Everolimus (Afinitor®, RAD001): Current and Future Development Across Multiple Indications

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Everolimus is a rapamycin derivative that acts as a signal transduction inhibitor. Its target is mTOR (mammalian target of rapamycin), a key serine-threonine kinase regulating protein synthesis and ultimately cell growth, cell proliferation, angiogenesis, and survival. Downstream of PI3/AKT, mTOR can be considered as a component in the PI3K/AKT/mTOR pathway known to be dysregulated in numerous human cancers.

Everolimus has been in development across a variety of tumor types in areas of significant unmet medical need since 2002, both as monotherapy and in combination. Two administration schedules have been thoroughly assessed: intermittent (70 mg weekly) and daily (10 mg) – the latter providing continuous inhibition of mTOR. Accumulating preclinical and clinical evidence suggests that continued mTOR inhibition is associated with a higher degree of efficacy.

Everolimus is currently under regulatory assessment for the treatment of patients with advanced renal cell carcinoma (RCC) after failure of VEGFR-TKI therapy (sunitinib and/or sorafenib). Median progression-free survival of 4.9 months and 1.9 months were reported for everolimus and placebo, respectively (HR 0.33, p<0.001). Efficacy results were consistent across subgroups (age, gender, prior therapy, race, … etc). Most common adverse reactions were stomatitis, rash, fatigue, and diarrhea.

Safety and efficacy data from a large number of phase-I/II trials have led to the development of several pivotal phase-III registration studies.
This broad development program reflects indications (both oncology and non-malignancies) where everolimus may convey potential benefit in areas of high unmet medical need. Updated safety and efficacy data will be presented.

Everolimus (Afinitor®, RAD001): placebo-controlled phase III clinical development program

Indication	Patient population	Main endpoints
10 mg daily monotherapy		
Renal cell carcinoma	2nd/3rd-line after failure of sunitinib and/or sorafenib N=416, 2:1 randomization	PFS, OS
Pancreatic islet cell tumors	1st/2nd-line N=392	PFS, ORR, OS
Gastric carcinoma	2nd/3rd-line after failure of fluoropyrimidine-containing therapy N=633, 2:1 randomization	OS, PFS
Tuberous sclerosis complex	Growing subependymal giant cell astrocytomas (SEGA) N=99, 2:1 randomization	ORR, TTP, seizure control, surgical intervention, cognitive function
	Large kidney angiomyolipoma (≥ 3 cm) N=99, 2:1 randomization	ORR, TTP, seizure control, surgical intervention, cognitive function
Lymphoma	DLBCL – maintenance therapy after complete response on R-CHOP N=915, 2:1 randomization	Time to recurrence, OS
10 mg daily combination therapy		
Carcinoid tumor	Progressing secretory tumors N=426	PFS, ORR, duration of response, OS Sandostatin LAR® Depot ± everolimus
Breast, Her2/neu +	1st line, no prior therapy for advanced disease N=717, 2:1 randomization	PFS, OS, ORR, CBR Paclitaxel (80 mg/m²) d1, 8, 15 q4 w + weekly trastuzumab ± everolimus
	Trastuzumab-resistant, ≤ 3 prior chemotherapy regimens for advanced disease, prior taxane treatment N=572	PFS, OS, ORR, CBR Weekly vinorelbine (25 mg) + weekly trastuzumab ± everolimus
Breast, ER+	Refractory to letrozole or anastrozole N=705, 2:1 randomization	PFS, OS, ORR, CBR Exemestane (25 mg daily) ± everolimus
7.5 mg daily monotherapy		
Hepatocellular carcinoma	Advanced disease after progression on or intolerance to sorafenib N=681, 2;1 randomization	OS, TTP

CBR: Clinical benefit rate; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; TTP: Time to progression