Lucitanib
Program Summary

November 2013

Executive Summary (1)

- Lucitanib is a dual-selective, oral tyrosine kinase inhibitor which targets both FGFR1-2 and VEGFR1-3
  - Completing a Phase 1/2a trial being conducted in Europe
  - 50% (6/12) response rate observed in heavily pre-treated breast cancer patients (median 6 lines of prior therapy) with FGF aberrations (FGFR1 and 11q gene amplification), found in ~25% of all breast cancer patients
  - Activity seen in other tumors, including thyroid, liver and kidney
- Through the acquisition of EOS (Ethical Oncology Science), a Milan-based biotechnology company, Clovis Oncology now holds exclusive US and Japanese rights to lucitanib
- European and ROW rights were licensed by EOS to Servier in a 2012 transaction which provides Clovis with potential future milestones and royalties
- Clovis and Servier are co-developing lucitanib with Servier providing the first €80MM to the joint research and development budget
- Composition of matter patent protection until 2030

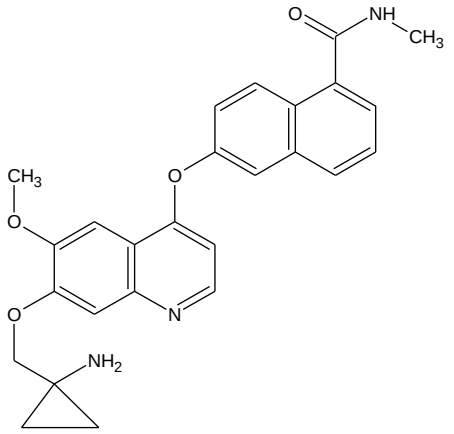
Executive Summary (2)

- Two Phase 2 monotherapy trials of lucitanib are in the advanced planning or initiation stage:
  - FINESSE – a European Phase 2 Breast International Group trial (N~120) in 3 populations of advanced BC patients (FGFR1-amplified, 11q-amplified and FGF wild-type).
  - Global Phase 2 study in FGFR1-amplified squamous lung cancer
- Clovis is also starting a US Phase 2 study of lucitanib in FGFR1- and 11q-amplified advanced breast cancer in 1H14
- In the US, a companion diagnostic for identification of FGF-aberrant tumors will be developed for PMA submission to FDA, concurrent with the NDA
- FGF aberrations are common in solid tumors, and represent a significant commercial opportunity
  - ~25% of invasive breast cancer
  - ~35% of squamous lung cancer

Lucitanib is a potent inhibitor of FGFR1-2 and VEGFR1-3

- Lucitanib is unique among FGF receptor antagonists:
  - Dual activity for FGFR1-2 and VEGFR1-3 <100 nM in cell based assays
  - No other significant inhibition of WT kinases
- Fibroblast growth factors (FGFs) and their receptors (FGFRs) promote tumor growth and angiogenesis in addition to regulating a wide range of homeostatic processes in the body
  - Genetic alterations in the FGF pathway, including receptor gene amplification and mutation, are frequently observed as driving events in cancer
- Vascular endothelial growth factors (VEGFs) and their receptors (VEGFRs) promote tumor growth by inducing tumor angiogenesis and are a validated target in oncology
- The dual-selective targeting by lucitanib results in its unique efficacy profile

Lucitanib structure:



Lucitanib kinase inhibition profile[1]:

KINASE		INHIBITION IC_{50} (nM)
FGFR family	FGFR1	18
	FGFR2	83
	FGFR3	238
	FGFR4	>1000
VEGFR family	VEGFR1	7
	VEGFR2	25
	VEGFR3	10
PDGFR family	PDGFRA	175
	PDGFRB	525
	KIT	456

[1]Bello et al Can Res 71:1396 (2011)

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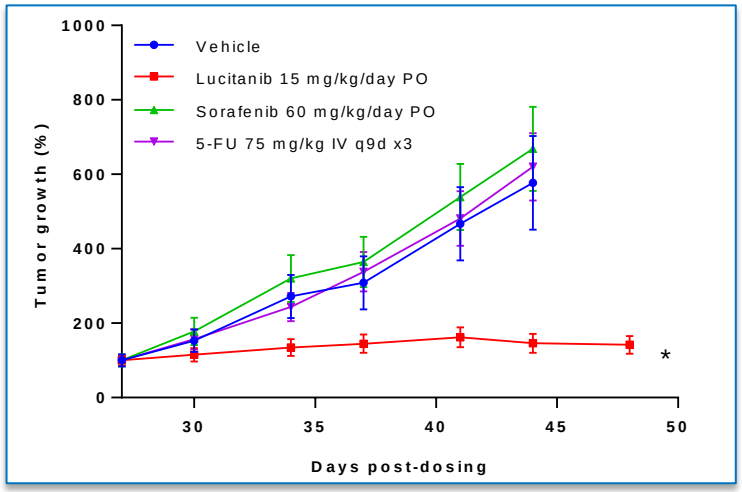
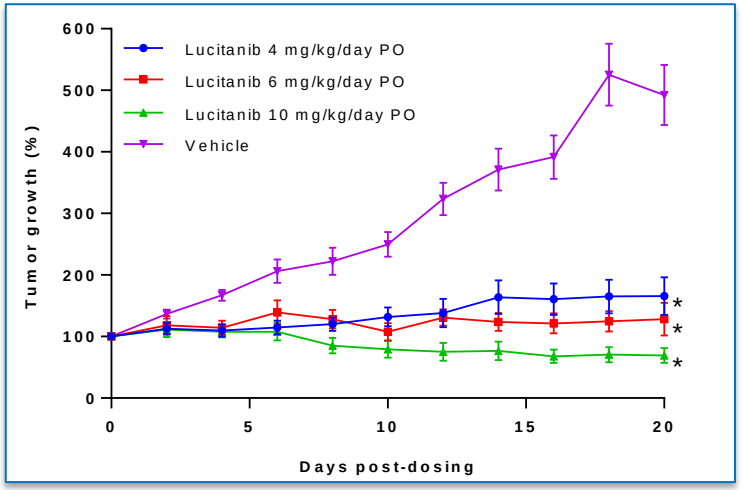
Lucitanib is an effective inhibitor of FGFR1-driven tumors in non-clinical studies

- *In vitro* lucitanib displays selective inhibition of cell lines that are driven by FGF/FGFR biology:
  - Lucitanib preferentially inhibits FGFR1 gene-amplified lung cancer cell proliferation
- *In vivo* lucitanib displays a broad anti-tumor efficacy profile including breast and lung tumor models

Anti-tumor activity of lucitanib in the MDA-MB-231 breast cancer xenograft model**



Anti-tumor activity of lucitanib in the FGFR1 gene amplified NCI-H1581 lung cancer xenograft model**



*P < 0.001 (statistically significant)
**Data on file

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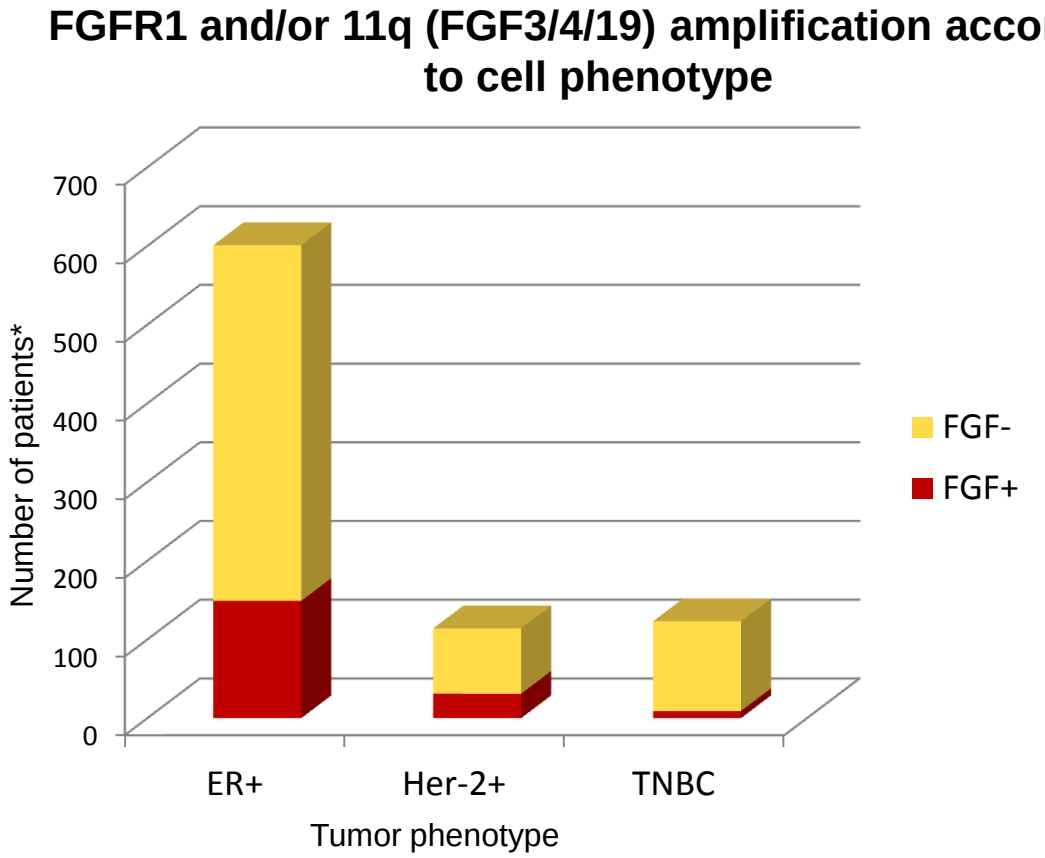
FGFR1 and 11q amplification seen broadly across solid tumor types in TCGA studies

Tumor type	FGFR1 amp freq	FGFR1 and/or 11q (FGF3/4/19) amp freq	n
Lung squamous cell carcinoma	16.9%	34.3%	178
Breast invasive carcinoma	10.0%	23.7%	825
Head and neck squamous cell carcinoma *	8.5%	34.6%	306
Sarcoma (soft tissue sarcomas across seven subtypes of disease)	5.3%	13.5%	207
Ovarian serous cystadenocarcinoma	3.9%	10.2%	489
Lung adenocarcinoma *	3.5%	14.3%	230
Bladder urothelial carcinoma *	3.4%	19.3%	88
Colon and rectum adenocarcinoma	3.1%	3.9%	257
Uterine corpus endometrioid carcinoma *	2.5%	6.1%	363

*Provisional TCGA data – not yet published.
Note: tumor types with FGFR1 amp freq under 2% not listed.
Amplification determined by Genomic Identification of Significant Targets in Cancer analysis of array CGH and SNP array data in TCGA studies

FGF aberrations are equally common in ER+ and Her-2+ subsets – consequently most FGF+ BC patients are ER+



FGFR1 and/or 11q amplification seen in 23% of ER+, 27% of Her-2+ and 7% of TNBC

**Captured in TCGA*

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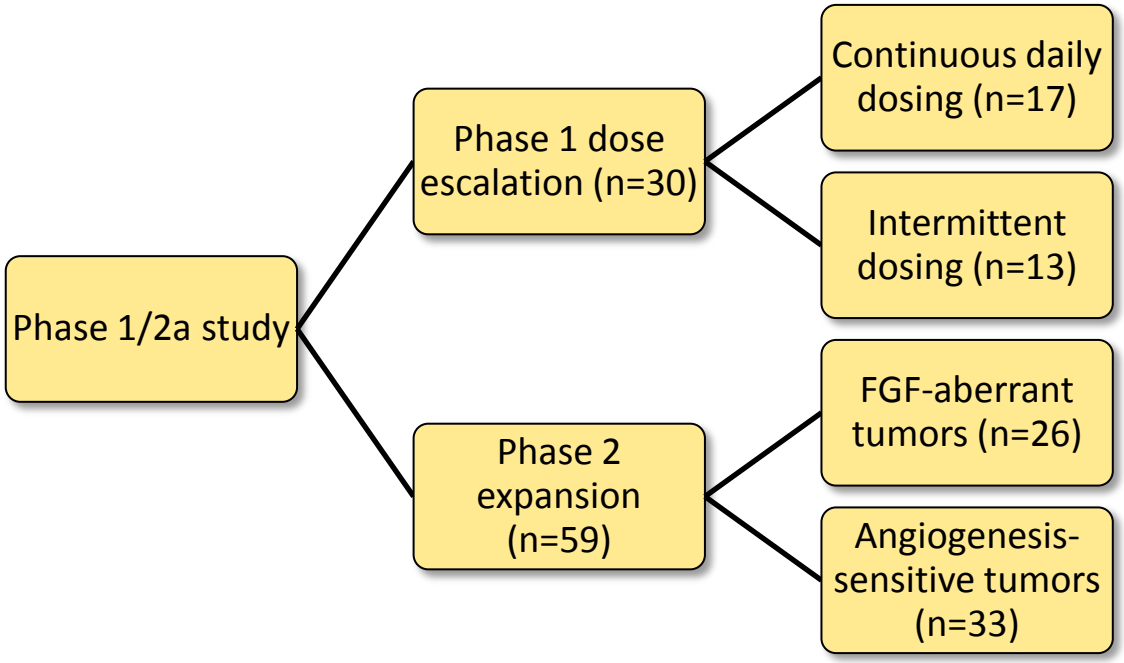
EOS Phase 1/2 study identified 20mgQD as MTD



- 5,10,20,30mg QD
- 20mg identified as MTD
- Dose reductions common from 20mg
- Completed

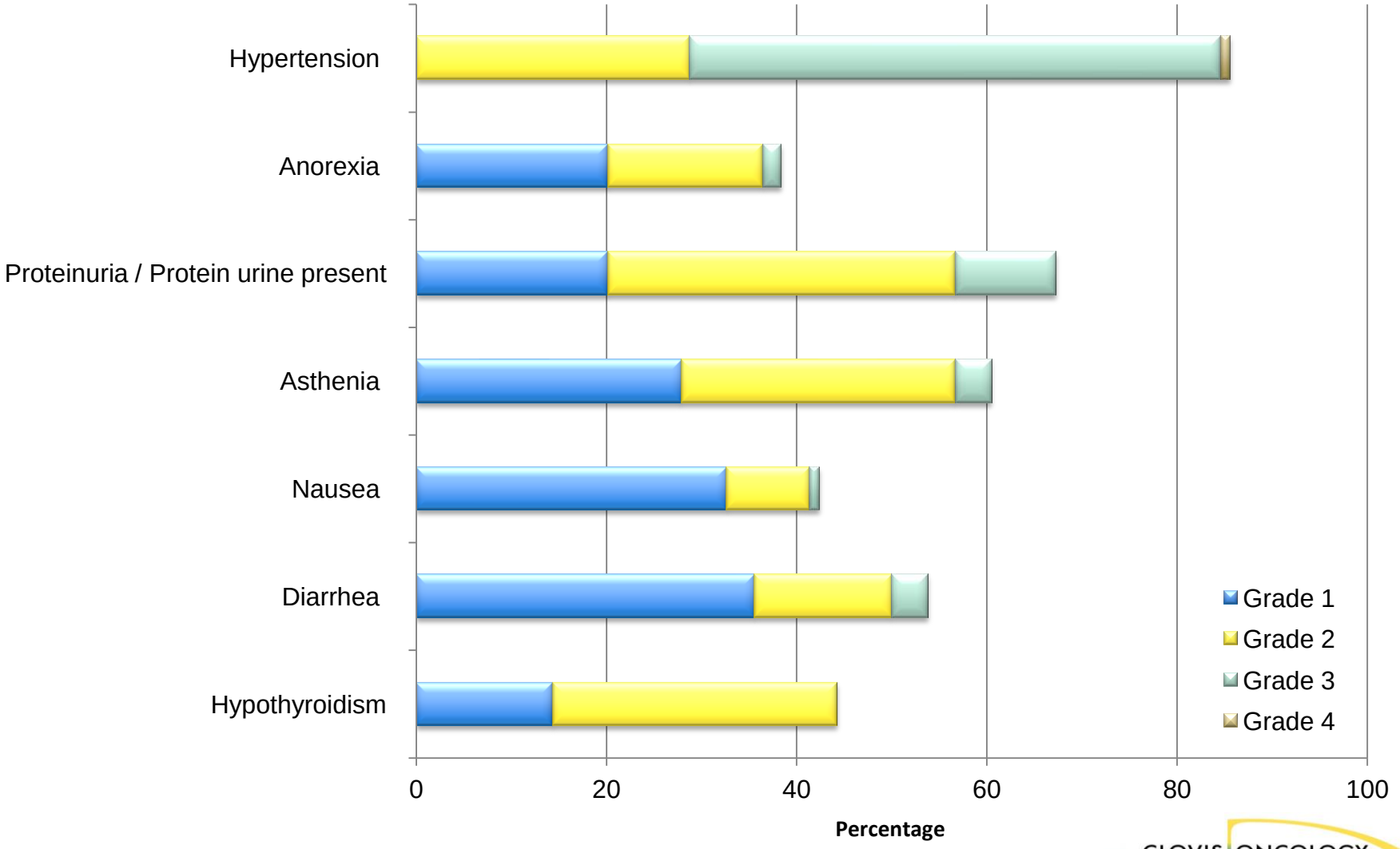
- No clear benefit over QD dosing
- On-going

- 10mg, 15mg and 20mg
- 16 BC patients, 12 evaluable
- On-going

- 10mg, 15mg and 20mg
- 24 evaluable
- On-going

Prof. Jean-Charles Soria (IGR) and Prof. Josep Tabernero (VHIO) are Principal Investigators

Most drug-related adverse events were mild in severity or asymptomatic and reflect VEGFR inhibition



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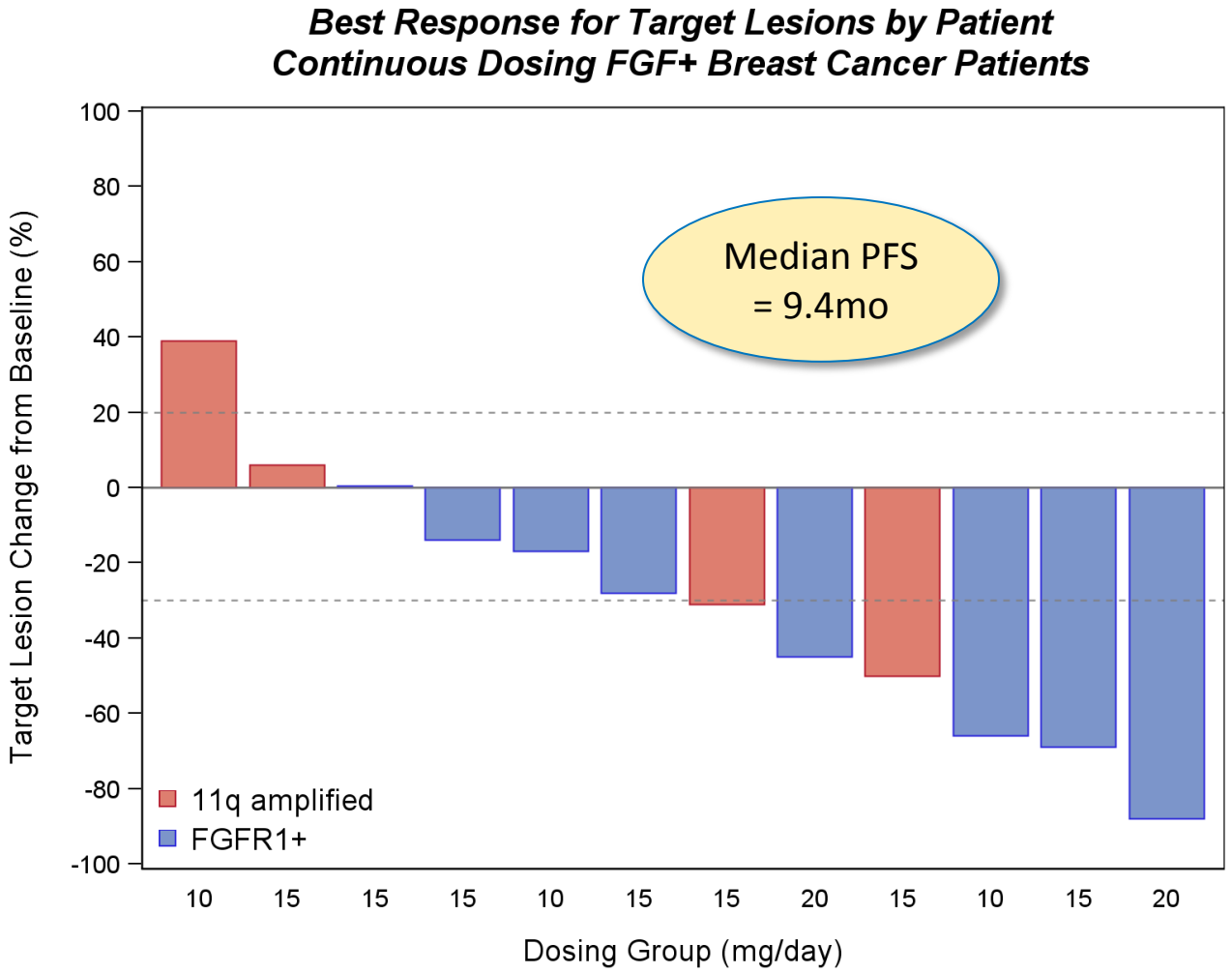
Lucitanib has 50% PR rate* in FGF-aberrant** BC patients

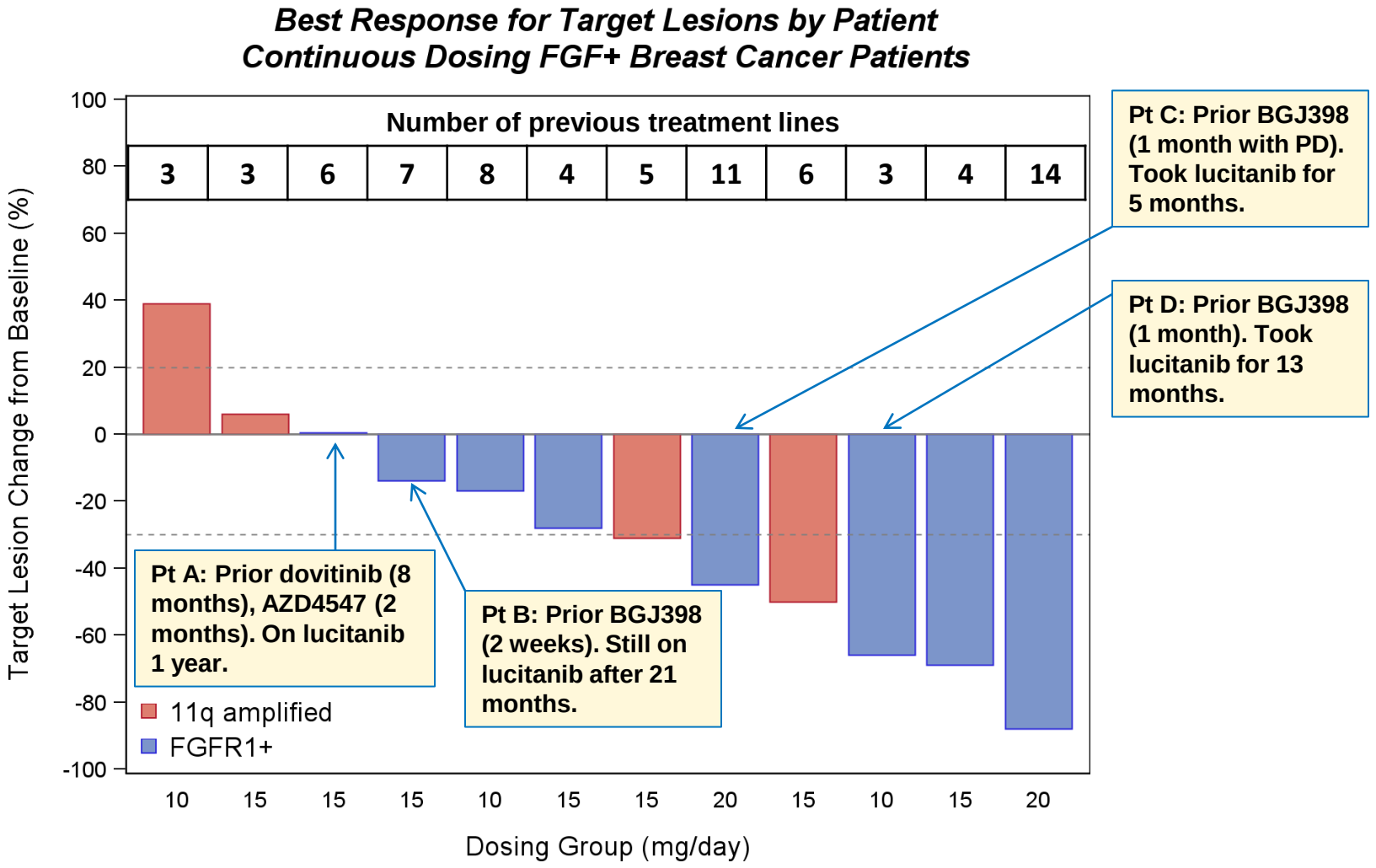


** 5/6 Partial Responses were confirmed*

*** Defined as either FGFR1 amplified or 11q amplified*

CLOVIS ONCOLOGY

Responses seen in heavily pre-treated patients, some of whom progressed on treatment with other FGFR inhibitors



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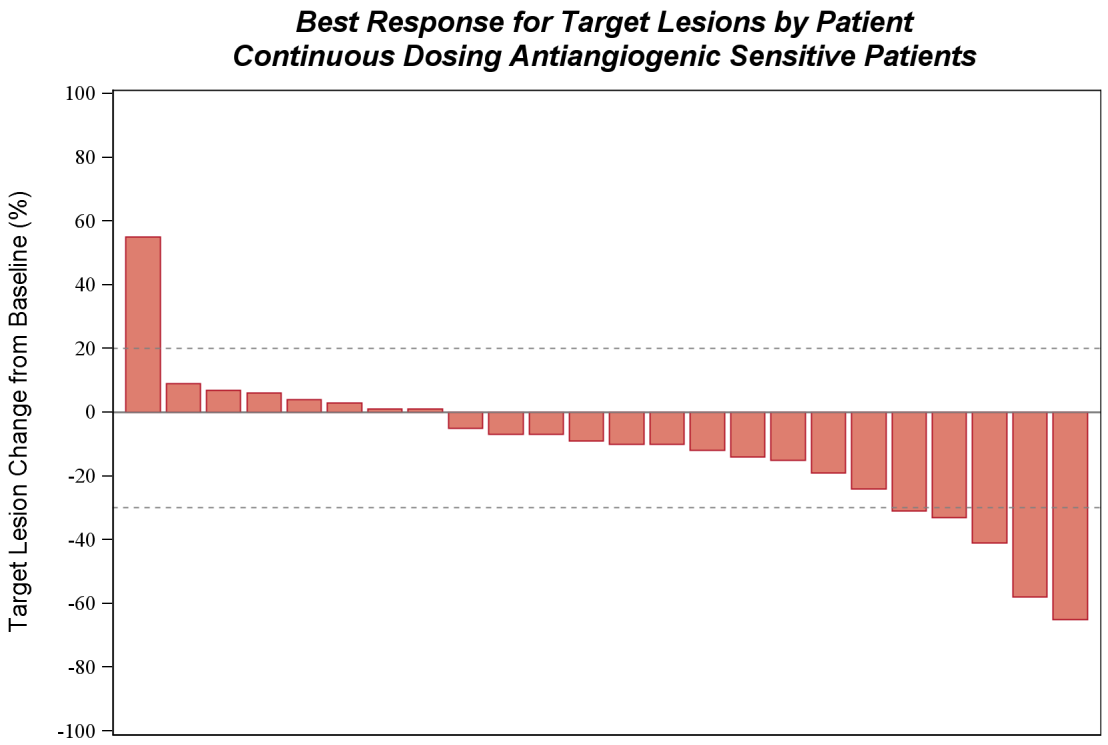
CLOVIS ONCOLOGY

Patients with angiogenesis-sensitive tumors* also derive apparent benefit from lucitanib



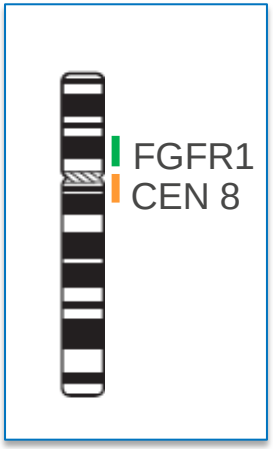
** Defined as having previously responded to anti-angiogenic (AA) therapy or being a tumor type known to respond to AA therapy(e.g. renal cell cancer, thyroid cancer)*

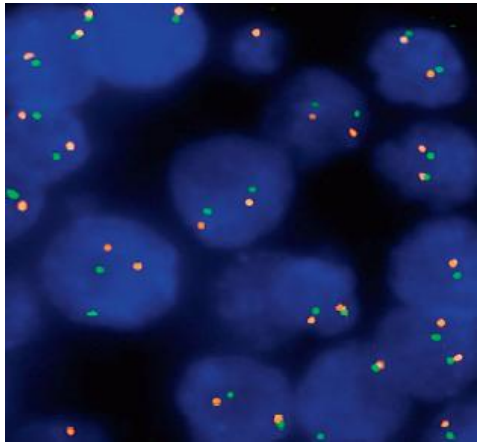
Best Overall Response

Tumor	PR	SD	PD
Breast	0	0	1
Colorectal	0	6	0
RCC	1	0	0
HCC	1	1	0
Lung	0	1	0
Ovary	0	1	0
Thymus	1	1	0
Thyroid	2	5	0
Other	0	1	2
Total	**5**	**16**	**3**

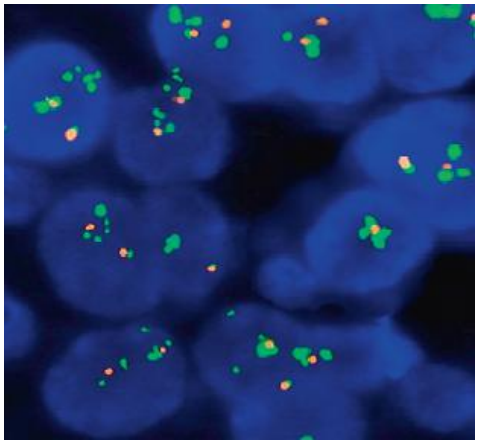
Fluorescence in situ hybridization (FISH) test is central approach for FGF+ identification

- Detecting amplification of FGFR1 and FGF ligands is central strategy in breast cancer
- FGFR1 (chr 8) and FGF3/4/19 (chr 11) amplification can be assessed by standard approaches
  - Fluorescent in situ hybridization (FISH)





Normal Cells



***FGFR1*^{amp} Cells**

Source: Zytovision

Joint Clovis-Servier development plan focuses on selected breast cancer and lung cancer patients

- Given strong evidence of activity in FGF-aberrant BC, two Phase 2 trials in this indication are starting:
  - FINESSE: a Servier-sponsored, European Phase 2 study of lucitanib in 3 cohorts of patients (FGFR1-amp; 11q-amp; FGF wild-type)
    - Up to 41 patients per cohort
    - Run by Breast International Group and led by Profs Andre (IGR, Paris) and Cortes (Vall d'Hebron, Barcelona)
  - A Clovis-sponsored US Phase 2 study of lucitanib in FGFR1- or 11q-amplified patients with advanced BC
    - Study will evaluate starting dose
    - Will be conducted at leading US centers
- In addition, Clovis will be initiating an international, proof-of-concept Phase 2 trial in FGFR1-amplified squamous lung cancer
  - Simon two-stage design
  - Prof. Jean-Charles Soria (IGR, Paris) is the PI

Lucitanib distinctively targets FGFR1-2 and VEGFR1-3

Class	Drug	*In vitro* targets (IC50<100nM)		
		VEGFR1-3	FGFR1-3	PDGFR
Dual-selective TKI	**Lucitanib[1]**	**+**	**1-2 only**	**-**
Pan-TKI	Dovitinib[2]	+	+	+
Selective FGFR TKI	AZD4547[3]	-	+	-
	BGJ398[4]	-	+	-

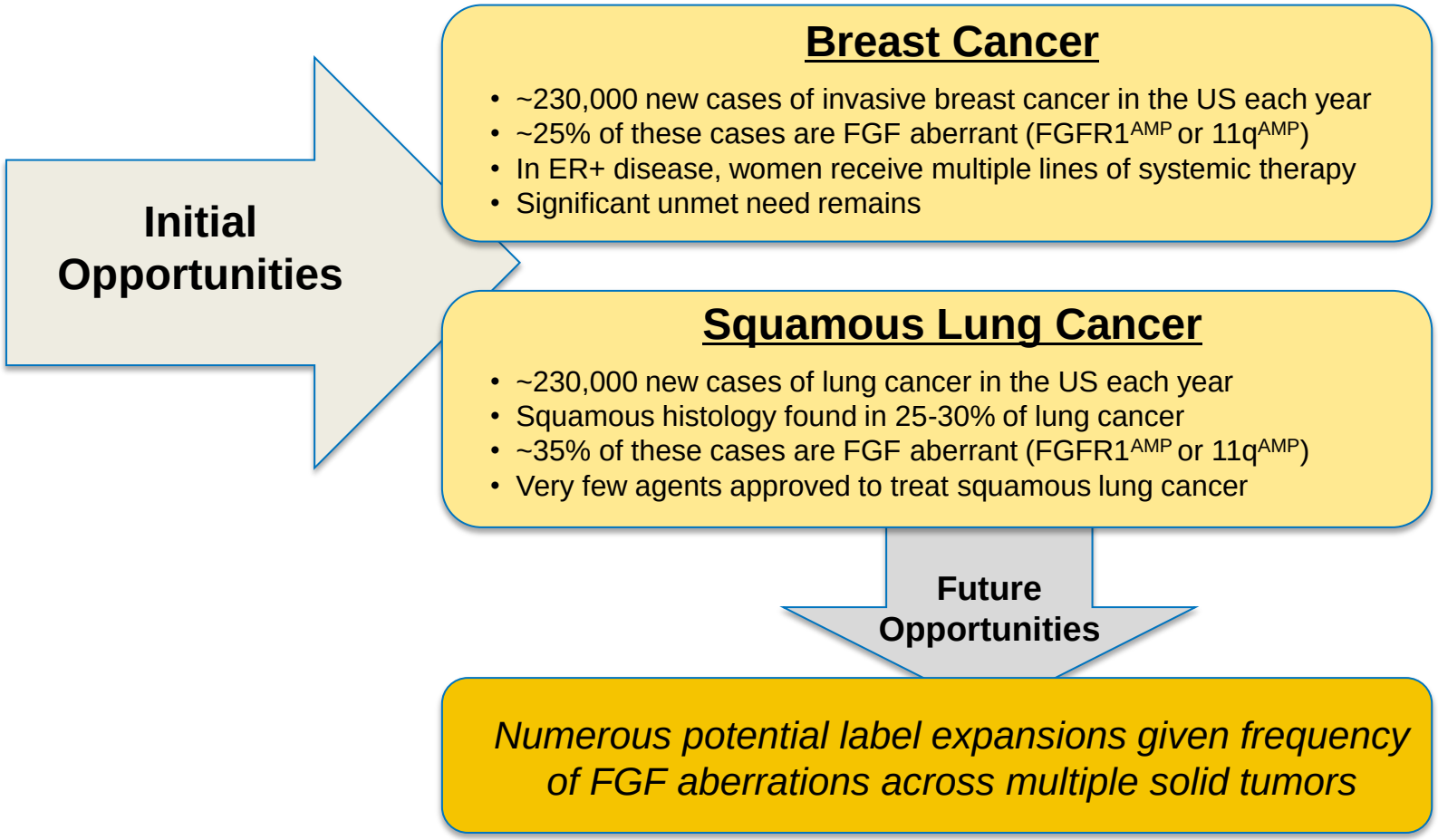
[1] Bello et al Can Res 71:1396 (2011); [2] Lee et al CCR 11:3633 (2005);
[3] Gavine et al Can Res 72:2045 (2012); [4] Guagnano et al Can Dis 2:1118 (2012)

Lucitanib's dual-targeting results in a unique efficacy profile

Class	Drug	Efficacy data reported to date	AEs: VEGFR inhibition	AEs: Total FGFR inhibition
			Hypertension, proteinuria	Hyperphosphatemia, elevated FGF-23
Dual-selective TKI	**Lucitanib**	**50% (6/12) ORR in FGFR1 or FGF-3/4/19 amplified BC**	**+ (>50%)**	**- (no↑PO_4)**
Pan-TKI	Dovitinib	0% (0/25) ORR in FGFR1 amplified BC[1]	<20%	-/+ (↑FGF23 (x2)but minimal ↑PO_4)
Selective FGFR TKI	AZD4547	5% (1/20) RR in FGFR1 amplified lung cancer out of 21 FGFR1/2 amplified solid tumor [2]	-	+
	BGJ398	0% (0/10) RR in FGFR1 amplified breast cancer 33% (1/3) RR in FGFR1 amplified lung cancer[3]	-	+

[1] Andre et al CCR 19:3693 (2013); [2] Andre et al Proc AACR (2013); [3]Wolf et al Proc AACR (2012)

Lucitanib may address two of the most common cancers



Sources: SEER; American Cancer Society; TCGA

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- FGF aberrations (FGFR1 and 11q amplification) are common in solid tumors, and represent a significant commercial opportunity
- Composition of matter patent protection until 2030