SOMATOSTATIN RECEPTORS IN HEPATOCELLULAR CARCINOMA

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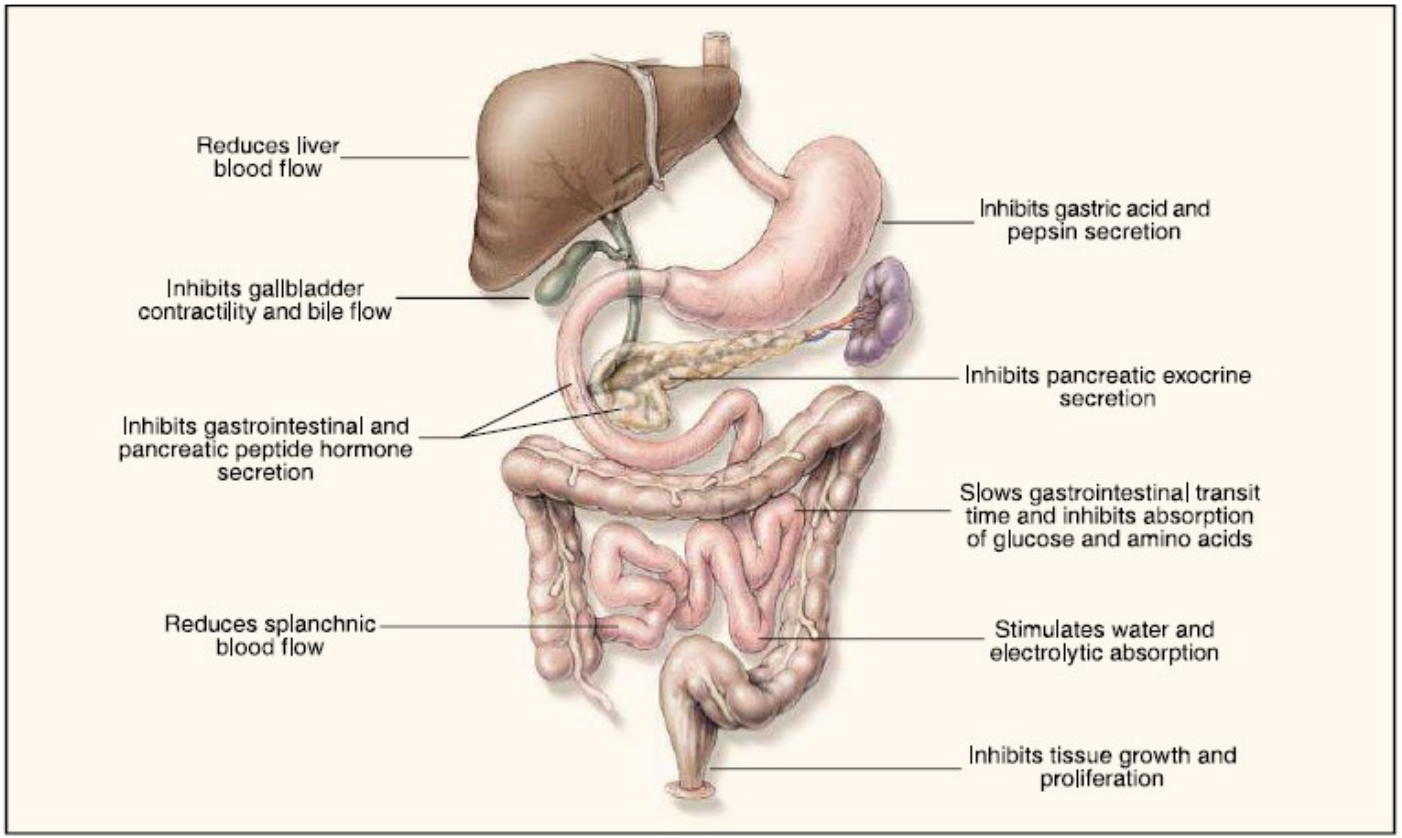
Somatostatin : SST

- Somatostatin (SST) protein : 2 active forms (alternative cleavage of a single one) : SST14 and SST28
- Somatostatin acts as an inhibitory peptide of various secretory and proliferative processes
- Effect on the hypothalamus : inhibition of GH, TSH and PRL

Lambert *et al* 1996

Effects of SST on gastrointestinal tract



Reduction of :

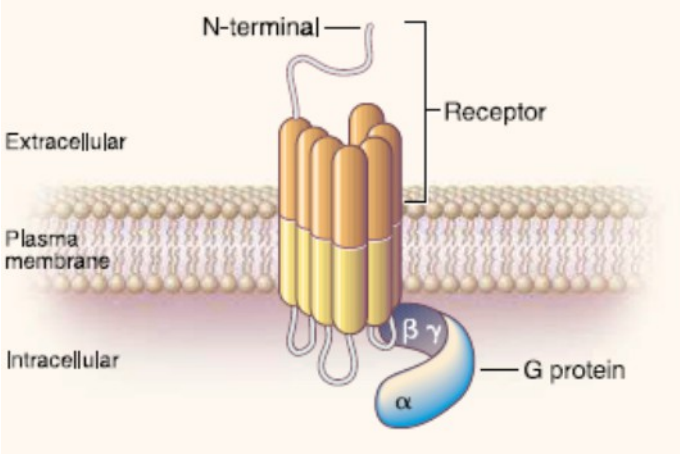
Gastrin
cholecystokinin
Glucagon
secretin
VIP
GIP
insulin

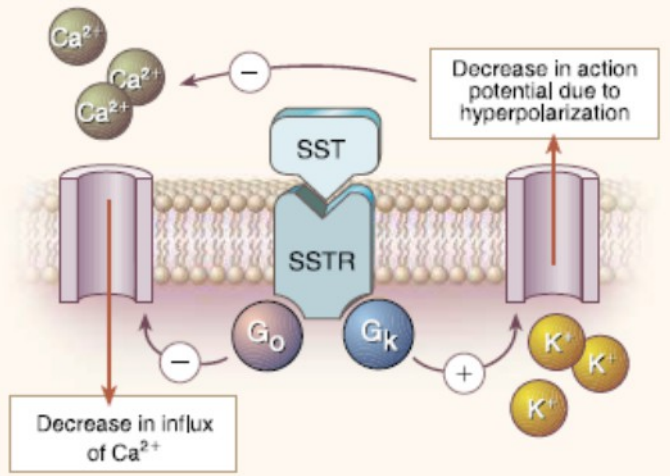
Lambert *et al* 1996

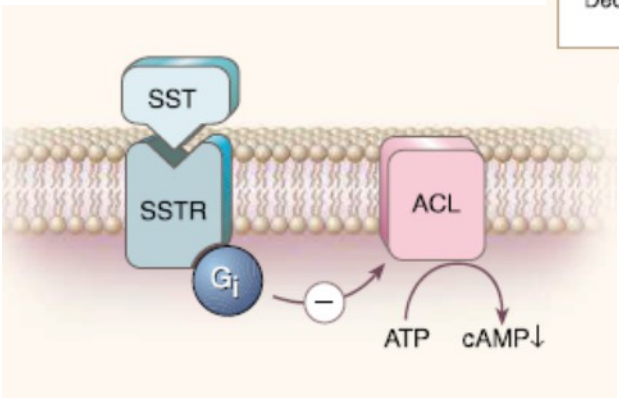
Somatostatin receptors : SSTRs

- 5 subtypes : SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5
- Both SST14 and SST28 binds all SSTR subtypes with high affinity
- Somatostatin analogs (octreotide, lanreotide and pasireotide) binding :
  - SSTR2 with high affinity
  - SSTR1, 3 and 5 with much less affinity
  - no binding demonstrated for SSTR4

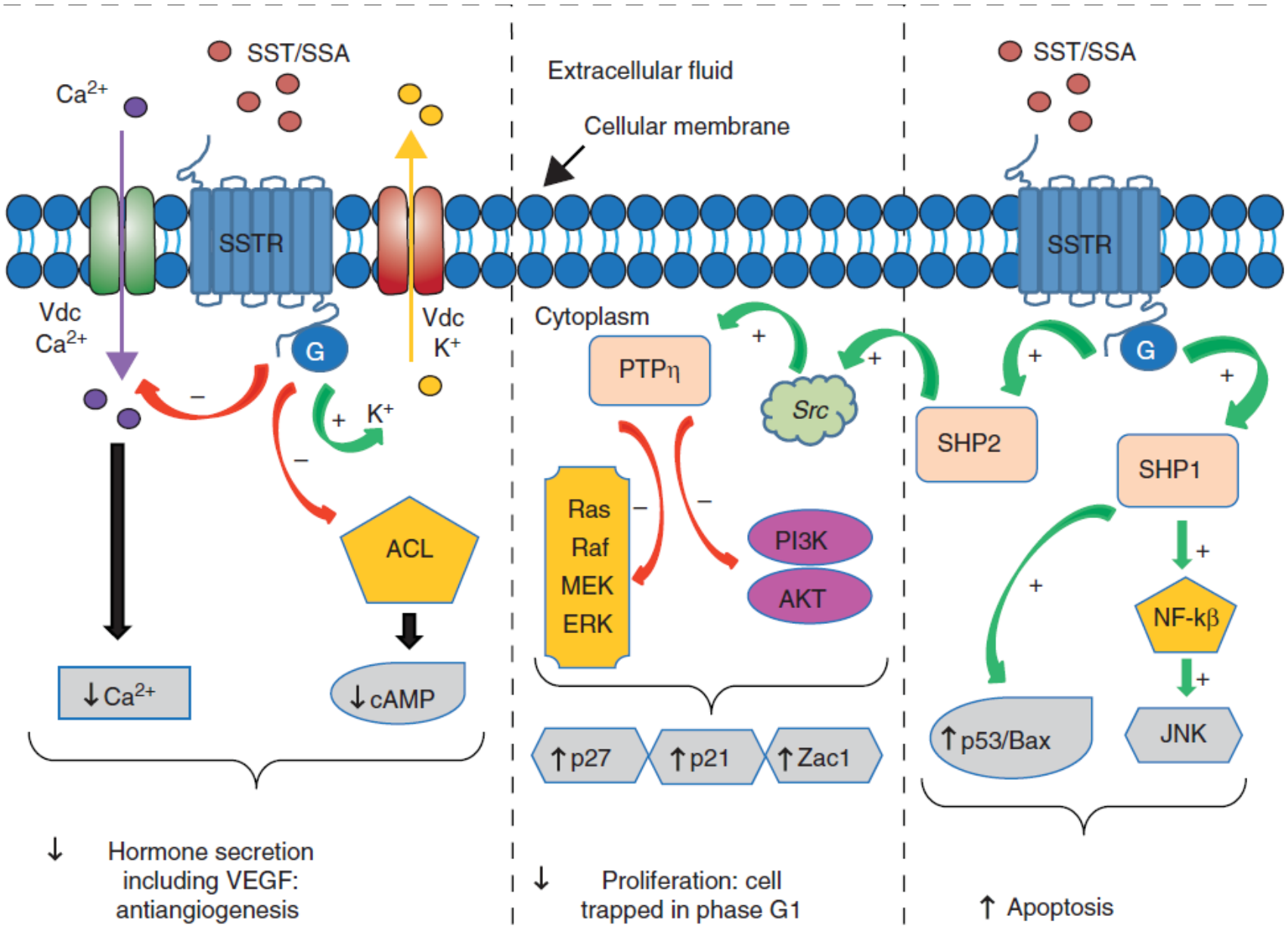
SSTR







Lambert *et al* 1996



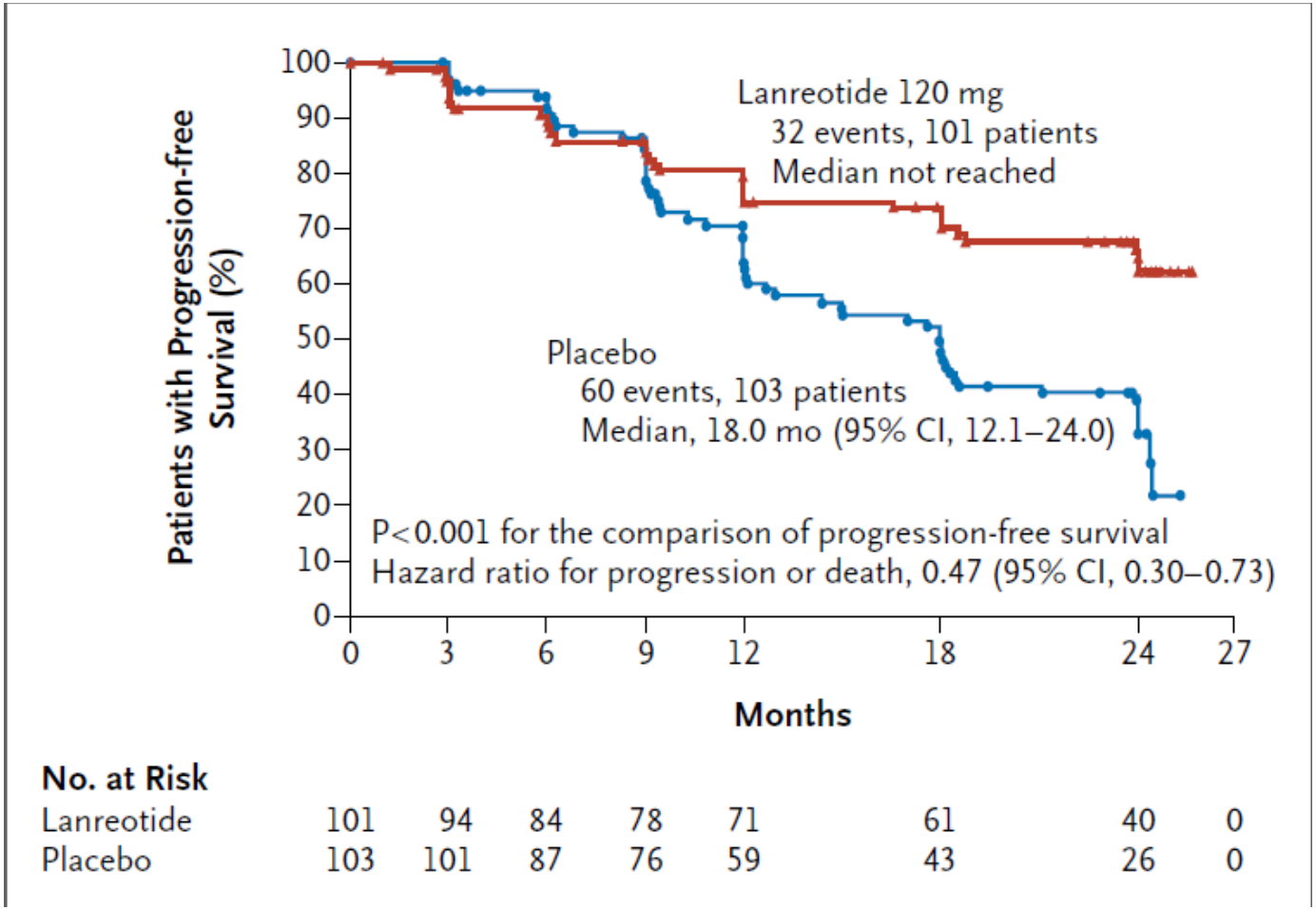
Abdel-Rahman *et al*. 2014

SSTRs and solid tumors

- Many translational studies : 2 main failures :
  - Breast Cancer (Ingle *et al* 1999- Bajetta *et al* 2002)
  - Colorectal cancer (Goldberg *et al* 1995)

- SSA therapy has been demonstrated in advanced NETs in 2 large randomized studies reporting significant and clinically relevant benefit :
  - PROMID (Rinke *et al* 2009)
  - CLARINET (Caplin *et al* 2014)

NET = the only clinical setting where SSAs can be used for tumor control outside a clinical trial



Progression-free Survival (Intention-to-Treat Population).

Caplin ME *et al*. NEJM 2014

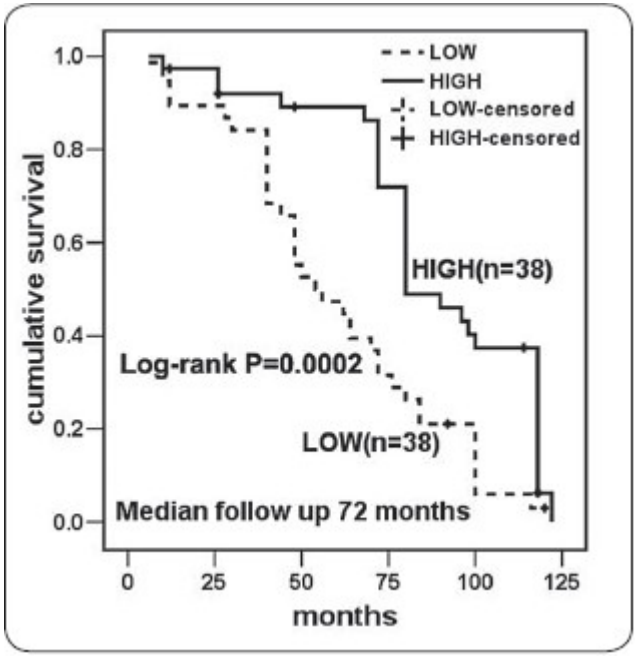
SSTR expression in HCC?

SSTR expression in HCC

1st Author	journal	Origin of tissue	Number of samples	Results for PCR	Results for IHC
Blaker	J hepatol 2004	resection, LT	56 for IHC 6 for PCR	-	SSTR 5 (75%) > SSTR3 (64%) > SSTR1 (46%) > SSTR2 (41%) SSTR 4 : 0%
Reynaert	Gut 2004	resection, LT	6 T/NT 3 normal liver	Positive for SSTR1 and 2 but no variation between T/NT SSTR 3 and 4 : almost undetectable in T	Nomal liver : 0 Cirrhotic hepatocytes : SSTR1> SSTR2, 3, 4, 5 HCC / SSTR1, 2> SSTR3, 4
Nguyen-Khac	Cancer biol ther 2009	Biopsies	7 T	-	SSTR2A detected in cytoplasm and at membran in 6 patients /7
Cebon	Brit J Cancer 2006	Archival paraffin-embedded tissue	20T	-	Not enough receptors for meaningful staining with the antiserum SS800.
Verhoef	Dig surg. 2007	Resection	45	-	SSTR2 detected by IHC in 30 tumors (67%)
Koc	Hepatogastro. 2013	Biopsies	41	-	SSTR 1 (76%), SSTR5 (51%)
Reubi	Gut 1999	Resection/ biopsies	59	-	SSTR1-5 expression using radiolabelled octreotide in 41% of HCC no expression in normal liver.
Xie	Ai Zheng 207 (chinese)		40 HCC 40 cirrhosis	-	In HCC : SSTR2 (70%)> SSTR5 (67%) >SSTR3(50%) surrounding cirrhotic tissue higher than HCC

Prognostic value of SSTR expression : one positive study

- 76 resected HCC HBV related and paired non tumoral tissue
- Immunohistochemical results :
  - 38 patients (50%) low SSTR-2 expression in T
  - 32 patients (42%) high SSTR-2 expression in T .
  - Improved survival in the high SSTR-2 group

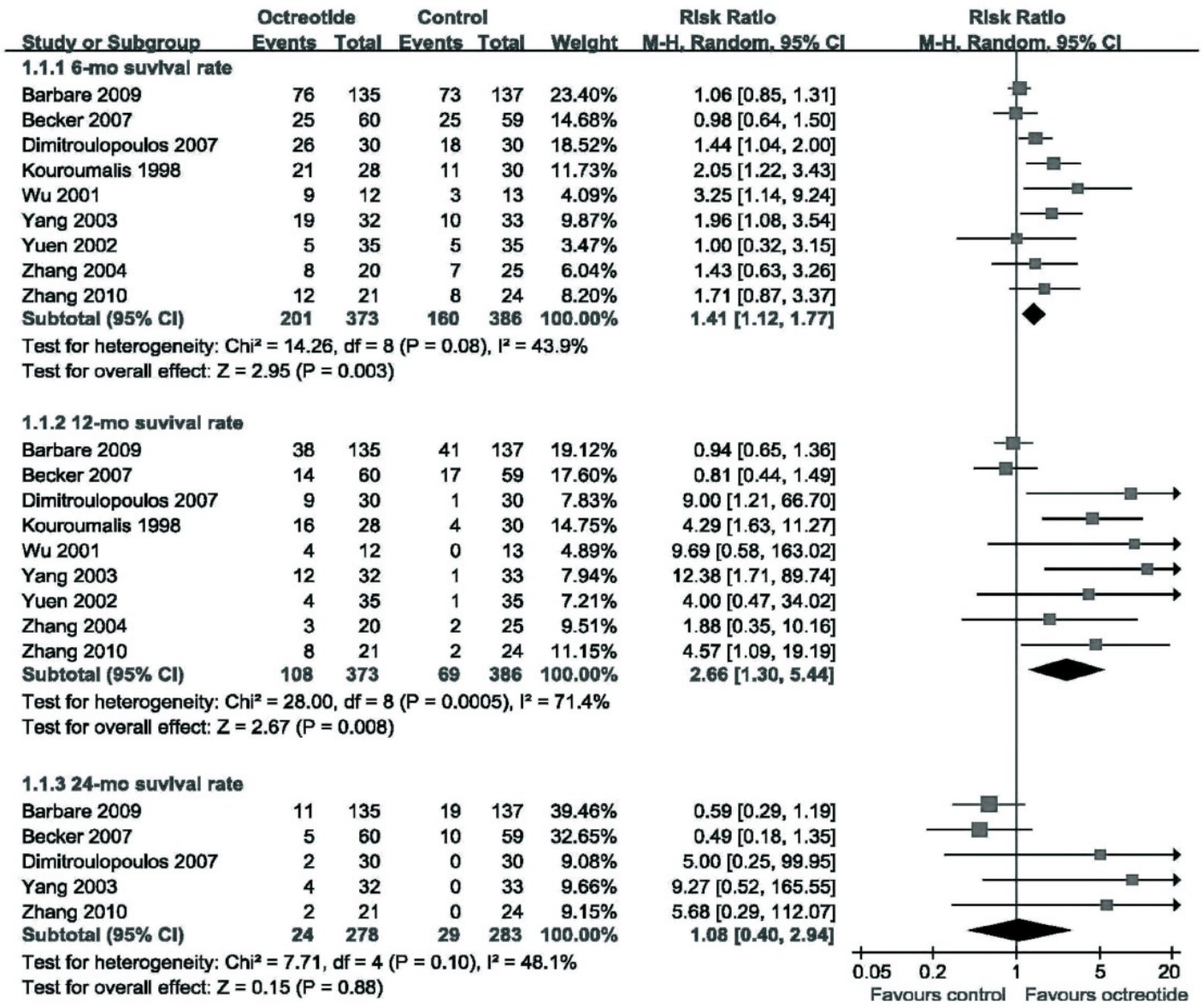


Li *et al* Hepatogastroenterology 2012

SSAs : treatment for HCC? Preclinical studies

- **In vitro** :
  - **Antiproliferative and Pro-apoptotic activity** of lanreotidin HepG2 cells (Raderer International J of Oncol 2000)
  - Activation of SSTR1 **reduces migration** of hepatoma cells and hepatic stellate cells (Reynaert, Gut 2004)
  - Octreotide **inhibited neovascularization and endothelial cell proliferation** with a **down regulation of VEGF** (Jia *et al* 2009)
- In **animal models** of HCC:
  - **inhibits tumor growth and occurrence** (Wang *et al* Natl Med J China, 2001, Jia *et al*. 2009, Borbath *et a*l 2010)
  - Using nude mice xenograft : **Inhibiton of the growth of HCC** in mice treated with octreotide (Hua *et a*l chemotherapy 2009)

Clinical experience SSAs in advanced HCC



Study or Subgroup	Octreotide Events	Octreotide Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 6-mo suvival rate						
Barbare 2009	76	135	73	137	23.40%	1.06 [0.85, 1.31]
Becker 2007	25	60	25	59	14.68%	0.98 [0.64, 1.50]
Dimitroulopoulos 2007	26	30	18	30	18.52%	1.44 [1.04, 2.00]
Kouroumalis 1998	21	28	11	30	11.73%	2.05 [1.22, 3.43]
Wu 2001	9	12	3	13	4.09%	3.25 [1.14, 9.24]
Yang 2003	19	32	10	33	9.87%	1.96 [1.08, 3.54]
Yuen 2002	5	35	5	35	3.47%	1.00 [0.32, 3.15]
Zhang 2004	8	20	7	25	6.04%	1.43 [0.63, 3.26]
Zhang 2010	12	21	8	24	8.20%	1.71 [0.87, 3.37]
Subtotal (95% CI)	**201**	**373**	**160**	**386**	**100.00%**	**1.41 [1.12, 1.77]**
Test for heterogeneity: $Chi^2 = 14.26$, df = 8 (P = 0.08), $I^2 = 43.9\%$						
Test for overall effect: Z = 2.95 (P = 0.003)						
1.1.2 12-mo suvival rate						
Barbare 2009	38	135	41	137	19.12%	0.94 [0.65, 1.36]
Becker 2007	14	60	17	59	17.60%	0.81 [0.44, 1.49]
Dimitroulopoulos 2007	9	30	1	30	7.83%	9.00 [1.21, 66.70]
Kouroumalis 1998	16	28	4	30	14.75%	4.29 [1.63, 11.27]
Wu 2001	4	12	0	13	4.89%	9.69 [0.58, 163.02]
Yang 2003	12	32	1	33	7.94%	12.38 [1.71, 89.74]
Yuen 2002	4	35	1	35	7.21%	4.00 [0.47, 34.02]
Zhang 2004	3	20	2	25	9.51%	1.88 [0.35, 10.16]
Zhang 2010	8	21	2	24	11.15%	4.57 [1.09, 19.19]
Subtotal (95% CI)	**108**	**373**	**69**	**386**	**100.00%**	**2.66 [1.30, 5.44]**
Test for heterogeneity: $Chi^2 = 28.00$, df = 8 (P = 0.0005), $I^2 = 71.4\%$						
Test for overall effect: Z = 2.67 (P = 0.008)						
1.1.3 24-mo suvival rate						
Barbare 2009	11	135	19	137	39.46%	0.59 [0.29, 1.19]
Becker 2007	5	60	10	59	32.65%	0.49 [0.18, 1.35]
Dimitroulopoulos 2007	2	30	0	30	9.08%	5.00 [0.25, 99.95]
Yang 2003	4	32	0	33	9.66%	9.27 [0.52, 165.55]
Zhang 2010	2	21	0	24	9.15%	5.68 [0.29, 112.07]
Subtotal (95% CI)	**24**	**278**	**29**	**283**	**100.00%**	**1.08 [0.40, 2.94]**
Test for heterogeneity: $Chi^2 = 7.71$, df = 4 (P = 0.10), $I^2 = 48.1\%$						
Test for overall effect: Z = 0.15 (P = 0.88)						

Ji *et al* 2011

Only one positive randomised study

	Octreotide n=31	Non-treated n=30	SSTR negative N=66
Overall survival time	**49 ± 6 wk**	28 ±1 wk (p<0.01)	28 ±2 wk

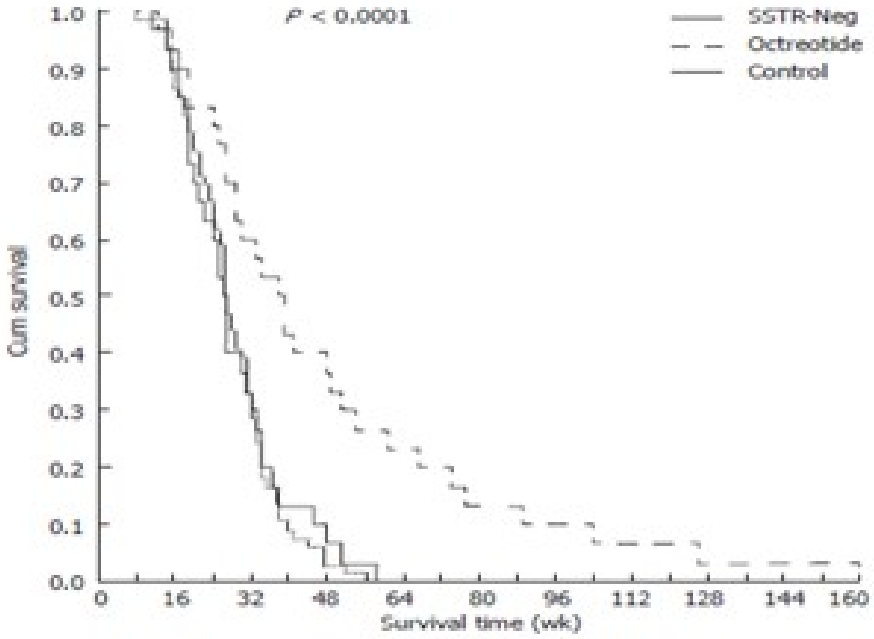


Figure 3 Survival probabilities in the groups of the study.

Dimitrilopoulos *et al* W J of gastroentero 2007

On going studies

- Phase II Trial with pasireotide (60 mg IM/28d) in patients with Unresectable Hepatocellular Carcinoma (after progression with sorafenib). (Still recruiting)

- Phase II trial single arm with pasireotide (60 mg IM/28d) and everolimus (7,5 mg/jour) in patients with advanced or metastatic HCC intolerant to sorafenib (end of screening 2014)

Limits of these studies

- Heterogeneity of patients and tumors
- Small number of patients
- Many retrospective studies
- Lack of patients screening relying on the SSTR status (especially SSTR2)
- Prognostic and predictive influences of SSTR expression cannot be evaluated in the setting of SSA treatment

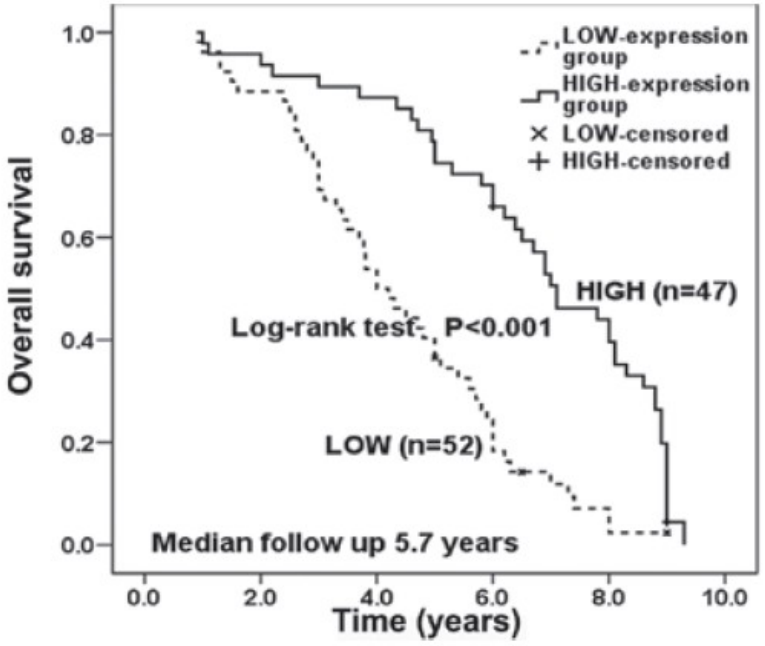
Rational for SSAs as Adjuvant treatment in HCC?

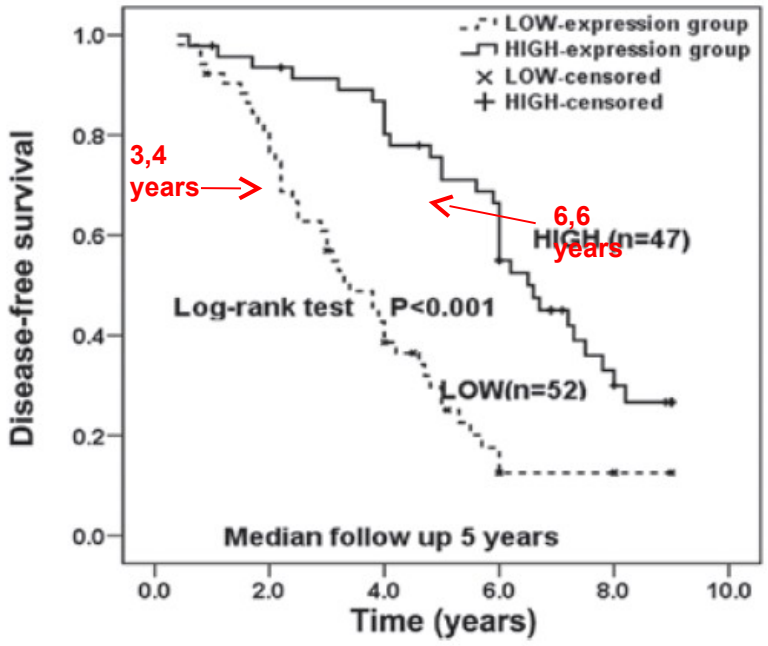
- Liver resection for HCC is associated with early recurrence and poor survival.
- predictors of early recurrence and poor survival :
  - Vascular invasion (both macroscopic and microscopic),
  - poor tumor differentiation
  - tumor size
  - cytokeratin-19 (CK-19) (>5%) (hepatobiliary progenitor marker)
  - AFP levels > 200 - 500 ng/ml

Llovet JM, Schwartz M, Mazzaferro V. Semin Liver Dis. 2005
Park SK, Lee JN, et al. Korean J Intern Med. Jul 2013
Colecchia A et al. World J Gastroenterol. may 2014
Govaere O, Roskams T. Clin Liver Dis. may 2015

SSAs as adjuvant treatment in HCC : one recent study

99 patients resected for early stage HBV related HCC
All patients treated with LAR octreotide
SSTR2 and 5 mRNA expression levels evaluated with qPCR (No IHC)
SSTR2 and 5 high expression : 64% of recurence versus 83% in low expression group (p=0,033)





Liu *et al* Oncol letter 2013

Rational for SSAs as Adjuvant treatment in HCC?

- Characterization of the SSTR status in a panel of resected HCC and paired non liver tissue (homogeneous population) :
  - SSTR2, SSTR3 and SSTR5 expression : transcript and protein by PCR and IHC
  - SSTR1, SSTR5TMD4 and SSTR5TMD5 (two truncated forms of SSTR5) only PCR.

- Correlations between high SSTR2 membrane staining and specific tumor or patient characteristics and/or peculiar clinical outcome were investigated (especially poor prognosis predictors)

THANK YOU FOR YOUR ATTENTION