Horizon Scanning in Oncology

Everolimus (Afinitor®) for the treatment of unresectable or metastatic neuroendocrine tumours of pancreatic origin

Ludwig Boltzmann Institut
Health Technology Assessment

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1 Drug description

Generic/Brand name/ATC code:

Everolimus/ Afinitor®/ L01XE10

Developer/Company:

Novartis Europharm Limited

Description:

everolimus is an mTOR inhibitor

Everolimus is a derivative of sirolimus and a selective inhibitor of the mammalian target of rapamycin (mTOR), a central regulator of tumour cell division and angiogenesis in cancer cells [1]. In cells, everolimus binds to the intracellular FK Binding Protein-12 (FKBP-12), forming a complex that inhibits activation of the mTOR complex-1. Inhibition of mTOR signalling pathway results in the inhibition of T- lymphocyte activation and proliferation associated with antigen and cytokine stimulation and in the inhibition of antibody production [1, 2].

recommended dose is 10mg once daily

Everolimus is administered orally. The recommended dose for the treatment of pancreatic neuroendocrine tumours (pNET) is 10 mg once daily. Management of adverse reactions may require dose alterations. If necessary, the dose is reduced to 5 mg daily [2].

Monitoring of renal function (blood urea nitrogen, urinary protein or serum creatinine), of fasting serum glucose and complete blood count is recommend prior to the start of therapy and periodically thereafter [3].

In patients with severe hepatic impairment everolimus should not be used. If patients develop severe symptoms of non-infectious pneumonitis or receive a diagnosis of invasive systemic fungal infection therapy should be discontinued. In case of infections discontinuation should also be considered [3].

2 Indication

for advanced pancreatic neuroendocrine tumours (pNET)

Everolimus is indicated for the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease.

3 Current regulatory status

approved by EMA for pNET and two other indications

In Europe, everolimus is approved by the European Medicines Agency (EMA) [2] under the trade name Afinitor® for

- the treatment of unresectable or metastatic, well- or moderately-differentiated neuroendocrine tumours of pancreatic origin in adults with progressive disease (August 2011) [2],
- the treatment of patients with advanced renal cell carcinoma (RCC) whose disease has progressed on or after treatment with VEGF-targeted treatment (2009),

and under the trade name Votubia® for

- the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) in 2011. In 2010, Votubia® was designated an orphan medicine.

In 2007 orphan designations were granted for the treatment of RCC and gastroenteropancreatic NETs. These orphan designations were withdrawn by the marketing-authorisation holder in 2011.

also approved in Europe for prophylaxis of organ rejection

Everolimus is also approved in Europe under the trade name Certican®

- for the prophylaxis of organ rejection in adult patients following allogeneic renal or cardiac transplant since 2003.

and approved by FDA

Everolimus is approved by the United States Food and Drug Administration (FDA) :

- under the trade name Afinitor® for progressive neuroendocrine tumours of pancreatic origin that is unresectable, locally advanced or metastatic in 2011,
- for the indication SEGA in 2010,
- and for RCC in 2009 [4],
- under the trade name Zortress ® for prophylaxis of organ rejection in adult kidney transplant recipients in 2010 [5].

4 Burden of disease

Neuroendocrine tumours (NETs) comprise a group of neoplasms that originate from neuroendocrine cells. Even though the nomenclature used is not consistent, the most common NETs are carcinoids which arise from lungs, bronchi, small intestine, appendix and rectum, whereas pNETs arise from the endocrine tissue of the pancreas [6, 7]. pNETs are described as having a different response to therapeutic agents and a more aggressive clinical course compared to carcinoids [8].

most common NETs are carcinoid and pancreatic

NETs can be further sub-classified histologically into well-differentiated and poorly-differentiated NETs. Furthermore, different grades can be assigned to these tumours (i.e. low-grade, intermediate-grade, high-grade) which reflect the aggressiveness of the disease [9].

pNETs are tumours of endocrine cells of pancreas (=islet cell tumours)

The term pNET - "islet cell tumour" (islet cells are hormone producing cells in the pancreas) is sometimes used as synonym - refers to well-differentiated low- or intermediate grade tumours, whereas poorly differentiated high grade tumours are referred to as pancreatic neuroendocrine carcinomas [9, 10].

If pNETs produce hormones and thus cause specific symptoms of hormone hypersecretion, the tumours are "functional" [11] and are called according to the main hormone. The most common functional tumours are "insulinomas", "glucagonomas" and "gastrinomas" which present with hypoglycaemia (due to insulin), diabetes mellitus (glucagon) or recurrent peptic ulcer disease (gastrin). Further types include somatostatinomas, VIPomas and PPomas [7, 11]. The malignant potential of functional pNETs depends on the type of the tumour and is low in insulinomas but high in glucagonomas or gastrinomas [7, 9, 11].

functional and non-functional pNETs

functional pNETs present with specific symptoms due to hormone hypersecretion

Non-functional pNETs, in contrast, do not produce specific clinical syndromes, and they thus present at later stages, e.g. with symptoms of tumour bulk [11]. Up to 90% of the non-functional tumours are malignant [6].

Even though functionality is discussed as having an impact on prognosis, functional tumours are classified according to grade and staging, like non-functional tumours. The evidence is conflicting which of these tumours are more frequent [2, 6, 10, 11]. Estimates for non-functional tumours range between 15% [6, 11] and 75% [2, 10], but functional status may also change with treatment or over time [12].

rare tumours

PNETs are rare, with an incidence of 0.2-0.4 per 100,000 people per year [7]. Peak incidence is around 40 - 69 years [6]. Malignant pNETs may account for circa 1% of pancreatic cancers by incidence and 10% by prevalence (NCCN). In Austria [13] approx. 1,400 new cases of pancreatic cancer were seen in the year 2009. Based on these figures, 14 new malignant pNET cases per year could be expected to occur (own calculation).

risk factors are poorly understood

The majority of pNETs are sporadic and risk factors are not well understood. They may occur as part of an inherited genetic syndrome, such as multiple endocrine neoplasia (MEN) type 1 or MEN2. In that case patients require different strategies than those with usually solitary, sporadic tumours [6, 11].

clinical course variable

The clinical course of the disease is said to be highly variable, even in the presence of liver metastases [14]. Five-year survival with localised and resected pNET is around 55%, but only about 15% when the tumour is not resectable [11].

5 Current treatment

surgery

Therapy of choice for patients with localised pNETs is surgical excision. Since patients with pNET frequently develop liver metastases, surgery of liver metastases and the primary tumour is also indicated, if possible.

hepatic regional therapy

For patients with unresectable liver metastases palliative treatment options comprise hepatic regional therapies, including arterial embolisation, radioembolisation, chemoembolisation and local ablative therapy such as radiofrequency ablation and cryoablation.

biological therapies

However, the majority of patients with advanced disease have unresectable tumours. If the disease is stable, tumour burden low and the tumour asymptomatic careful observation may be best [6]. For patients who are clinically symptomatic from tumour bulk and/or those with significantly progressing disease systemic treatment options include [6, 15]:

- Biologically targeted agents such as sunitinib which is approved for the treatment of unresectable or metastatic well-differentiated pNET with disease progression in adults.

somatostatin analogues

- Somatostatin analogues include octreotide and lanreotide. Patients with symptoms of hormone secretion can be considered for treatment to manage their symptoms. Only octreotide is approved for symptomatic treatment of VIPomas and Glucagenomas with clinical features.
- Cytotoxic chemotherapy for unresectable or metastatic disease. Combinations (none of which are approved in pNET) include

chemotherapy

  - streptozocin combinations: streptozocin plus doxorubicin, streptozocin plus 5-fluorouracil and doxorubicin
  - dacarbazine- and temozolomide-based regimens: dacarbazine alone or temozolomide either alone or in combination with other agents (e.g. capecitabine)

6 Evidence

In addition to a free text search, a systematic literature search was conducted in Embase, Ovid Medline, CRD Database and Cochrane Library. 91 references were identified. Regarding the approved indication pNET, one phase III trial (Radiant-3 [16]) and 2 phase II trials [8, 12] were identified.

one phase III trial in pNET

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title A randomised double-blind phase III study of RAD001 10mg/d plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced pancreatic neuroendocrine tumour [2, 16]			
Study identifier	ClinicialTrials.gov number: NCT00510068, RADIANT-3, EUdraCT: 2006-006819-75, Sponsor's Protocol Code Number: CRAD001C2324		
Design	Phase III, randomised, double-blind, multicentre (82 centres in 18 countries), placebo controlled		
	Duration	Enrolment: July 2007 until May 2009 Median follow-up: 17 months Cut-off date for final analysis: 28th February 2010	
Funding	Novartis Oncology		
Hypothesis	Superiority		
Treatment groups	Intervention	Everolimus 10mg (could be reduced to 5mg) once daily plus best supportive care (BSC)	
	Control	Placebo once daily plus BSC	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Time from randomization to documented disease progression defined according to RECIST 1.0 (19) or death due to any cause
	Overall survival	OS	Time from randomisation to death due to any cause
	Objective response rate	ORR	Complete response or partial response according to RECIST 1.0
Results and analysis			
Analysis description	Primary analysis: The primary analysis was performed in the full analysis set population and based on the local investigator assessments. The primary analysis was analysed using a stratified one-sided log-rank test. The test was stratified by whether or not patients had received prior cytotoxic chemotherapy and by WHO performance status (0 versus 1 or 2) at baseline. PFS and OS were analysed by Kaplan–Meier method and study groups compared with log-rank test. Groups were stratified according to prior receipt of chemotherapy and WHO performance status. Hazard ratio was estimated with stratified Cox proportional hazards model.		
Analysis population	Inclusion	Advanced (unresectable or metastatic) biopsy-proven pNET, radiological documentation of disease progression within 12 months, confirmed low-grade or intermediate-grade NET, measurable disease per RECIST 1.0, WHO – PS ≤2	

	Exclusion	Poorly-differentiated or high-grade NET; hepatic-artery embolisation within 1-6 months or cryoablation or radiofrequency ablation of hepatic metastasis within 2 months before enrolment; severe or uncontrolled medical condition; prior therapy with an mTOR inhibitor	
	Characteristics	Median age: I 58 years (range 23 -87) vs. C 57 years (20 – 82) Gender: Females: I 47% vs. C 42%, Male: I 53% vs. C 58% WHO-PS: 0-1: I 97% vs. C 97% Histology: well differentiated: I 82% vs. C 84%, moderately: I 17% vs. C 15%, unknown: I 1% vs. C 1% Prior therapy: biopsy: I 74% vs. C 72%, other surgery: I 59% vs. C 59%, any medications: I 58% vs. C 58%, chemotherapy: I 50% vs. C 50%, targeted therapy: I 5% vs. C 7%, immunotherapy: I 3% vs. C 4%, hormonal therapy: I 1% vs. C 1%, other: I 10% vs. C 13%, any radiotherapy: I 23% vs. C 20% Further characteristics: liver metastases: I 92% vs. C 92%; gastrinoma, glucagonoma, VIPoma, insulinoma or somatostatinoma: present in 24% (I and C)	
Descriptive statistics and estimated variability	Treatment group	*Control*	*Intervention*
	Number of subjects	203	207
	PFS by INV (months) Median 95% CI	 4.6 3.1-5.4	 11.0 8.4-13.9
	PFS by IAC (months) Median 95% CI	 5.4 4.3-5.6	 11.4 10.8-14.8
	OS (months) Median 95% CI	 NA	 NA
	ORR (%) by INV 95% CI Partial Response (%) Complete Response (%) Stable Disease (%) Progressive Disease (%) Unknown (%)	2.0 0.5-5.0 2.0 0 50.7 41.9 5.4	4.8 2.3-8.7 4.8 0 72.9 14.0 8.2
Effect estimate per comparison	*Comparison groups*		*Intervention vs Control*
	PFS (INV)	Hazard ratio	0.35
		95% CI	0.27-0.45
		P value (log-rank test)	<0.001
	PFS (IAC)	Hazard ratio	0.34
		95% CI	0.26-0.44
		P value (log-rank test)	<0.001
	OS (data cut-off February 2010)	Hazard ratio	1.05
		95% CI	0.71-1.55
		P value (log-rank test)	0.594
	OS (90-Day Safety Update, data cut-off June 2011)	Hazard ratio	0.99
		95% CI	0.68 - 1.43
		P Value	NA

	OS (CHMP requested update, data cut-off 23 February 2011)	Hazard ratio	0.89
		95% CI	0.64 - 1.23
		P Value	NA
	ORR	P value	0.091

Abbreviations: WHO-PS= WHO - Performance status, INV= local investigator assessment, IAC= central adjudication committee assessment, NA = not available, CHMP = Committee for Medicinal Products for Human Use

Table 2: TRAEs according to grade, TRAEs leading to discontinuation or dose modification, AEs leading to death (study NCT00510068 [16])

Grade (according to CTC version 3.0)	**Outcome, n (%)**	**Control** (n=203)	**Intervention** (n=204)
All Grades, occurring at least in ≥20%	Stomatitis	34 (17)	131 (64)
	Rash	21 (10)	99 (49)
	Diarrhoea	20 (10)	69 (34)
	Fatigue	29 (14)	64 (31)
	Infections	12 (6)	46 (23)
	Nausea	37 (18)	41 (20)
	Peripheral oedema	7 (3)	41 (20)
	Decreased appetite	14 (7)	40 (20)
Grade 3 or 4, occurring at least in ≥4%	Stomatits	0 (0)	14 (7)
	Anaemia	0 (0)	12 (6)
	Hyperglycaemia	4 (2)	11 (5)
	Thrombocytopenia	0 (0)	8 (4)
Most common TRAEs leading to dose modification	Stomatitis	(<1)	(10)
	Pneumonitis	NA (0)	NA (7)
	Thrombocytopenia	NA (0)	NA (7)
	Diarrhoea	NA (0)	NA (4)
	Anaemia	NA (0)	NA (3)
Others	TRAEs leading to discontinuation	NA (2)	NA (13)
	AEs leading to death	1 (<1)	7 (3)

Abbreviations: TRAE= treatment related adverse event, AE=adverse event, NA = not available

phase III trial in pNET

to show superiority of everolimus versus placebo in PFS

In the **phase III Radiant-3** trial [2, 16] everolimus 10mg daily (N=207) was compared to placebo (N=203) in patients who had advanced, low- or intermediate-grade pNET and radiologic progression within the previous 12 months. Patients were stratified according to prior chemotherapy and WHO-PS [16]. Primary end point was progression-free survival (PFS), originally planned as per central adjudication committee assessment, but then amended to PFS as per local investigator assessment. Secondary end points included overall survival (OS), overall response rate (ORR) and safety. Treatment continued until disease progression, unacceptable toxicity, drug interruption for ≥ 3 weeks, or withdrawal of consent. Data for PFS was censored at time of last adequate tumour assessment before the cut-off date. Tumour measurements (CT, MRT) were performed at baseline and repeated every 12 weeks. Scans were reviewed at the local site and centrally.

PFS was 11.0 compared to 4.6 months, HR was 0.35 (significant)

no significant difference in OS but immature data and cross-over to everolimus allowed

The primary efficacy analysis was conducted when 274 PFS events had occurred ; median follow-up time was 17.0 months. Median PFS (by local investigator assessment (INV)) was with 11.0 months significantly longer in the everolimus arm than with 4.6 months in the placebo arm (HR: 0.35, 95% CI: 0.27-0.45, $p<0.001$). This was supported by the results of the central adjudication committee (IAC) assessment which found 11.4 months compared to 5.4 months (HR: 0.34, 95% CI: 0.26–0.44, $p<0.001$). In contrast, ORR was low in both groups (everolimus: 4.8% vs. placebo: 2.0%) and even these numbers were achieved only due to partial responses, corresponding to 36 patients needed to be treated with everolimus to achieve one partial response which would have not been achieved with placebo. The authors correctly mentioned that the primary benefit from everolimus is thus stabilisation of disease rather than tumour shrinkage. No statistically significant difference was observed between the treatments with respect to OS as of cut-off date February 2010. But these data were not mature and since 148 (73%) of the 203 patients initially assigned to placebo crossed-over to open-label everolimus, any future investigation of the presence of a survival benefit will be confounded.

subgroup analysis supported PFS results

A subgroup analysis showed consistent results across all subgroups in PFS (by e.g. age, gender, WHO-PS, liver involvement, well- vs. moderately differentiated tumour grade, prior vs. no prior chemotherapy). Exploratory investigation of biomarker levels (CgA, NSE, Ki67) did not show that they were predictive of response.

dose adjustment due to stomatitis, pneumonitis, thrombocytopenia

most common grade 3 or 4 events were stomatitis, anaemia, hyperglycaemia

In the Radiant-3 trial treatment related adverse event (TRAEs) leading to discontinuation were seen in 13% of the patients who received everolimus vs. 2% of those with placebo. Dose adjustment was required by 59% of patients in the everolimus group vs. 28% of those in the placebo group. Most commonly this was due to stomatitis, pneumonitis and thrombocytopenia. Serious TRAEs occurred in 22% of individuals treated with everolimus group and in. 4% treated with placebo. 3.4% (i.e. 7 patients) in the everolimus and 0.5% (i.e. 1 patient) in the placebo group died due to AEs, yielding a number needed to harm of 34 patients. Causes of death in patients treated with everolimus included acute renal failure, acute respiratory distress (ARDS), cardiac arrest, death with unknown cause, hepatic failure, pneumonia and sepsis. In one case ARDS was the AE considered to be related to everolimus. The most frequently occurring TRAEs of all grades were stomatitis, rash and diarrhoea, those of grade 3 or 4 were stomatitis, anaemia and hyperglycaemia.

6.2 Efficacy and safety - further studies

A **phase II, open-label, non-randomised, uncontrolled trial** [2, 12] (NCT00363051) investigated everolimus 10mg daily in patients with metastatic pancreatic NETs who experienced progression on or after chemotherapy. Patients were stratified according to prior octreotide treatment. Stratum 1 (s1) consisted of 115 patients who had not received prior octreotide, whereas stratum 2 (s2) comprised 45 patients with prior octreotide treatment, who continued with their entry dose of octreotide long-acting release (LAR intramuscularly every 28 days) in addition to everolimus.

everolimus with/ without octreotide

Primary endpoint was ORR (ICR). It was seen in 9.6% of patients in stratum 1 (95% CI: 4.9-16.5%) and in 4.4% (95% CI: 0.5-15.1%) in stratum 2. Again, these results are attributable to partial responses only. Median PFS (IRC) was 9.7 months (95% CI: 8.3-13.3 months) in s1 and 16.7 months (95% CI: 11.1 months–not available) in s2. Median OS was 24.9 months (95% CI: 20.2–27.1 months) in s1, but had not been reached for s2. The most frequent TRAEs of any grade were stomatitis, rash, diarrhoea, fatigue and nausea. The most frequent TRAEs of grade 3 or 4 were asthenia in s1 (5%) and thrombocytopenia in s2 (9%). AEs most commonly requiring dose adjustment or interruption were hyperglycaemia (8%), stomatitis (7%) and diarrhoea (5%) in s1 and thrombocytopenia (11%), pyrexia (11%) and stomatitis (9%) in s2. Pneumonitis or interstitial lung disease was seen in 6/7 patients (s1/s2), all were grade 1 or 2.

PFS 9.7 months with mono-therapy, 16.7 with prior and continued octreotide

most frequent TRAEs asthenia or thombocytopenia

Another **phase II non-randomised, uncontrolled trial** [8] investigated everolimus 5mg/d and 10mg/d in combination with octreotide LAR (30mg every 28 days) in patients with advanced (metastatic or unresectable) low- to intermediate-grade NETs. 30 patients with carcinoid and 30 with islet cell tumours (including MEN1) were enrolled; proportionally more patients with carcinoid were treated with 5mg/d whereas those with islet cell tumours received mainly 10mg/d everolimus.

2 dosages, with octreotide

in carcinoid and pNET

ORR was 20% in the intention to treat and 22% in the per protocol population. Again, these results were solely attributable to partial responses (carcinoid: 17%, islet cell tumour: 27%). Overall, median PFS was 60 weeks (95% CI 54-66 weeks) - 63 weeks in patients with carcinoid (95% CI: 55-71 weeks) and 50 weeks in those with islet cell tumours (95% CI: 31-70 weeks). Median PFS was 50 weeks with 5mg/d (95% CI: 23-78 weeks) and 72 weeks with 10mg/d (95% CI: 60-83 weeks). Most common grade 3 or 4 AEs were fatigue, diarrhoea and hypophosphataemia (all: 11%). In the 5mg/d cohort no pneumonitis was seen, but in the 10mg/d cohort 9% had grade 2 and 3% had grade 3 pneumonitis.

PFS 60 weeks, 63 in carcinoid, 50 in pNET

pneumonitis only seen in higher dose with 12%

7 Estimated costs

The price for one package Afinitor® 10 mg, containing 30 tablets and therefore lasting for a month, is € 3,600 [17]. This corresponds to € 120 for one tablet daily. These costs occur as long as clinical benefits can be observed and toxicity remains acceptable. In the phase III trial, Radiant-3, median duration of treatment with everolimus was 38 weeks. Assuming the same

monthly costs of €3,600

treatment duration, overall costs in addition to expenses for previous therapies would be € 31,920.

Because the preferred sequence of available therapies in advanced pNET is not clear, some of these costs could be additive and others alternative to existing ones.

8 On-going research

One on-going phase III trial investigating everolimus in NETs was found on the EU Clinical trials Register [18]:

- CRAD001k24133: An open-label, multi-centre, expanded access study of everolimus in patients with advanced NET. The study evaluates the safety of everolimus in patients with advanced NET of gastrointestinal, lung or pancreatic origin.

range of on-going phase II trials in pNET

A range of on-going or recently completed phase II trials investigating everolimus in NETs including those of the pancreas, was found on ClinicalTrials.gov [19]. These trials investigate everolimus as mono-therapy or in combination with pasireotide, temozolomide, octreotide, or octreotide and bevacizumab (NCT00843531, NCT01469572, NCT01229943, NCT01374451, NCT00576680).

range of on-going phase III trials in different indications

A range of on-going phase III trials investigating everolimus in the following indications were found on ClinicalTrials.gov [19]:

- breast cancer, skin cancer, B-cell lymphoma, gastric cancer, oesophagogastric junction cancer, hepatocellular carcinoma
- renal, cardiac, liver and lung transplantation
- polycystic kidney disease, renal interstitial fibrosis, coronary artery disease

9 Commentary

Everolimus (Afinitor®) was approved by the EMA for the treatment of advanced pNET in patients with progressive disease in August 2011 [2]. This decision was mainly based on the results of the Radiant-3 trial, which showed a prolongation of PFS by 6.4 months (as assessed by the local investigators) for patients treated with everolimus in comparison to patients treated with placebo. No advantage in OS was observed with everolimus compared to placebo as of the final analysis, but data were not mature and since patients were allowed to cross-over to the active treatment arm, the analysis will be impaired. Therefore, it remains unclear whether the observed improvement in PFS will translate into survival benefit.

everolimus for pNET licensed in August 2011

positive effect on PFS compared to placebo

unclear whether it translates into survival benefit

In patients with unresectable or metastatic pNET, but stable and asymptomatic disease, careful observation may be best [6]. For patients with progressive disease treatment options are limited. Among available therapies, sunitinib, another targeted therapy, was approved by the EMA for the treatment of unresectable or metastatic, well-differentiated pNET with disease progression in November 2010 [20]. For sunitinib, a gain of 5.9 months in PFS was found in comparison to placebo within a phase III trial [21].

treatment option once disease progression is observed

Since tumour response was observed in only 4.8% of patients treated with everolimus, all of which were partial responses, the effect of everolimus primarily lies in disease stabilisation. Hence it is questionable if patients with considerable symptomatic tumour bulks will benefit best from everolimus or if chemotherapeutic regimens which have yielded higher response rates are preferable [6, 15]. Therefore, head-to-head studies comparing these regimens would be of interest in order to elicit the most beneficial therapy. In the absence of comparative efficacy data the choice of agents thus may also be based on the toxicity profiles [15].

other options sunitinib, chemotherapy

comparative data of interest

For poorly differentiated, highly aggressive malignancies other treatment options are recommended (such as platinum-based chemotherapy [15, 22]). Also, everolimus has not shown to be superior to placebo in *carcinoid* tumours, because one phase III study, the Radiant-2 trial, failed to show that everolimus plus octreotide had a significant effect on PFS (boundary for statistical significance was not met), OS or ORR in these tumours [2, 23].

everolimus has not shown improvements for carcinoid tumours

Another open question concerns the best sequence of therapies. EMA's Committee for Medicinal Products for Human Use (CHMP) mentioned that due to the low number of treatment-naïve patients in the trial assessing sunitinib, evidence for the first-line setting is limited [20]. The Radiant-3 trial does also not clearly answer in which setting everolimus is indicated best, because about half of the study population had received prior chemotherapy and the other half had not. However, at least a subgroup analysis of the Radiant-3 trial provides some results on the influence of prior or no prior chemotherapy on PFS, always favouring the everolimus group.

sequencing of therapies?

everolimus best for first- or second-line?

no quality of life data

As quality of life was not included as an endpoint in Radiant-3, it is not known whether the improvement in PFS was achieved without negatively affecting quality-of-life. Also, dose adjustments were necessary in 59% of patients in the everolimus group (C 28%). The most common TRAEs making dose adjustment necessary were stomatitis, pneumonitis, thrombocytopenia, diarrhoea and anaemia and 3.4% in the everolimus and 0.5% in the placebo group died due to AEs [16]. According to the CHMP safety of everolimus in pNET has shown to be largely consistent with what is already known from previous studies in oncology. Adverse events were mostly low-grade and reversible, but were higher compared to other indications such as renal cell carcinoma. In the safety population (pooled data set of phase III studies Radiant-3, Radiant-2 and phase II trial NCT00363051) the incidence of grade 3 and 4 AEs was around 70% [2].

e.g. stomatitis, pneumonitis

AEs low-grade but higher compared to other indications

everolimus under investigation also for other indications

high potential for off-label use

As pNETs are very rare tumours which affect only few people, overall costs for everolimus therapy are in the first instance not high for this indication. Because the drug is currently tested as combination therapy in phase II studies with drugs like pasireotide, temozolomide, octreotide, or octreotide and bevacizumab, costs for the treatment of pNET patients might increase considerably. Since everolimus is also under investigation for several other indications such as breast cancer, skin cancer, B-cell lymphoma or gastric cancer, the potential for off-label use is high.

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