis, urological malignancies.

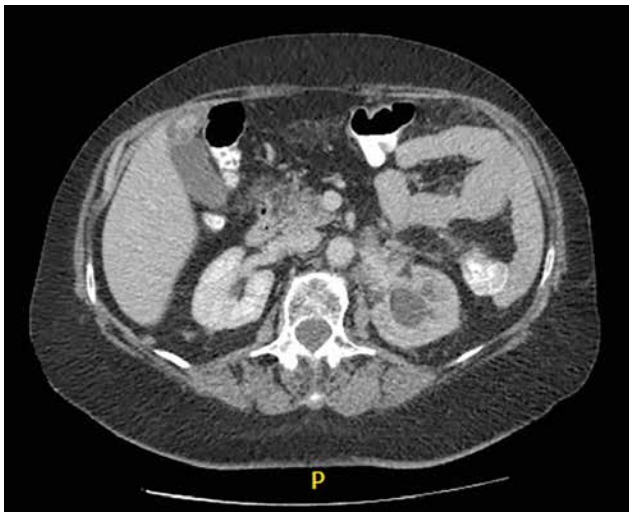

FIGURE 1. Suspicious lesion in the left kidney.

logical examination demonstrated a poorly differentiated metastatic deposit of the known invasive lobular adenocarcinoma of the breast. The tumour (ER positive, PR negative, HER2 negative) had also expanded into the perirenal fat and in the adrenal gland. Invasion of the wall of the renal artery and vein was present, as well as invasion of the wall of the ureter.

Post-operatively, the patient started first-line hormonal therapy, in particular letrozole and ribociclib.

DISCUSSION

This is the second report in medical literature of a renal metastasis originating from an invasive lobular adenocarcinoma of the breast. It is an unusual finding that has to be considered when encountering a renal mass during staging examinations of this type of invasive breast cancer. Initial urine cytology was deceptive because it was shown to be suggestive for a transitional cell carcinoma. Therefore, the correct diagnosis was made only after surgical resection.

Urine cytology is extensively used for the diagnosis and follow-up of patients with urothelial malignancies. Despite the widespread use, a meta-analysis showed that this test has a very low sensitivity (34%) and a high specificity (99%).[7] Barkan *et al.* introduced the first standardised reporting system for urine cytology, but it was designed for diagnosing high-grade urothelial carcinoma.[8] At present, there are no publications in medical literature on diagnostic criteria for non-urothelial malignancies in urine cytology.

In 2017, a study by Chen *et al.* to identify the differences in the clinical characteristics and prognoses between invasive lobular adenocarcinoma (ILC) and invasive ductal carcinoma (IDC) was published.[9] They analysed nearly 800,000 patients with ILC (10.7%) and IDC (89.3%) and published the metastatic pattern of these tumours. While bone metastasis was the most common in both breast cancer types (91.52% in ILC; 76.04% in IDC), the liver, followed by the lungs and the brain were the most frequent metastatic sites in ILC compared to the lungs, liver and brain in IDC.

In a retrospective study, an attempt was made to characterise the pattern of metastatic disease in patients with breast cancer.[10] This study found that ILC metastasised more to the bone marrow and the peritoneum compared to IDC that metastasised more to lung, pleura and bone. Patients with ILC or IDC who presented initially with bone involvement had the same survival rates.

Other reports show that ILC has the possibility to metastasise to nearly all organs.

In medical literature, different articles on metastases of ILC can be found, but a literature search on PubMed by the authors produced no other results than the case report of Al-Jarrah *et al.* on the topic of renal metastasis in ILC.[6] We can conclude that this is an unusual metastatic location in this type of breast cancer.

Invasive lobular adenocarcinoma constitutes 5-15% of all invasive breast carcinomas and a correct diagnosis provides the information needed for the initiation of the treat-

TABLE 1. Common primary cancer sites of renal metastatic lesions.

Primary organ site	N	%
Lung	66	43.7
Colorectal	16	10.6
ENT	9	6.0
Breast	8	5.3
Soft tissue	8	5.3
Thyroid	8	5.3
Unknown	8	5.3
Gynaecologic	7	4.6
Skin	5	3.3
Pancreas	4	2.7
Haematological	3	2.0
Prostate	3	2.0
Bone	2	1.3
Peritoneum	2	1.3
Small bowel	1	0.7
Thymus	1	0.7

ENT: ear, nose, throat.

KEY MESSAGES FOR CLINICAL PRACTICE

1. A renal mass in a patient with an invasive lobular adenocarcinoma may be a metastasis, although it is an infrequent finding.

2. Urine cytology and computed tomography may be deceptive in making the diagnosis of such renal masses.

ment.[11] The prognosis of an advanced stage ILC is poor, with a five-year overall survival rate of only 20%.[12] Differentiating between invasive ductal adenocarcinoma and invasive lobular adenocarcinoma is important because of the poorer prognosis of the latter.

Non-renal malignancies have the capability to metastasise to the kidney. Although the kidneys receive roughly 20% of the cardiac output, renal metastases are a rare entity.[13] The frequency of metastases to the kidney in cancer patients is 7-13% in large autopsy series.[14] Common primary cancer sites are shown in *Table 1* (from Zhou *et al.* who analysed 151 patients diagnosed with a primary non-renal malignancy with renal metastasis).[15] The most common primary histology is a carcinoma in 80.8% and a sarcoma in 11.9% of the study population.

In 10.9-43.7% of lung cancer cases, renal metastases are detected, compared to 2.7-10.6% in colorectal cancers and 5.3-15% in breast cancer.[5,14,16]

Most of the renal metastases of non-renal malignancies are asymptomatic, but some patients present with haematuria or flank pain. Renal function may be unchanged from baseline. Creatinine and blood urea levels may increase rarely unless a bacterial infection or another complication occurs.

This case report highlights the importance of accurate anatomopathological examination in suspicious renal lesions: urine cytology, in association with computed tomography, can be deceptive in making a diagnosis of this type of lesion.

CONCLUSION

In this case report of a 75-year-old woman with a renal metastasis of an invasive lobular adenocarcinoma, we emphasised that, when examining renal masses, a consideration of metastatic deposits of primary breast tumours is important for a correct diagnosis. Isolated renal metastasis of invasive lobular adenocarcinoma is not a frequent finding, though should be kept in mind.

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HER2 overexpression in gastroesophageal adenocarcinoma, prognostic and predictive value and diagnostic approach

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SUMMARY

Gastric (including gastroesophageal junction) adenocarcinoma ranks top three in global cancer mortality. Between 4-30% of patients have human epidermal growth factor receptor 2 (HER2) driven disease, and targeting HER2 receptor signalling improved prospects in metastatic setting. HER2 status is assessed by immunohistochemistry and *in situ* hybridisation. However, determination and interpretation of HER2 status remains challenging due to intra- and intertumoral heterogeneity and lack of data on the biological relevant cut-off. Currently, only trastuzumab is approved for treatment of *HER2* amplified advanced gastric cancer. The strength of *HER2* amplification at baseline and after progression should be integrated in future prospective randomised trials. HER2 loss occurs predominantly in cases with initial moderate immunostaining for HER2 and can lead to clinical resistance to trastuzumab. We review the use of liquid biopsies as an alternative to traditional tissue biopsies to overcome heterogeneity and to allow monitoring the dynamics of the plasma HER2 status. We believe that early detection of plasma HER2 loss can identify patients at risk for loss of response to anti-HER2 therapy. Based on a clinical case, we tried to define the implications and clinical relevance of HER2 positivity. We illustrate the usefulness of re-determination of the HER2 status in metastatic lesions after disease progression and provide the prospects of non-invasive testing.

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CASE

A 38-year-old woman was diagnosed with metastatic Barrett's oesophageal adenocarcinoma, clinically staged GxT2-3N2M1 (FDG/PET-positive thoraco-abdominal adenopathies). Human epidermal growth factor receptor 2 (HER2) status was determined on four endoscopic biopsies. The pathology report counted 25 viable tumour cells showing strong amplification of HER2 detected by two-probe chromogenic *in situ* hybridization (CISH). Treatment with cisplatin-5-fluorouracil (5FU) and trastuzumab was started for three months. Re-evaluation by PET/CT scans showed no metabolic active adenopathies. Hence, radiochemotherapy with curative intent was started (cisplatin-5FU, irradiation of the oesophagus and involved lymph node areas). After completion, an oesophagectomy with partial gastrectomy and extended lymphadenectomy was performed, with a definitive ypT-

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

Keywords: gastric adenocarcinoma, HER2, HER2 status, intra-and intertumoral heterogeneity, liquid biopsy, trastuzumab.

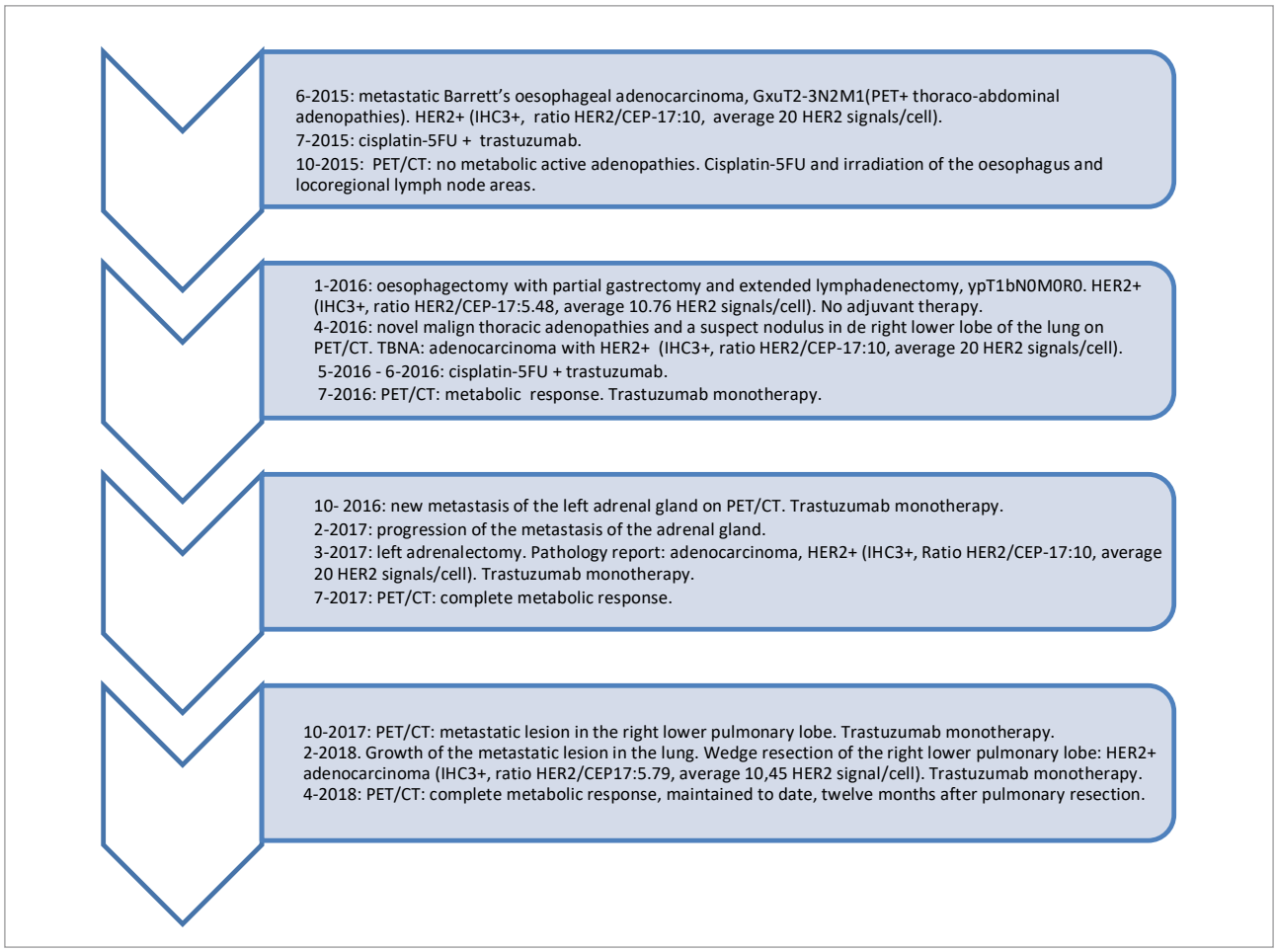

FIGURE 1. Disease course.

HER2: human epidermal growth factor receptor 2, IHC: immunohistochemistry, CEP-17: centromeric probe for chromosome 17, 5FU: 5-fluorouracil, TBNA: Transbronchial needle aspiration.

1bN0M0R0 staging. The resection specimen showed HER2 positivity (HER2+). No adjuvant therapy was administered. After three months, novel thoracic adenopathies and a pulmonary metastasis in the right lower lobe developed. A transbronchial needle aspiration confirmed metastatic disease, again HER2+. Cisplatin-5FU and trastuzumab was restarted, with a complete metabolic response after four cycles. Trastuzumab was continued in monotherapy. Three months later, the patient developed a metastasis of the left adrenal gland. After four months, a left adrenalectomy was performed because of significant progression under trastuzumab monotherapy in absence of other metastatic disease. The pathology report showed adenocarcinoma with HER2+. Trastuzumab monotherapy was restarted. After six months, PET/CT scans showed recurrence of the solitary lung lesion. Trastuzumab was continued. Four months later, a wedge resection metastasectomy was performed because of further tumour progression on trastuzumab. Again, HER2+ adenocarcinoma was reported. Therapy with trastuzumab was continued. PET/CT scans showed a complete metabolic response maintained to date, twelve months after surgery.

The disease course of the patient is summarised in *Figure 1*, including details on HER2 status. The patient developed new HER2+ lesions despite anti-HER2 therapy. Furthermore, all lesions showed strong homogenous *HER2* amplification, which points to other unknown resistance mechanisms acquired by these lesions.

INTRODUCTION

According to the recently published new GLOBOCAN 2018 data, gastric cancer (including gastroesophageal junction [GEJ]) is the fifth most common cancer worldwide (5.7% of all new cases).[1] *HER2* is a proto-oncogene, located on chromosome 17, encoding for a membrane-bound tyrosine kinase receptor. It is also called NEU, *ERBB2* or HER2/neu. The pathogenesis and progression of several epithelial malignancies is driven by amplification of the *HER2* gene leading to overexpression of the membrane bound HER2 recep-

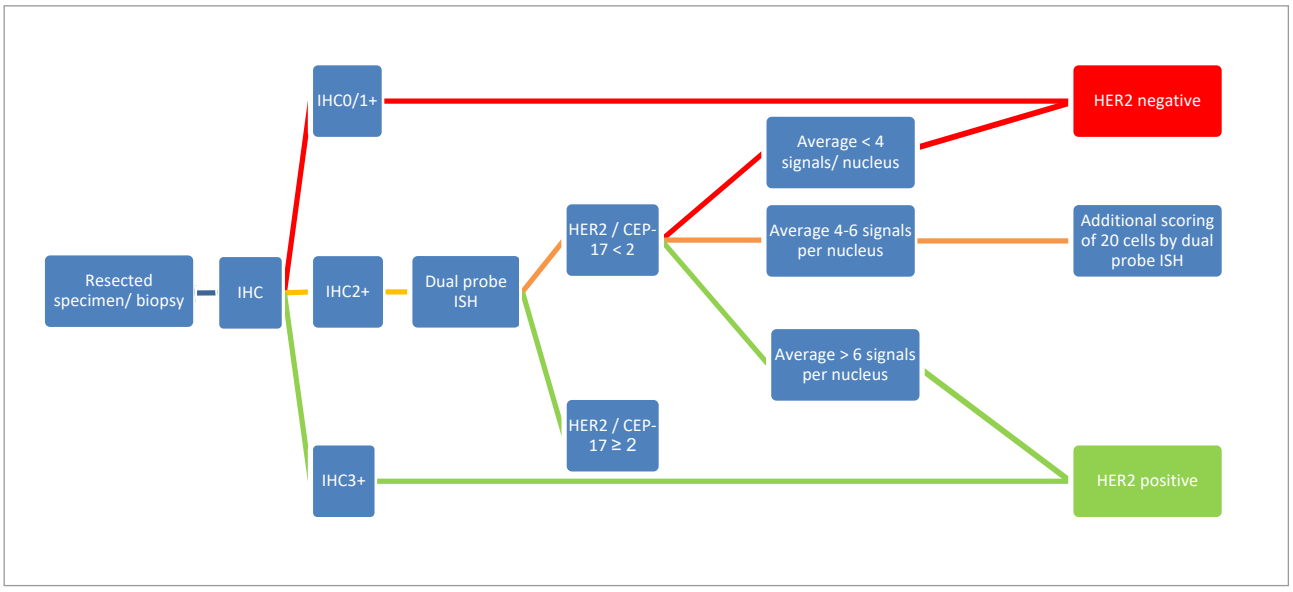

FIGURE 2. Interpretation of testing tissue HER2 status as proposed by the ASCO/CAP guideline.[1]
IHC: immunohistochemistry, ISH: in situ hybridisation, HER2: human epidermal growth factor receptor 2, CEP-17: centromeric probe for chromosome 17.

tor. Overexpression is observed in 12-17% of the oesophageal adenocarcinomas and in 13-22% of the gastric tumours. Expression ranges towards 30% in tumours of the GEJ.[2,3] HER2+ is the first target approved for treatment with trastuzumab in advanced gastric (including GEJ) cancers. Unfortunately, the interpretation of *HER2* molecular tests towards predicting outcome and therapy response is not yet well defined, and biological variability exists within the *HER2* amplified population. In this article, we try to provide further information on these issues.

METHODOLOGY

An electronic search was performed to search literature reporting HER2 status in primary gastric adenocarcinoma in PubMed and ASCO using the keywords gastric, stomach, gastroesophageal, cancer, tumour, neoplasm, carcinoma, HER2, neu and heterogeneity. We also manually screened the reference lists of the retrieved articles to identify other relevant publications. We collected and analysed clinical data up to and including October 2018.

DISCUSSION

ASSESSING HER2 STATUS

HER2 status assessment is performed by using immunohistochemistry (IHC) staining or *in situ* hybridisation (ISH) techniques, such as CISH, fluorescence ISH (FISH) and silver ISH. HER2 receptor overexpression is determined by IHC, whereas *HER2* gene amplification is assessed by ISH. There is a high concordance between biopsies and resected specimens, so both are suitable for HER2 analysis.[3-5] The determination of the HER2 status in gastric carcinoma was based on the experience gained with HER2 testing in breast carcinoma. Initially, HER2 testing in breast carcinoma occurred by IHC: IHC2+ and IHC3+ were considered positive. Since retrospective analysis showed greater benefit from anti-HER2 therapy in IHC3+, additional testing was necessary to identify those IHC2+ patients who would benefit most.[6] Complementary data confirmed that merely 24% of the IHC2+ showed *HER2* amplification when determined by ISH. In contrast, concordance of IHC0, IHC1+ and ICH3+ is respectively 97, 93 and 89%.[7]

Since the membranous staining in gastric cancer is often incomplete with heterogeneous HER2 expression, the guidelines for assessment of IHC status in breast carcinoma do not apply to gastric carcinoma and would lead to false negative results.[8,9] The IHC scores are categorised according to the Ruschoff/Hofmann method, used in the ToGA trial.[4] In gastric carcinoma, the membranous reactivity is assessed in at least one cluster of ≥5 tumour cells for biopsies and in ≥10% of tumour cells for surgical specimens.

Immunohistochemistry scores range from IHC0 to IHC3+:

- IHC0: no reactivity;
- IHC1+: scarcely perceptible reactivity;
- IHC2+: moderate/weak complete or basolateral membranous staining;
- IHC3+: strong complete or basolateral membranous staining.[4,8,9]

Amplification can be determined using single- or dual-probe assays. Single probe assays measure the average number of *HER2* copies per cell. This method is prone to bias, since slice

TABLE 1. Specific tumoral components used as biomarkers.

First author, year	Design (N° patients)	Plasma Component	Technique	Tissue HER2 amplification	+ / -	Cut-off Plasma Component
Saito M, 2016[15]	Prospective, multicentre (224)	ECD	Direct chemi-luminescence	IHC/FISH	Low sensitivity (0.226) High specificity (1.00)	>28 ng/ml
Shoda K, 2017[18,19]	Retrospective (70)	ctDNA HER2 ratio	Digital droplet PCR	FISH	High specificity (0.933) Sensitivity (0.733)	>2.1
Gao J, 2017[16]	Prospective (70)	ctDNA CNV	NGS	IHC/DISH	High concordance (91.4%, Kappa index= 0.784, p<0.001)	/
Shi H, 2017[13]	Retrospective (239)	ECD	ELISA	IHC/FISH	Low sensitivity (0.53) High specificity (0.93)	>15 ng/ml
Wang H, 2018[17]	Retrospective (20) + Prospective (36)	ctDNA HER2 copy number	NGS	IHC/DISH	High concordance (91.0%, Kappa index= 0.820, p<0.001)	>2.2
Bardelli S, 2018[14]	Retrospective (26)	ctDNA pCNA	NGS	FISH	High sensitivity (0.94) Metastatic CRC°	≥3 copies

°These data could probably be extrapolated from gastric cancer. *ECD: extracellular domain, ctDNA: circulating tumour DNA, HER2: human epidermal growth factor receptor 2, CNV: copy number variations, pCNA: plasma copy number amplification, PCR: polymerase chain reaction, NGS: next generation sequencing, IHC: immunohistochemistry, FISH: fluorescence in situ hybridisation, DISH: dual in situ hybridisation, CRC: colorectal cancer.*

thickness can affect the absolute counts per cell.[8] Dual-probe assays can additionally determine the number of *HER2* copies relative to the centromere 17 copies per nucleus (HER2/centromeric probe for chromosome 17 [CEP-17] ratio).[10] Guidelines recommend the use of dual-probe ISH. In a minority of cases, the interpretation can be challenging, due to anomalies such as deletion/duplication of subchromosomal regions that include CEP-17 and/or the *HER2* gene, coamplification of HER2/CEP-17 signals and heterogeneous amplification.[8,11] The ASCO/CAP guideline for HER2 testing in gastric cancer recommends IHC testing first, since the benefit from the addition of trastuzumab correlated with HER2 protein expression in the ToGA trial.[4] Cases with an IHC0 and IHC1+ showed positive *HER2* amplification by ISH in respectively 11 and 12% of the cases. Because these patients did not significantly benefit from trastuzumab, they are considered HER2 negative, and no further ISH assay is warranted. Patients with a high HER2 protein expression or positive amplification benefit significantly from HER2 directed therapy and are considered HER2 positive.[4] In the case of IHC3+, there is a concordance of 94% with ISH positivity, so no further testing for *HER2* amplification is needed.[8] In the case of IHC2+, *HER2* amplification is observed in 30-50%, so IHC2+ must be confirmed by ISH.[8]

In gastric cancer, at least 20 tumoral cell nuclei have to be evaluated for signal enumeration by ISH, and a HER2/ratio of ≥2 is positive. *Figure 2* shows the scoring of HER2 as proposed by ASCO/CAP.[8]

The Belgian guideline recommends ISH as the sole assay to select patients eligible for trastuzumab treatment and consequently to define HER2+. Furthermore, it recommends starting with IHC, but solely to facilitate the identification of amplified regions.[12] For reimbursement of trastuzumab, amplification of *HER2* should be demonstrated by ISH, even in IHC3+ tumours.

PROBLEMS IN ASSESSING HER2 STATUS

INTRATUMORAL HETEROGENEITY

Heterogeneity is defined by intratumour variation of genotype or gene expression and is common in gastric cancer. Although the NCCN guideline recommends six to eight endoscopic biopsies to provide an adequate-sized material for histologic interpretation, data about optimum numbers of biopsies to account for intratumoral heterogeneity of HER2 expression are controversial.[13] A recent trial showed that ≥4 containing fragments (tissue fragments with ≥10 viable tumour cells) significantly increase the rate of HER2 IHC3+.[14]

Since the IHC3+ positivity rate was unaffected by the amount of biopsies, a listing of the number of tumour-containing fragments in the pathology report seems useful. Repeated biopsies are profitable when the biopsy specimen has ≤4 tumour-containing fragments and a negative IHC.[14] In the GASTHER-1 trial, re-evaluation of HER2 expression through repeat assessment in primary and metastatic sites led to a 72.2% relative increase of HER2+. Patients with HER2 IHC1+ or IHC2+ primary tumours were 3.1 times as likely as those with HER2 IHC0 tumours to show HER2+ on repeat biopsy.[15] Yagi *et al.* retrospectively examined the endoscopic biopsies of 78 patients receiving trastuzumab for HER2+ gastric cancer. They found a prolonged median overall survival (29.3 *vs* 14.4 months, HR 0.352 [95% CI 0.20-0.61], p<0.001) and prolonged progression-free survival (10.8 *vs* 6.1 months, HR 0.469 [95% CI 0.29-0.77], p=0.003) in patients with a homogenous strong HER2 expression in all the cancer cells, compared to those with a heterogeneous HER2 expression.[16] This data suggest that the latter will benefit more from anti-HER2 therapy.

INTERTUMORAL HETEROGENEITY

In breast cancer, practice guidelines recommend taking new biopsies of metastatic disease at first recurrence when the HER2 status is unknown or not overexpressed.[10] Although trastuzumab-based therapy is used to treat metastatic gastric cancer, biopsies are usually only taken from the primary lesion, assuming that the HER2 status is equal in the primary tumour and the metastasis. Peng *et al.* resumed the published data on HER2 status discordance between paired primary lesions and corresponding metastasis. They showed that there is a discordance of 7% (95% CI 5-10%). Pooled proportions of HER2 status shifting from positive to negative and *vice versa* were 17% (95% CI 7-29%) and 4% (95% CI 2-6%) respectively.[17] In the GASTHER-1 trial, reassessment of the HER2 status in metastatic or recurrent sites showed an overall positive conversion rate of 5.7%. Positive conversion occurred about six times more in liver metastases than at other sites.[15] This finding confirms clonal heterogeneity of receptor status and changing protein expression in gastric and GEJ carcinoma. These data correlate with the earlier published data of Peng *et al.* and implicate that 4-5.7% of the patients may miss the potential profit of anti-HER2 treatment, if the HER2 status is only assessed on the primary tumours. Therefore, HER2+ should be tested in both primary and metastatic sites, and repeat testing to identify changes in *HER2* amplification at times of progression is recommended.[17,18]

LIQUID BIOPSIES

The current methods have some limitations. For example, due to the invasiveness of tissue sampling, it cannot be used to monitor dynamic changes in HER2 status and therapy response. Healthy and tumour tissue release their components into the bloodstream by apoptosis. Therefore, plasma contains cell-free DNA (cfDNA) and other components derived from tumour tissue and can be considered as a valuable resource of representative material of the tumour (*Table 1*).[18-25] Tumour-specific genetic alterations, such as copy number variations, can be analysed in the cfDNA by different next generation sequencing (NGS) approaches.[26]

Since HER2 expression in gastric cancer is heterogeneous in space and time, routine tissue sampling could lead to a misinterpretation of the HER2 status. Shoda *et al.* described that the plasma HER2 ratio correlates with tumour size. They found positive HER2 ratios in HER2 negative cases with larger tumour sizes.[24] It is not clear to what extent these tumours benefit from trastuzumab-based therapy. *HER2* amplification can be acquired or lost in recurrent gastric cancer. If it is impossible to take biopsies of new lesions, a liquid biopsy could serve as a surrogate for temporal and spatial heterogeneity by following the dynamics of the plasma HER2 status during treatment.[24,25] Shoda *et al.* compared pre-and post-operative HER2 ratios in a small population of 21 patients with gastric cancer. The post-operative ratios were significantly lower than the pre-operative ratios. In three cases with a higher HER2 ratio than the cut-off, an early relapse occurred. Blood samples are easily obtained making liquid biopsies a perfect tool for monitoring therapeutic efficacy. Plasma *HER2* amplification seems to correlate with the effects of trastuzumab in tumours with HER2 expression. This suggests that HER2 plasma ratios could be used as a sensitive prognostic and predictive biomarker.[24,25] However, NGS techniques on cfDNA are challenging due to the requirement of high sensitivity, complex bioinformatics and inter-laboratory standardisation and are at present not accessible to the majority of patients.

RESISTANCE TO TRASTUZUMAB

Until now, in trials with HER2 targeting agents, only trastuzumab could show significant survival benefit in HER2+ advanced gastric (including GEJ) adenocarcinomas.[3,4]

Efficacy of HER2 antagonists is limited by acquired resistance, due to treatment-induced selective eradication of HER2 overexpressing cancer clones, and thus progression of the HER2 negative clones. Loss of HER2+ during treatment is known in breast cancer but may be more pronounced in gastric (including GEJ) adenocarcinoma, due to intra- and intertumoral heterogeneity.[27] Pietrantonio *et al.* published an observational prospective cohort study in which 22 HER2+ advanced gastric adenocarcinomas with acquired clinical resistance after

KEY MESSAGES FOR CLINICAL PRACTICE

1. Human epidermal growth factor receptor 2 (HER2) status is determined by using immunohistochemistry (IHC) staining and in situ hybridisation (ISH) on tissue biopsy or resection specimen.
   - HER2 positivity: detection of *HER2* amplification by ISH (or IHC3+, which predicts a positive ISH).

2. Inter-/intratumoral heterogeneity:
   - Heterogeneity is defined by variation of genotype or gene expression, leading to focal positivity by IHC/ISH.
   - Six to eight endoscopic biopsies are recommended.
   - ≥4 tumour-containing fragments are desired to account for intertumoral heterogeneity. Prior IHC staining can detect areas of high HER2 intensity, which indicate areas of *HER2* amplification in heterogeneous tumours.
   - Repeat biopsies in case of negative HER2 status and ≤4 tumour-containing fragments.
   - HER2 overexpression should be tested in both primary and metastatic sites to overcome intratumoral heterogeneity.

3. Components derived from tumour tissue circulate in the plasma and could serve as liquid biopsies. In the future, these liquid biopsies could make HER2 assessment in oesophago-gastric cancer less challenging. Liquid biopsies could serve as:
   - biomarkers;
   - a prognostic/predictive marker;
   - a surrogate for temporal and spatial heterogeneity by following the dynamics of the plasma HER2 status during treatment.

trastuzumab treatment underwent new tumour sampling for retesting HER2+. They showed that almost one third of patients with initially HER2+ adenocarcinoma developed HER2 loss (the likelihood of losing HER2+ was significantly higher in patients with initial IHC2+ versus IHC3+ [80 *vs* 14%, overall response: 24 (95% CI 1.7-344.8), p=0.008]). Limitations of this study were the small sample size and the possible influence of intratumoral heterogeneity on the results.[27]

On the other hand, the mechanisms of resistance are probably heterogeneous, and not all disease progression is due to loss of HER2 overexpression (as in our patient).

Based on the experience in HER2+ breast cancer, molecular mechanisms of trastuzumab resistance have been investigated in gastric carcinoma.

First, some specific mutations resulting in the activation of alternative tyrosine kinase receptors (FGFR2 and MET/HER3) or signalling pathways (as PI3K/PTEN, SRC and NOTCH1) have been associated with resistance to trastuzumab.[27,28] Second, *in silico* studies have shown a coamplification of *HER2* with *EGFR* or *MET*.[29] Pietrantonio *et al.* showed that the simultaneous assessment of various primary resistance mechanisms (*PTEN* mutation, *EGFR* mutation/amplification, *MET* mutation/amplification, *KRAS* mutation/amplification, *BRAF* mutation), together with HER2 IHC, could identify patients with primary resistance with an accuracy of 84%.[28]

Intriguingly, liquid biopsy can become a tool for early detection of molecular mechanisms of trastuzumab resistance.

CONCLUSION

HER2+ is found in merely 30% of GEJ tumours and in 13-22% of gastric tumours. Targeting the HER2 pathway with trastuzumab showed significant improvement of overall survival in advanced disease. A major factor of treatment failure is the intra- and intertumoral heterogeneity, which makes HER2+ an unstable treatment target.

First, data about the optimal number of biopsies to account for false negatives are conflicting. Since ≥4 tumour-containing fragments significantly enhance HER2+, it is recommended to take new biopsies when the specimen contains ≤4 tumour-containing fragments. Second, mainly biopsies of the primary tumour are tested for determining the HER2 status. In this way, discordances in HER status between primary tumour and metastasis could misidentify patients with a potential benefit from anti-HER2 therapy. Moreover, loss of HER2+ can be induced by HER2 antagonists, and HER2 status can change in recurrent gastric cancer. Recently, some molecular mechanisms of trastuzumab resistance have become clear in gastric carcinoma.

The challenge is to identify those patients with an unstable target, upfront or during therapy. Hence, it requires multiple

and repeat biopsies in both primary tumour and metastasis to account for intra- and intertumoral heterogeneity. This approach is bothersome for the patient and increases the financial burden. Non-invasive detection of *HER2* amplification by molecular techniques on liquid biopsies is a promising approach for the dynamic monitoring of therapy response.

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Highlights of the Gastrointestinal Cancers Symposium 2019

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SUMMARY

At the background of the Golden Gate Bridge with a view on the Pacific Ocean, the annual Gastrointestinal Cancers Symposium was held from 17-19 January 2019 in the Moscone Congress Center in San Francisco, California. The meeting further underlined the invasion of immunotherapy in the treatment landscape of gastrointestinal tumours, both in the upper and lower digestive tract. In addition to immunotherapy, lots of efforts were made in the molecular profiling of gastrointestinal cancers in every possible tumour location, which will hopefully fuel more biomarker-driven medicine in this setting in the near future. In this report, the most important headlines will be discussed, with comments on the clinical relevance of the different studies.
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OESOPHAGEAL, GASTRIC AND GASTROESOPHAGEAL JUNCTION CANCER

According to the KEYNOTE-181 trial, second-line therapy with pembrolizumab (anti-PD1) reduced the risk of death by 31% in patients with PD-L1 positive metastatic oesophageal (adenocarcinoma and squamous cell carcinoma) or gastroesophageal junction (GEJ) cancer in comparison to chemotherapy. In this randomised phase III trial, 628 patients pre-treated with cisplatin and 5-FU were randomised (1:1) between pembrolizumab and chemotherapy consisting of taxanes or irinotecan. Patients in the study were stratified according to histological subtype, geographical origin and PD-L1 expression scored by a combined positivity score (CPS) system. In patients with a PD-L1 CPS of 10 or more, the investigators reported a significant improvement in overall survival (OS) from 6.7 months with second-line chemotherapy to 9.3 months with the checkpoint inhibitor (hazard ratio [HR] 0.69).[1]

A small clinical trial including 35 patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic gastric or GEJ adenocarcinoma evaluated first-line therapy with a combination of chemotherapy (XELOX/FOLFOX) plus trastuzumab and pembrolizumab. The combination led to an overall response rate (ORR) of 87% in 32 evaluable patients, which is very promising. The investigators hypothesised that combining an anti-PD-1 agent and HER2-directed therapy could induce a T-cell activation, augment antibody-dependent cellular cytotoxicity and potentiate anti-tumour immune response in HER2-positive disease.[2] A phase III study (KEYNOTE-811) to validate these findings is ongoing.

Another promising strategy under evaluation in patients with advanced gastric adenocarcinoma combines nivolumab (an-

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ti-PD-1) with ramucirumab (anti-VEGFR2). The combination showed activity in patients with previously treated advanced gastric adenocarcinoma (NivoRam study). In this phase I/II study, the combination resulted in a six-month progression-free survival (PFS) rate of 37% and a median OS of 17.05 months.[3]

Finally, results of the TAGS trial suggest that TAS-102 (trifluridine/tipiracil) might have a roll in the management of previously treated gastric and GEJ cancer. The results of this trial were already presented at ESMO 2018 and showed that TAS-102 was associated with a 31% reduction in the risk of death compared to placebo. Patients in TAGS were randomised (2:1) to receive TAS-102 (N=337) or placebo (N=170). The median OS was 5.7 months with TAS-102 as compared to 3.6 months with placebo. A subgroup analysis presented during the ASCO GI 2019 conference showed that patients who underwent a prior gastrectomy derived a survival benefit that was similar to what was seen in the overall population. Also, treatment exposure was similar in the gastrectomy subgroup.[4]

The ASCO GI conference also featured a few negative studies. One of these studies was the phase III GAMMA trial that studied the efficacy and safety of the MMP9 inhibitor andecaliximab in combination with FOLFOX as first-line treatment for patients with advanced gastric and GEJ adenocarcinoma. Unfortunately, the study did not meet its primary endpoint, as it could not demonstrate an OS benefit with the experimental agent.[5]

PANCREATIC CANCER

Two notable clinical studies and three molecular projects in the field of pancreatic cancer were presented at ASCO GI 2019. When a pancreatic ductal adenocarcinoma (PDAC) is deemed resectable at diagnosis, resection followed by adjuvant chemotherapy is the standard of care anno 2019. In this setting, the best results were obtained with FOLFIRINOX as the adjuvant chemotherapy regimen. The phase II/III Prep-02/JSAP-05 trial conducted in Japan is the first study to demonstrate the efficacy of neoadjuvant therapy in resectable PDAC. In this randomised study, the oral fluoropyrimidine combination of tegafur/gimeracil/oteracil (S-1) + gemcitabine prior to surgery improved the median OS by approximately ten months compared to upfront surgery in patients with resectable PDAC.[6]

Delivery of adjuvant S-1 following PDAC resection is standard in East Asia. In the trial, 364 patients with resectable or borderline resectable PDAC without arterial abutment from 57 Japanese centres were enrolled from January 2013 to January 2015. Patients were randomly assigned to two cycles of neoadjuvant chemotherapy or upfront surgery, after which all patients who fully recovered within ten weeks of curative resection received adjuvant S-1 for six months. The neoadjuvant regimen consisted of gemcitabine 1000 mg/m^2 on days 1 and 8 + S-1 80 mg/m^2 daily for 14 days, followed by a 7-day rest. The phase III portion of the study met its primary endpoint of OS. The medians reached 36.72 months with neoadjuvant gemcitabine + S-1 as compared to 26.65 months with upfront surgery, translating into a 28% reduction in the risk of death (p=0.015). The two-year OS rate was 63.7% with neoadjuvant therapy as compared to 52.5% with upfront surgery. Following resection, the incidence of node-positive disease based on pathology (pN1) was significantly decreased with neoadjuvant chemotherapy compared to upfront surgery (59.6% *vs* 81.5%, p<0.01). Recurrence under form of liver metastases was significantly lower with neoadjuvant gemcitabine + S-1 compared to upfront surgery (30% *vs* 47.5%, p=0.01). In the neoadjuvant chemotherapy group, the most commonly reported grade 3/4 adverse events (AEs) were leukopenia and neutropenia (72.8%). The resection rate, R0 resection rate and surgical morbidity were equivalent in the two groups. Additionally, neither group had any perioperative mortality.[6]

In conclusion, perioperative chemotherapy with neoadjuvant gemcitabine + S-1 and adjuvant S-1 improves OS for Japanese patients with resectable PDAC, the first study to show the value of neoadjuvant chemotherapy in this setting. Neoadjuvant chemotherapy could be a new standard for patients with resectable PDAC, at least in Japan. How this study compares to adjuvant and neoadjuvant FOLFIRINOX/gemcitabine + nab-paclitaxel in a Western population remains to be seen.

The efficacy of immunotherapy as monotherapy is very limited in advanced PDAC, and pancreatic cancer is considered as an immunogenic 'cold' tumour type. Stereotactic body radiotherapy (SBRT) is effective in locally advanced PDAC and enhances anti-tumour immunity. Immunotherapy + SBRT can potentially improve immunomodulatory effects in advanced PDAC, resulting in a greater clinical benefit.

In the presented phase I/II study, eligible patients with advanced PDAC were enrolled in one of four treatment cohorts.

- cohort 1: durvalumab 1500 mg every 4 weeks + SBRT 1 fraction x 8 Gy on day 1;
- cohort 2: SBRT 5 fractions x 5 Gy followed by durvalumab;
- cohort 3: durvalumab + tremelimumab 75 mg every 4 weeks + SBRT 1 fraction x 8 Gy on day 1;
- cohort 4: SBRT 5 fractions x 5 Gy followed by durvalumab + tremelimumab.

Immunotherapy was continued until unacceptable toxicity or disease progression. In total, 51 patients with advanced PDAC were enrolled, and 31 patients were evaluable for efficacy. Grade 3/4 AEs were lymphopaenia and anaemia. One patient in cohort 1 and two in cohort 4 achieved a confirmed partial response (PR). Seven cases of stable disease (SD) were seen across the four treatment arms. Median PFS and OS were

1.7 and 3.4 months in cohort 1; 2.6 and 9.1 months in cohort 2; 1.6 and 3.0 months in cohort 3; and 3.2 and 6.4 months in cohort 4, respectively.[7]

In conclusion, the combination of immunotherapy with SBRT is safe and well tolerated in patients with advanced PDAC. The ORR of 9.6% including two patients who achieved a durable PR lasting over twelve months, suggests meaningful clinical activity. As such, immunotherapy + SBRT is a potential new treatment for advanced PDAC. However, more studies are needed to position their exact role in the treatment algorithm. In addition, the combination of chemotherapy and immunotherapy also deserves further study.[7]

PDACs exhibit a wide range of genetic mutations and metabolic aberrations that allow them to survive during chemotherapy. Large-scale genetic sequencing to identify mutations and transcriptional features that could offer the potential for targeted treatment is underway in the ongoing COMPASS trial.[8] In this trial, advanced PDAC patients agreed to submit tumour tissue for whole-genome sequencing (WGS) and RNA sequencing before the initiation of first-line chemotherapy with modified FOLFIRINOX or gemcitabine/nab-paclitaxel. In a second step, treatment outcomes will be linked back to pre-treatment molecular characteristics. To date, enriched tumour tissue was analysed by WGS and RNA sequencing in 154 and 145 patients, respectively. A median of 39 days between time of biopsy and the results of the sequencing analyses was reported. The prospective COMPASS data suggest that response to chemotherapy differs depending on the transcriptional features of the tumour. More specifically, the best PFS was observed in patients who had the classical subtype and were treated with FOLFIRINOX (median PFS: 7.17 months). Conversely, significantly worse outcomes were seen in patients with a basal-like tumour type who received FOLFIRINOX (median PFS: 2.5 months). Patients with the basal-like subtype under gemcitabine/nab-paclitaxel had a median PFS of 5.65 months, which was comparable with the progression-free interval in patients with the classical subtype who received the same treatment (median PFS: 4.93 months). This result suggests that the basal-like subtype confers resistance to FOLFIRINOX.[8] The detection of *GATA6* expression through RNA *in situ* hybridisation was withheld as a surrogate biomarker to classify patients into *GATA6* high (= classical PDAC)- and low (= basal-like PDAC)-expressing groups.[8] Approximately 40% of the patients had potentially actionable mutations identified through genomic profiling. For example, 25% of patients with *KRAS* mutations had co-occurring mutations suitable for targeted therapy (e.g., activating mutations in *PIK3CA* and *ERBB3*, or *HER2* amplification), as did 8% of patients with *KRAS* wild-type disease (e.g., *BRAF* mutation and *NTRK3-EML4* fusion). Another 6% of patients had homologous recombination deficiencies. In addition, a novel group of patients with duplicator genotypes in which *BRCA1* remained intact, but who were characterised by prevalent genome duplications and genomic instability, was discovered. These patients tended to overlap with the classical PDAC RNA subtype, and the disease typically responded well to first-line chemotherapy.

In other work, performed for the Know Your Tumor Program, exome sequencing was carried out on tumour samples from 882 patients with PDAC in an attempt to identify outcomes based on the proficiency or deficiency of DNA damage repair (DDR) pathways. DDR-deficient PDAC seems to respond well to platinums and PARP inhibitors. This raises the question to whether DDR deficiency is just a favourable prognostic marker. Among patients naïve to platinum-based therapy, no differences in median OS were observed between DDR-proficient and DDR-deficient patients, regardless of whether patients had resected or advanced disease.

This suggests that DDR-deficiency is unlikely to be prognostic. In contrast, advanced PDAC with DDR-deficiency demonstrated improved median OS compared to DDR-proficiency when treated with platinums (2.37 *vs* 1.45 years, $p<0.0001$).[9] Because 50% of patients in the advanced setting get first-line therapy with non-platinum-based treatment, and only 50% will go on to receive second-line therapy, this is a very relevant finding. In fact, approximately 75% of patients with DDR-deficient disease might not be receiving optimal platinum-based therapy. Multiple genes, not only *BRCA1*/2, were included in the analysis of DDR-deficiency. More basic work is needed to show that these genes are equally relevant in terms of the biology of DNA damage repair and in influencing treatment outcomes.

Genomic analyses led to the development of targeted therapies in oncology and may enable the discovery of new treatment options. However, biopsy in PDAC often yields limited tissue, hampering tissue-based profiling opportunities. Circulating tumour DNA (ctDNA) profiling in PDAC in clinical practice is under study. ctDNA next generation sequencing (NGS) analysis in patients with advanced PDAC was performed. ctDNA analysis was performed using Guardant 360 (Guardant Health, CA), which detects single nucleotide variants, amplifications, fusions and specific insertion/deletion mutations in up to 73 different genes. Among 171 patients (206 samples in total), ctDNA NGS revealed at least one genomic alteration in 150 patients (88%). The median number of alterations per patient was three. The total number of unique alterations was 450 with the most commonly altered genes being: *TP53* (40%), *KRAS* (26%), *CDKN2A* (5%), *SMAD4* (3%), *EGFR* (2.4%), *PIK3CA* (2%) and *GNAS* (1.5%). Amplifications were noted in sixteen genes, including *BRAF, CCND2, CCNE1,*

CDK4, CDK6, EGFR, ERBB2, FGFR1, FGFR2, KIT, KRAS, MET, MYC, PDGFRA, PIK3CA and *RAF1*. Therapeutically relevant alterations were seen in 95 of 150 patients (63%). Tissue-based profiling was performed in 56 of the 171 patients (33%). *KRAS* and *TP53* were the most common gene mutations found in patients with both liquid and tissue biopsy results.[10]

In summary, ctDNA plasma profiling of patients with advanced PDAC is a feasible alternative method to gather comprehensive genomic data and to look for therapeutic targets

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma (HCC) is an active field of clinical research. Especially the results of trials evaluating the role of immunotherapeutic compounds (mainly nivolumab and pembrolizumab) compared with sorafenib in first-line, or to placebo in second-line, are eagerly awaited. During the ASCO GI, no practice-changing data were brought to our attention.

Kudo et al. presented an interesting analysis of the REFLECT trial, recently published in the Lancet, that demonstrated non-inferiority of lenvatinib *versus* sorafenib in advanced HCC. Authors retrospectively investigated the relationship between ORR assessed by the modified RECIST (mRECIST) criteria and OS in the whole study population. This landmark analysis nicely showed that patients who responded to treatment (154/954, 16%) had a statistically longer OS than non-responders (22 *vs* 11.4 months, HR: 0.61, p<0.001). Objective response according to mRECIST was an independent predictor of OS regardless of treatment. Although appealing and statistically valid, these data are based on a retrospective analysis, do not differentiate the effect of the drug and need to be validated prospectively.[11]

Kaseb *et al.* reported results of an original strategy evaluating perioperative immunotherapy for resectable HCC. Using a combination of nivolumab +/- ipilimumab given pre- and postoperatively in preliminary 8 surgically resected patients (of a total of 30 scheduled patients), they could show a pathological complete response (pCR) in 3 of 8 patients. The main interest of this small cohort was in the translational analysis. Indeed, authors could show an increase in CD3+/CD8+ lymphocytes and in the PD-L1 expression after neoadjuvant treatment. They also showed a correlation between the level of immune infiltration after neoadjuvant treatment and pathological response to therapy. Tolerance was good in this very preliminary, but promising, trial.[12]

Also, the poster session included interesting new data. A SEER-Medicare database analysis was performed looking at HCC survival by aetiology. Authors analysed the database to evaluate whether HCC survival varied by aetiology. A total of 11,522 SEER-Medicare HCC cases met criteria to assess survival differences among the risk factors for hepatitis C virus (HCV) infection, hepatitis B virus (HBV) infection, alcohol disorders and metabolic disorders. HBV-associated cases had the highest proportion of single nodules (40% *vs* 33% overall), localised stage disease (57% *vs* 49%), treatment (40% *vs* 27%) and greatest frequency of resection (18.6% *vs* 9%). Compared to cases with HBV infection, the risk of death was highest for alcohol-related HCC (HR: 1.69) followed by multiple aetiologies (HR: 1.40), metabolic disorders (HR: 1.32), HCV infection (HR: 1.30) and HCC of unknown aetiology (HR: 1.22). As such, patients with HBV-associated HCC had a better OS than patients with HCC of other aetiologies.[13]

A few posters derived from the REFLECT trial showed:

- that one third of the patients could receive post-trial treatment. Their OS differed if they received lenvatinib (OS: 21 months) or sorafenib (OS: 17 months) as first-line treatment.[14]
- that 8 mg for patients <60 kg or 12 mg for patients ≥60 kg were very similar in terms of efficacy and tolerance and support the 8 mg and 12 mg starting doses based on body weight of <60 kg and ≥60 kg, respectively.[15]
- that AEs of special interest, such as hypertension (OS: 18 *vs* 11 months, HR: 0.64, p<0.001) and hypothyroidism (OS: 20 *vs* 13 months, HR: 0.72, p=0.02) seem to correlate with a longer OS, although authors acknowledge the possible role of confounding baseline characteristics.[16]

BILIARY TRACT CANCER

Different discussants have insisted on the importance of mutational analysis in biliary tract cancers (BTC) and the identification of potential targets for treatment. In intrahepatic cholangiocarcinoma, the presence of *FGFR2* fusions, *IDH1/2* and *BRAF* mutations might represent targetable genes. Similarly, genomic aberrations in *HER2* and *EGFR* might be targetable in gallbladder tumours, while *BRCA1/2* and *KRAS* mutations can potentially be targeted in extrahepatic cholangiocarcinoma.

The results of the biliary tract cancer cohort of the ROAR trial (NCT02034110) were presented. ROAR is a phase II, open-label, basket trial in which patients with $BRAF^{V600E}$ mutated cancer (nine tumour types) were included. Eligible patients have advanced or metastatic cancer and have been previously treated with ≥1 prior systemic therapy. Patients were treated with dabrafenib (150 mg BID) and trametinib (2mg QD) until progression or unacceptable toxicity or death, and the primary endpoint was investigator-assessed ORR. In the BTC cohort, 32 of the 33 included patients were evaluable, and 78% had received at least two prior lines of therapy. The investigator-assessed ORR was 41% (12/32, 95% confidence interval [CI] 24-59%) with 6 of 13 responses ongoing at data cut-off. The median PFS was 7.2 months (95% CI 4.6-10.1 months), and a

favourable safety profile was reported. Grade 3/4 AEs in ≥3 patients included increased gamma-glutamyltransferase (N=3) and a decreased white blood cell count (N=3).[17]

In conclusion, the combination of dabrafenib and trametinib has demonstrated a promising efficacy in patients with *BRAF*^{V600E} mutated BTC, with favourable safety profile.

REACHIN (NCT02162914) is a Belgian academic (BGDO) multicentre, double-blind, placebo-controlled, randomised phase II study that evaluates the safety and efficacy of regorafenib (REG) in patients with locally advanced (non-resectable) and metastatic histologically proven BTC, progressing after gemcitabine-platinum chemotherapy. In total, 66 patients were randomised (1:1) to receive best supportive care (BSC) plus REG 160 mg/day, 3 weeks on/1 week off (cycle= 4 weeks) or BSC + placebo until progression or unacceptable toxicity. The primary endpoint is PFS, with ORR, OS and safety as secondary objectives.[18] Of the 66 patients that were treated (26 females/40 males), 42 tumours were intrahepatic, 6 peri-hilar, 9 extrahepatic and 9 originated in the gallbladder. One patient remains on REG treatment, and 9 patients are still alive at data analysis. The median PFS with REG was 3.0 months (95% CI 2.3-4.9) as compared to 1.5 months (95% CI 1.2-2.0) with placebo resulting in a HR of 0.49 (95% CI 0.29-0.81, p=0.005). Rates of PR+SD are 23/33 (70%) for REG and 11/33 (33%) for placebo (p=0.002). The median treatment duration was 11 weeks for REG as compared to 6.3 weeks for placebo (p=0.002). Dose reductions were applied in 14/33 patients in the REG arm and in 5/33 patients treated with placebo. There were no unexpected or new safety signals. After a median follow-up of 20 months, the median OS was 5.3 months for REG and 5.0 months for placebo (p=0.31).[18]

In conclusion, regorafenib significantly increases median PFS and tumour control in patients with previously treated metastatic/unresectable BTC.

COLORECTAL CANCER

For many years, colorectal cancer (CRC) data has been the core of GI oncology meetings. Since the introduction of immunotherapy in the management of GI cancer, a very interesting and promising new landscape is developing.

RECTAL CANCER

The main clinical practice-changing topic at the ASCO GI related to total neoadjuvant treatment (TNT) in rectal cancer and the way this approach could change the multimodality management.

Surgery

With respect to surgery, the need of a very accurate staging of rectal cancer was stressed. Endoscopic ultrasonography and MRI are complementary to show depth of invasion, CRM, mesorectal nodes, extramural vascular invasion and lateral lymph nodes but also to assess clinical response to neoadjuvant treatment.

Total mesorectal excision (TME) is still the gold standard, and this can be performed in an open, laparoscopic (with equal survival data if performed in the hands of experts) or robotic (with a higher number of nodes retrieved) manner.[19] For transanal TME, prospective data are still lacking.

What about the lateral lymph nodes (LLN)? If they are larger than 7 mm, a higher risk for local recurrence is seen. If LLN are still ≥4 mm after neoadjuvant treatment, this is marked as a high potential for local recurrence (but there was no impact on survival). The question remains on how to change the outcome in this group of patients: should we use a more intensive neoadjuvant treatment? Could a higher dose of radiation add benefit? Anyhow, an accurate assessment of the response after neoadjuvant treatment is crucial and a LLN dissection should be considered if they are ≥4 mm (as LLN dissection reduces local recurrence even after chemoradiation).[20]

With respect to a watch-and-wait strategy after neoadjuvant treatment, the available data are mainly retrospective. However, the OPRA trial might reveal a highly selected group of patients in whom the surgical modality could be skipped. In this trial, patients with distal rectal cancer were randomised to neoadjuvant chemotherapy (FOLFOX/CAPOX) for 16-18 weeks, followed by 5.5 weeks chemoradiation or *vice versa*. When restaged, patients who did not respond underwent TME, while patients who did show a clinically significant response were followed-up with a non-operative approach. More insight into the potential of a watch-and-wait strategy could come from the international Watch and Wait Registry. This registry already includes 880 patients from 47 centres in 15 countries.[22]

Radiotherapy: beyond the German Rectal Trial (preoperative versus postoperative chemo-radiotherapy)

A Polish study identified a better schedule of neoadjuvant chemoradiation for 'unresectable' rectal cancer and shows that a short course of high-dose preoperative radiotherapy (5 x 5 Gy) followed by consolidation chemotherapy yields the same local efficacy as compared to a conventional chemo-radiotherapy approach, but it offers improved patient convenience. The trial included 515 patients with a fixed cT3 lesion or a cT4 rectal tumour involving or abutting adjacent organs or structures but without distant metastasis. These patients received either a 5 x 5-Gy radiotherapy schedule followed by three courses of FOLFOX4 after one week of rest (the experimental arm) or 50.4 Gy of radiotherapy delivered in 28 fractions over 5.5 weeks with concurrent 5-fluorouracil, leucovorin and

oxaliplatin (the control arm). The R0 resection rate (i.e., a resection margin >1 mm; primary endpoint) turned out to be comparable between the experimental and control arms (77% *vs* 71%, p=0.07). These findings were supported by comparable pathological complete response rates between the respective arms (16% *vs* 12%, p=0.21). Interestingly, the OS at three years significantly favoured the experimental arm over the control arm (73% *vs* 65%, p=0.046). This finding has yet to be explained, particularly given that the three-year rates of disease-free survival (DFS) (53% *vs* 52%, p=0.85), local failure (22% *vs* 21%, p=0.82) and distant metastasis (30% *vs* 27%, p=0.26) did not differ between the two respective groups. A major boon for the 5 x 5-Gy regimen with consolidation chemotherapy was the improved toxicity profile compared to standard chemoradiation. The rates of acute events (73% *vs* 81%) and toxicity-related deaths (1% *vs* 3%) favoured the experimental arm over the control arm.[23]

The phase III GRECCAR-6 randomised controlled trial assessed whether a longer waiting period after neoadjuvant radiochemotherapy improves the oncological prognosis of rectal cancer (7 or 11 weeks). In this trial, there seemed to be no difference in the pCR rate between both arms (15% for 7 weeks *vs* 17.4% with 11 weeks, p=0.60). However, the 11-week strategy was associated with a higher morbidity mainly due to medical complications (more fibrosis) and a worse TME quality (44.4% *vs* 32%, p=0.04).[24]

Organ preservation is a concept proposed for patients with rectal cancer after a good clinical response to neoadjuvant chemotherapy, to potentially avoid morbidity and side effects of rectal excision. In this light, the randomised phase III GRECCAR-2 study compared local excision and TME in patients with a good response after chemo-radiotherapy for lower rectal cancer.[25] A total of 145 patients with lower rectal cancer (<8 cm from the anal verge and <4 cm large) underwent preoperative chemo-radiotherapy. The poor responders (having a scar >2 cm) underwent TME, while the good responders (scar <2 cm) were randomised to local excision or TME. Within the local excision group, pT0-1 patients were followed-up every 4 months for up to 5 years, while pT2-3 or R1 patients completed TME. Of the 89 patients who underwent TME, no patients with pT0-1 had positive lymph nodes, as compared to 8% in the pT2 group and 40% among pT3 patients. Remarkably, 40% of patients had a pCR. A take home message here was that completion surgery probably should be limited to <10% of patients for ypT2/N1 and ypT3.[25]

ONCOLOGY: CHEMOTHERAPY FOR RECTAL CANCER

Current stage II/III rectal cancer patients have a five-year local relapse rate of 5-10%. Despite the good local control with TME and neoadjuvant chemo-radiotherapy, the pCR rate is <20% and the five-year DFS and OS rates are 65% and 75%, respectively. Extrapolation of clinical data with adjuvant therapy in colon cancer to the rectal cancer setting has been controversial due to deletion, delay and dose reduction in postoperative chemotherapy.

By changing the paradigm to a total neoadjuvant treatment in phase II trials, results show a safe strategy without excess of surgical complications and less than 2% of patients who develop disease progression. In the postoperative space, patients were allowed to recover and undergo stoma reversal. Patients with a persistently poor prognosis can be included in clinical trials evaluating novel agents.

Is there a role for chemotherapy alone in the neoadjuvant treatment for rectal cancer patients? In the phase III FOWARC trial, perioperative modified FOLFOX6 alone had inferior results and a lower pCR rate than chemo-radiotherapy but led to a similar downstaging rate as fluorouracil-radiotherapy, with less toxicity and fewer postoperative complications.[26] More insights on the potential of chemotherapy alone in this setting will come from the recently closed American PROSPECT trial. In this study, 1180 patients are treated with FOLFOX once every 2 weeks for 6 cycles total over a period of 12 weeks. If the tumour has not decreased at least 20% after completing FOLFOX, the patient will receive chemo-radiotherapy while patients with a tumour decrease of at least 20% proceed directly to surgery without radiation. If all borders of the tumour are normal post-surgery, the patient receives six additional cycles of FOLFOX. In case of positive margins, the patient receives chemoradiation therapy for 5.5 weeks after surgery.

Several trials are also looking into non-operative strategies for rectal cancer patients. Neoadjuvant chemoradiation and post-treatment response evaluation will be needed to select patients where surgery can be avoided. An ongoing trial in the US, NRG-GI002 TNT, includes different non-comparative neoadjuvant experimental arms in high-risk locally advanced rectal cancers to improve delivery of systemic treatment, assess biologic response and develop biomarkers.

COLON CANCER

Segal *et al.* presented safety and efficacy results of durvalumab monotherapy in advanced CRC patients with microsatellite instability-high tumours. In this trial, 36 CRC patients were treated with durvalumab at a dose of 10 mg/kg intravenously (IV) every 2 weeks for 12 months. Durvalumab was associated with a tolerable safety profile and promising anti-tumour activity. The ORR in the colorectal cohort was 22% with a two-year OS rate of 54%. After one year, 38% of durvalumab treated CRC patients were free of progression.[27]

In the randomised phase II CCTG CO.26 study, durvalumab (D; 1500 mg IV q28 days) + tremelimumab (T; 75 mg IV q28 days for the first four cycles) was compared to BSC in patients with advanced refractory CRC. The primary endpoint of OS was met in the study with a median OS of 6.6 months with the experimental combination *versus* 4.1 months with BSC (HR [95% CI]: 0.72 [0.54-0.97], p=0.07).[28] A circulating DNA analysis was performed which showed that 117 patients in the D+T arm and 49 patients in the BSC arm were microsatellite stable. The median PFS was short in both arms (1.8 and 1.9 months for D+T and BSC, respectively). The disease control rate (DCR) was reported at 22.6% for D+T as compared to 6.6% with BSC (p=0.006). As such, this is the first study in which immune checkpoint blockade is shown to be effective in CRC patients who are unselected for DNA mismatch repair. However, phase III confirmation is warranted.[28]

Finally, the multicenter randomised COLOPEC trial evaluated the potential of adjuvant HIPEC in patients with colon cancer at high risk of peritoneal metastases.[29] Despite adjuvant chemotherapy, patients with T4 or perforated colon cancer are still at a high risk (~25%) of peritoneal metastases (PM). Moreover, the sensitivity of imaging modalities for PM is limited, and as a result, the majority of patients is diagnosed in a palliative setting. In the COLOPEC study, 204 patients with T4 (either cT4 or pT4, N0-2, M0) or perforated colon cancer, who underwent curative resection, were randomised to adjuvant HIPEC followed by routine adjuvant systemic chemotherapy or to adjuvant systemic chemotherapy alone (1:1). Adjuvant HIPEC with oxaliplatin was performed simultaneously (9%) or within five to eight weeks (91%) after the primary tumour resection. Patients without evidence of recurrent disease at 18 months based on CT imaging underwent a diagnostic laparoscopy in both arms. The primary endpoint was PM-free survival (PMFS) at 18 months. The trial revealed no difference in 18 months PMFS: 77% (control) *versus* 81% (experimental) (HR [95% CI]: 0.836 [0.489-1.428]). Also, no differences were observed in 18 months DFS (HR: 1.016) and OS rates (HR: 1.139). Of note, HIPEC was associated with substantial morbidity in this trial.[29]

NEUROENDOCRINE TUMOURS

Two relevant studies in patients with neuroendocrine tumours (NETs) were presented: KEYNOTE-158 and – updated results from – the phase II TALENT trial (GETNE 1509).[30,31]

Earlier findings from the phase I KEYNOTE-028 trial, which studied pembrolizumab in a number of solid tumours, showed activity of immunotherapy in some patients with heavily pre-treated NETs. The phase II basket trial KEYNOTE-158 studied the efficacy and safety of pembrolizumab in ten different tumour types, including NETs. At ASCO GI 2019, *Strosberg et al.* presented the analysis of 107 patients including the NET cohort of KEYNOTE-158. This cohort included grade 1/2 NETs of the lung, appendix, small intestine, colon, rectum and pancreas, with disease progression on or intolerance to at least one line of standard therapy. Patients received 200 mg of pembrolizumab every three weeks for two years or until progression, intolerable toxicity or physician or patient decision. Tumour imaging was performed every nine weeks for the first year and then every twelve weeks.

The median age of patients enrolled in the trial was 59 years; 67.3% had received two or more prior therapies. Sixteen percent of participants had a PD-L1-positive NET. The primary endpoint was ORR, while the secondary objectives included duration of response, PFS, OS and safety. After a median follow-up of 18.6 months, an ORR of 3.7% was reported, with no complete responses and four PRs (three in patients with a NET of the pancreas and one in a patient with a gastrointestinal [unknown primary] NET). All four patients with a response to pembrolizumab had PD-L1-negative disease. In addition to the four responders, 61 patients had stable disease as their best response. Three of the four responses were ongoing after nine months of follow-up. The six-month OS was 84.6%. The median PFS was 4.1 months with a six-month PFS rate of 38.2%.[30] Treatment-related AEs occurred in approximately three-quarters of patients (most frequently fatigue), and 20.6% of patients experienced a grade 3/4 AE. In conclusion, pembrolizumab monotherapy showed only limited anti-tumour activity in NETs grade 1/2 and will probably not find its way into routine clinical practice. Maybe other approaches under study like combination therapy (e.g., immunotherapy + angiogenesis inhibition) or peptide receptor radionuclide therapy, are more promising.

Capdevila *et al.* updated the results of the phase II TALENT trial, which studies the efficacy of lenvatinib 24 mg/day in metastatic patients with grade 1/2 advanced pancreatic (pan) NETs and gastrointestinal (gi)NETs. The ORR with current targeted agents like sunitinib and everolimus in NETs ranges from 2-9%. The ORR with lenvatinib in panNETs reached 40.4% and 18.5% in giNETs. The median PFS in panNETs was 15.8 months, while giNET patients had a median PFS of 15.4 months. Dose reductions/interruptions were needed in 91.8% of patients resulting in a median lenvatinib dose of 20 mg/day. No new toxicities were reported.[32]

In conclusion, lenvatinib showed the highest reported ORR with a targeted agent in panNETs and giNETs with a promising PFS in a pre-treated population. The benefit was observed across all investigated subgroups, including patients who were previously treated with targeted agents.

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New oncology reimbursements in Belgium

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Overview of Belgian reimbursement news
(BELG J MED ONCOL 2019;13(4):150-151)

CHAPTER VIII FOR "PERSONALISED DRUGS"

From July 1st 2019, a new chapter will be introduced in the reimbursement of drugs: "chapter VIII". This chapter collects drugs for which reimbursement is conditioned by the presence/absence of a molecular biomarker. Chapter VIII very much resembles chapter IV: the reimbursement conditions of the drugs are listed in different paragraphs and a priori authorisation by the Insurance Agency is required. Next to a list of these drugs, chapter VIII also holds a list of the coupled predictive biomarkers. This makes it possible to link the reimbursement of both drug and biomarker, so both can be assessed in the same reimbursement procedure and reimbursement can start simultaneously after a uniform decision. For the moment, chapter VIII only holds drugs with a companion molecular biology test. Drugs that are merely linked to an immunohistochemistry or hereditary test are not in this scope and stay in chapter IV. Some drugs have an indication linked to a molecular biomarker and another indication without a link. These drugs will have a paragraph in chapter VIII but also a paragraph in chapter IV. More information on the new chapter and the linked reimbursement can be found on the RIZIV/INAMI website.

Drugs that are reimbursed via chapter VIII as of July 1st are: tretinoin, trastuzumab, imatinib, arsenic trioxide, erlotinib, cetuximab, panitumumab, lapatinib, gefitinib, nilotinib, vemurafenib, crizotinib, bosutinib, dabrafenib, pertuzumab, afatinib, trastuzumab emtansine, ibrutinib, dasatanib, idelalisib, ponatinib, ceritinib, osimertinib, trametinib, venetoclax, cobimetinib, alectinib, and midostaurine. Reimbursement demand forms for these drugs can be found at the same locations as the demand forms for drugs in chapter IV. As a transitional measure, authorisations for the drugs in chapter IV that were delivered before the entry into force of chapter VIII can retain their validity in accordance with the provisions stated on these authorisations.

DURVALUMAB (IMFINZI®)

Durvalumab (Imfinzi®) is reimbursed when administered for any indication approved by the European Medicines Agency (EMA).

Durvalumab (Imfinzi®) as monotherapy is currently approved for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

The efficacy of durvalumab was evaluated in the **PACIFIC** study, a randomised, double-blind, placebo-controlled, trial in 713 patients with locally advanced, unresectable NSCLC who had completed at least two cycles of platinum based definitive chemotherapy with radiation within 1 to 42 days prior to initiation of the study and who had not progressed following chemoradiation. Patients were randomised 2:1 to receive durvalumab 10 mg/kg or placebo every two weeks

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for up to twelve months or until unacceptable toxicity or confirmed disease progression.

TABLE 1. Results of the PACIFIC study.

		Durvalumab	Placebo
N		476	237
OS			
	median (months)	NR	28.7
	95% CI	34.7-NR	22.9-NR
	HR	0.68	
	95% CI	0.53-0.87	
	p	0.00251	
	at 24 months	66.3%	55.6%
	95% CI	61.7-70.4	48.9-61.3
	p	0.005	
PFS			
	median (months)	16.8	5.6
	95% CI	13.0-18.1	4.6-7.8
	HR	0.52	
	95% CI	0.42-0.65	
	p	<0.0001	
	at 12 months	55.9%	35.3%
	95% CI	51.0-60.4	29.0-41.7%
	at 18 months	44.2%	27.0%
	95% CI	37.7-50.5	19.9-34.5

N: number of patiens; OS: overall survival; PFS: progression-free survival; CI confidence interval; HR: hazard ratio; NR: not reached

The study demonstrated a statistically significant improvement in progression-free survival (PFS) and overall survival (OS) (co-primary endpoints) (*Table 1*).

LIPOSOMAL IRINOTECAN (ONIVYDE®)

Liposomal irinotecan (Onivyde®) is reimbursed in association with 5-fluorouracil and leucovorin for the treatment of metastatic adenocarcinoma of the pancreas in irinotecan-naïve patients with an Eastern Cooperative Oncology Group performance status <2, progressing after gemcitabine.

In **NAPOLI-1**, 417 patients with metastatic adenocarcinoma of the pancreas who had documented progression after gemcitabine or gemcitabine-containing chemotherapy were randomised to receive liposomal irinotecan 70 mg/m² followed by folinic acid 400 mg/m² followed by 5-FU 2400 mg/m² over 46 hours every two weeks (n=117), or folinic acid 200 mg/m² followed by 5-FU 2000 mg/m² over 24 hours administered on day 1, 8, 15, and 22 of a six week cycle (n=149), or liposomal irinotecan 100 mg/m² every three weeks (n=151). Key eligibility criteria included Karnofsky Performance score (KPS) ≥70, normal bilirubin, albumin ≥3 g/dL.

The primary endpoint was OS. Median OS was 6.1 months (95% confidence interval [CI] 4.8-8.9) in patients assigned to liposomal irinotecan plus folinic acid/5-FU *vs.* 4.2 months (95% CI 3.3-5.3) in patients assigned to folinic acid/5-FU (HR 0.67; 95% CI 0.42-0.92; p=0.012).

There was no difference between patients who received liposomal irinotecan alone and those who received folinic acid/FU (HR 0.99; 95% CI 0.77-1.28; p=0.94).

OSIMERTINIB (TAGRISSO®)

Osimertinib (Tagrisso®) is now also reimbursed as **first** line treatment in patients with locally advanced or metastatic NSCLC presenting an epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R mutation.

Congress Calendar 2019

JUNE

31 MAY - 4 JUNE
ASCO 2019
Chicago, Illinois, United States
Website: https://am.asco.org/

5-8 JUNE
30th European Society of Gastrointestinal and Abdominal Radiology 2019: Annual Meeting
Rome, Italy
Website: https://www.esgar.org/

8-11 JUNE
SIO 2019: World Conference on Interventional Oncology
Boston, Massachusetts, United States
Website: http://www.sio-central.org/page/sio-2019-conference-program

13-16 JUNE 2019
24th Congress of EHA
Amsterdam, The Netherlands
Website: https://ehaweb.org/congress/eha24/

14-15 JUNE 2019
6th Gastro Update Europe
Budapest, Hungary
Website: https://gastro-update-europe.eu/

14-16 JUNE 2019
3rd Masterclass on Systematic Reviews in Cancer Care, Guidelines and Research
Belfast, United Kingdom
Website: http://bit.y/3MasterclassSystematicReviewsCancerCareGuidelinesResearch

21-23 JUNE 2019
MASCC/ISOO Annual Meeting on Supportive Care in Cancer
San Francisco, California, United States
Website: https://masccmeeting.org/2019

22 JUNE 2019
22nd Post-ASCO Meeting
La Hulpe, Belgium
Website: https://congresscare.com/congress/22nd-post-asco-meeting/

JULY

3-6 JULY 2019
ESMO 21st World Congress on Gastrointestinal Cancer
Barcelona, Spain
Website: https://www.worldgicancer.com/

19-22 JULY 2019
Immune Cell Therapies for Cancer: Successes and Challenges of CAR T Cells and Other Forms of Adoptive Therapy
San Francisco, California, United States
Website: https://www.aacr.org/Meetings/Pages/MeetingDetail.aspx?EventItemID=178

AUGUST

25-29 AUGUST 2019
ICRR 2019
Manchester, United Kingdom
Website: http://icrr2019manchester.com

29-31 AUGUST 2019
Advanced Prostate cancer consensus conference: APCCC 2019
Basel, Switzerland
Website: https://www.apccc.org/apccc2019.html

SEPTEMBER

5 SEPTEMBER 2019
ASCO Oncology Practice Conference
San Diego, California, United States
Website: https://opc.asco.org/

6-7 SEPTEMBER 2019
ASCO Quality Case Symposium
San Diego, California, United States
Website: https://quality.asco.org

7-10 SEPTEMBER 2019
IASLC 20th World Conference on Lung Cancer
Barcelona, Spain
Website: https://www.iaslc.org/events

12-14 SEPTEMBER 2019
ECCO 2019 European Cancer Summit
Brussels, Belgium
Website: https://www.eccosummit.eu

12-15 SEPTEMBER 2019
21st Annual John Goldman Conference on Chronic Myeloid Leukaemia: Biology and Therapy
Bordeaux, France
Website: http://www.esh.org/conferences/

15-18 SEPTEMBER 2019
ASTRO's 61st Annual Meeting
Chicago, IL, United States
Website: http://bit.ly/astro2019

18-22 SEPTEMBER 2019
14th Meeting of the World Federation of Neuro-Oncology (EANO)
Lyon, France
Website: https://www.eano.eu/

19-21 SEPTEMBER 2019
IGCS The global meeting of the International Gynaecologic Cancer Society
Rio de Janeiro, Brazil
Website: https://igcs2019.com/

20-22 SEPTEMBER 2019
ILCA 2019 – The International Liver Cancer Association's 13th Annual Conference
London, United Kingdom
Website: http://ilca2019.org/

27 SEPTEMBER - 1 OCTOBER 2019
ESMO 2019 Congress
Barcelona, Spain
Website: https://www.esmo.org/Conferences

OCTOBER

3-5 OCTOBER 2019
ESHNR 2019
Palermo, Sicily, Italy
Website: http://www.eshnr.eu/meetings/future-meetings/

Congress Calendar 2019

9-13 OCTOBER 2019
28th EADV Congress
Madrid, Spain
Website: https://www.eadv.org/calendar/2019

19 OCTOBER
13th Respiratory Oncology Update Meeting
Dolce La Hulpe, La Hulpe, Brussels, Belgium
Website: https://www.update-respiratoryonco.be/

23-26 OCTOBER 2019
51st SIOP 2019
Lyon, France
Website: https://siop19.kenes.com/

25-26 OCTOBER 2019
Palliative and Supportive Care in Oncology Symposium
San Francisco, California, United States
Website: https://pallonc.org/about/dates-overview

NOVEMBER

2-5 NOVEMBER 2019
21st ESGO Congress
Athens, Greece
Website: https://www.esgo.org/esgo2019/

7-9 NOVEMBER 2019
7th Trends in Head and Neck Oncology (THNO-7)
Athens, Greece
Website: https://congresscare.com/congress/7th-trends-in-head-and-neck-oncology/

13-15 NOVEMBER 2019
BSIR Annual Meeting
Manchester, United Kingdom
Website: https://www.bsir.org/meetings/

14-15 NOVEMBER
Oncologiedagen voor Nederland en Vlaanderen 2019
Papendal, Arnhem, The Netherlands
Website: http://www.nvmodagen.nl

14-16 NOVEMBER
19th SIOG Annual Conference
Geneva, Switzerland
Website: https://www.siogconference.org

14-16 NOVEMBER 2019
Advanced Breast Cancer 5th ESO-EMSO International Consensus Conference
Lisbon, Portugal
Website: http://www.abc-lisbon.org/

14-17 NOVEMBER 2019
11th European Multidisciplinary Congress on Urological Cancers (EMUC19)
Location not yet available
Website: http://uroweb.org/events/calendar/

17-19 NOVEMBER 2019
3rd International Oncology Leadership Conference (IOLC)
Antwerp, Belgium
Website: http://oncologyleadership.org/register

21-23 NOVEMBER 2019
27th COGI Congress
Paris, France
Website: http://cogi-congress.org/

DECEMBER

7-10 DECEMBER 2019
61st ASH Annual Meeting
Orlando, Florida, United States
Website: http://www.hematology.org/

10-14 DECEMBER 2019
42nd San Antonio Breast Cancer Symposium
San Antonio, Texas, United States
Website: https://www.sabcs.org/