August 11, 2014

OUTPERFORM

Reason for report:

PROPRIETARY INSIGHTS

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LEERINK

IGNYTA, INC.

A Closer Look at Cdc7 and RET as Oncology Targets

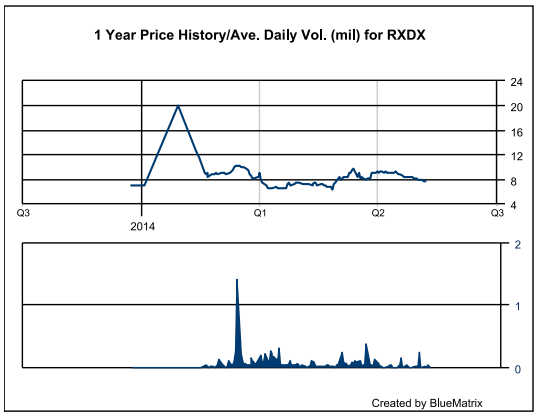
• **Bottom Line:** Following RXDX's recent partnership with Nerviano, we conducted a deep dive analysis and spoke with 3 MEDACorp key opinion leaders (KOLs) on its new pipeline candidates against Cdc7 (a cell cycle kinase, RXDX-103) and RET (a receptor tyrosine kinase, RXDX-104). Although both assets are still in early preclinical development (Phase I in 2016), '103 may have first-mover advantage due to limited competition, and '104 as a cleaner RET inhibitor could achieve a better efficacy/ safety profile vs. competitors despite a substantial lag in development. Leveraging RXDX's technology platform for companion diagnostics, these two assets are in line with RXDX's focus on targeted therapy and diversifying the pipeline beyond Trk/ALK/ROS1 assets. For future acquisitions, it could be an advantage for RXDX to focus on assets either already in the clinic or with a shorter timeline to human studies. Given the expanded pipeline, a promising Trk inhibitor (RXDX-101) with first-ever reported clinical activity and near-term update (2H:14), we view RXDX's valuation as attractive. Our price target remains $14.

• **Cdc7 is considered as an attractive therapeutic target by the KOLs, limited competition could provide first-mover advantage for '103; however, drug development has been challenging.** Inhibition of Cdc7 (cell division cycle 7, essential for the initiation of DNA replication) could lead to apoptosis in tumor cells but spares normal cells, supporting it as a unique target for cancer therapy. However, historical drug development for Cdc7 has been challenging (see pages 2+). '103 as a 2nd-generation Cdc7 inhibitor appears to achieve a better metabolic profile in preclinical studies. However, it is unclear if PK issue has been resolved in human and the real de-risking event will be Phase I data (1H:16). A favorable outcome could position RXDX-103 as a first-in-class candidate for multiple cancer opportunities.

• **'104 as a cleaner RET inhibitor could achieve a better efficacy/ safety profile despite a substantial lag in development.** Although several approved drugs (see pages 10+) have potent activity against RET, their primary targets limit their dosing capability due to on-target toxicities; therefore, '104 as a cleaner RET inhibitor could potentially reach higher activity given higher dosing limit. That said, initial activity from low-dose Cometriq in 3 RET+ lung cancer patients was promising, which could set a high bar for '104 if this magnitude of activity holds in larger trials. Additionally, the activity against KIF5B-RET (important commercially as it represents ~90% of RET fusion in lung cancer) is still unclear.

• **Deal structure comparable to the previous licensing, low upfront favorable for cash preservation.** RXDX will pay Nerviano upfront $3.5M and $102M in development and regulatory milestones ($68M for '103 and $34M for '104). Sales royalties will be mid-single to low-double digit. This deal structure appears similar to the previous one ('101 & '102).

Key Stats:	**(NASDAQ:RXDX)**
S&P 600 Health Care Index:	**1,298.82**
Price:	**$7.50**
Price Target:	$14.00
Methodology:	Probability-weighted DCF analysis, 10% discount rate
52 Week High:	$20.00
52 Week Low:	$1.00
Shares Outstanding (mil):	19.6
Market Capitalization (mil):	$147.0
Book Value/Share:	$5.37
Cash Per Share:	$5.13
Dividend (ann):	$0.00
Dividend Yield:	0.0%
Book Value: Pro Forma	
Cash Per Share: Pro Forma	



Dec Yr	1Q	2Q	3Q	4Q	FY Rev	1Q	2Q	3Q	4Q	FY EPS	P/E
2013A	--	--	--	--	0.0	--	--	--	--	($3.83)	NM
2014E - New	**0.0A**	**0.0**	**0.0**	**0.0**	**0.0**	**($0.28)A**	**($0.26)**	**($0.37)**	**($0.41)**	**($1.35)**	**NM**
2014E - Old	0.0A	$0.2A	0.0	0.0	$0.2	($0.28)A	($0.28)A	($0.58)	($0.46)	($1.63)	NM
2015E - New	**--**	**--**	**--**	**--**	**0.0**	**--**	**--**	**--**	**--**	**($1.81)**	**NM**
2015E - Old	--	--	--	--	0.0	--	--	--	--	($2.00)	NM

Source: Company Information and Leerink Partners LLC Research

INVESTMENT THESIS

RXDX is a biotech company with a focus on targeted therapies and molecular diagnosis in oncology. RXDX's approach of targeting molecular oncogenic drivers has historically resulted in highly effective agents. Despite low incidence of many genetic alterations including Trk and ROS1 rearrangement, molecular screening started to become a standard practice in NSCLC where oncogenic driver mutations have been identified in ~70% of adenocarcinoma patients. Clinical successes with EGFR, ALK, ROS1, HER2, BRAF inhibitors have shown high efficacy in several cancer types. Although RXDX's lead candidate RXDX-101 (oral pan-Trk, ROS1 and ALK inhibitor) is still in early-stage clinical development, we believe historical precedence suggests a higher-than-average chance of success in identifying highly effective agents, which we believe is increasingly the direction for the development of new cancer therapies. We believe the main value for RXDX-101 lies in the market potential for cancers with Trk genetic alteration, an emerging target for NSCLC. Although many compounds have activity against Trk, so far only a handful of companies have focused clinical programs targeting Trk, whereas RXDX has dedicated effort to target Trk in multiple tumor type with the potential to develop a first-in-class Trk inhibitor. Although still early with limited clinical data, observed ALK activity and initial Trk activity (seen in one patient) bode well for RXDX-101 as a Trk inhibitor, where in vitro activity is ~10X more potent vs. ROS1 and ALK. The new global Phase I study with modified continuous dosing schedule could provide insight on safety and clinical activity. A recent licensing deal with Nerviano further expands the pipeline targeting Cdc7 (cell cycle kinase inhibitor) and RET (tyrosine kinase inhibitor). Additionally, the Technology platform and integrated Rx/Dx strategy with genomic and epigenomic mining of oncolome provide potentially six targeted therapies with companion diagnostics in 2015 and beyond.

Challenges in Cdc7 Drug Development

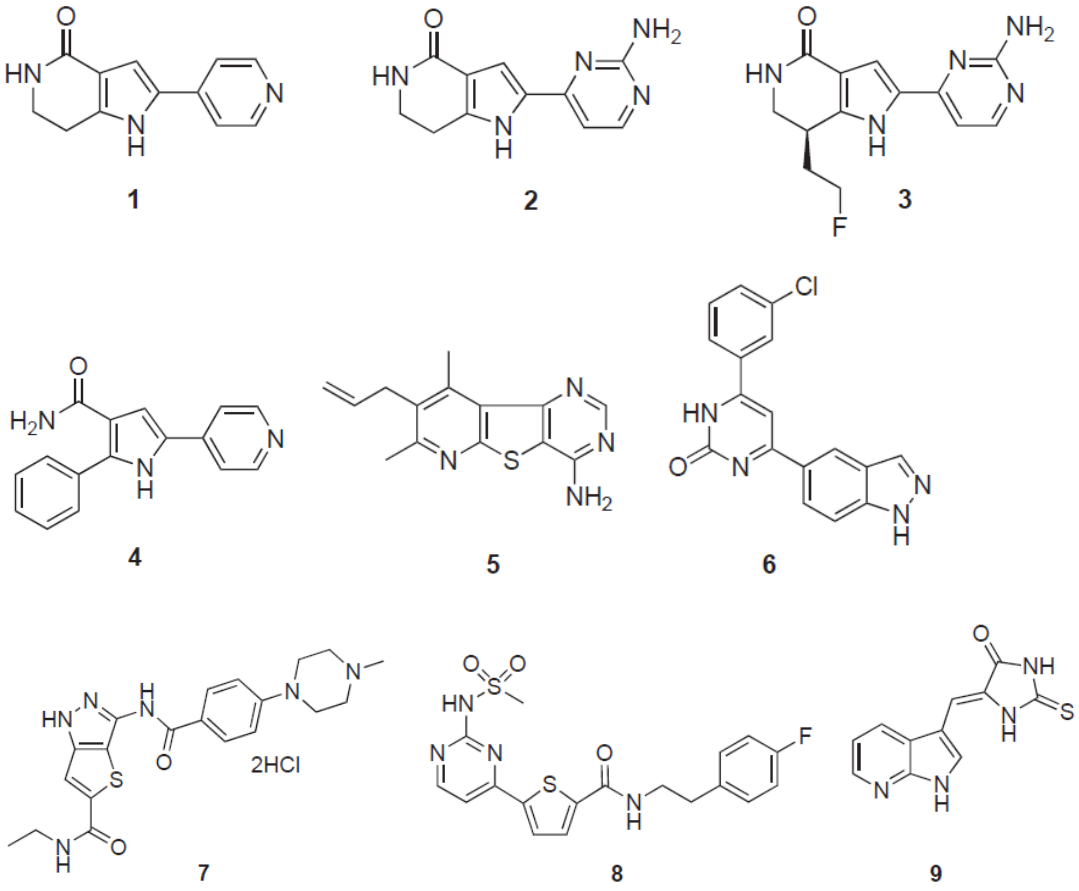
Only a handful of Cdc7 kinase inhibitors have been reported historically. A series of pyrrolopyridinone compounds were reported by Nerviano Medical Sciences (NMS); the compounds have potent activity against Cdc7, among which PHA-767491 (Compound #1 in table on page 3) was characterized as an ATP-competitive inhibitor of Cdc7 (IC50=10nM). It inhibits phosphorylation of Mcm2, a substrate of Cdc-6, as well as DNA synthesis, which leads to cell death in multiple cancer cell lines but did not affect the viability of normal cells (Montagnoli et al., Nat Chem Biol 2008, 4:357). Subsequent optimization of this scaffold led to compound #2 (IC50=7nM, see names in the chart), and further optimization resulted in identification of Compound #3 (IC50=2nM), which has >60 fold selectivity over other kinases. Modifications to the pyrrolopyridinone scaffold also led to NMS-354 (IC50=3nM, Compound #4), which was active in different xenograft tumor mouse model (at 20mg/kg) and in DMBA induced carcinoma rat model. It also showed high selectivity against 120 cancer cell lines. BMY/EXEL reported BMS-863233, a Cdc7 inhibitor that belongs to benzofuropyrimidinone. Additionally, Roche, NVS, PFE and Sanofi-Aventis have also reported Cdc7 inhibitors in early development; however, no further progress has been reported on these compounds.

Cdc7 Inhibitors – Development Stage

Company	Cdc7 Inhibitor	Chemical Class	Description	Phase	Indication	Status
BMY/EXEL	BMS-863233/ XL-413	benzofuropyrimidinone	Unfavorable PK profile in human	Phase I/II	Solid and hematolgoic tumors	Suspended in 2010
Nerviano	PHA-767491 (Compound #1)	pyrrolopyridinone	IC50 = 10nM	Preclinical		Unknown
	Compound #2	3-aminopyrimidine analog	IC50 = 7nM, poor membrane permeability	Preclinical		Unknown
	Compound #3	(S)-2-(2-minopyrimidiny-4-yl)-7-(2-fl uoroethyl)-1,5,6,7-tetrahydropyrrolo [3,2-c] pyridinone	IC50 = 2nM, >60X selectivity over earlier compounds, active at an oral dose of 60mg/kg in mouse xenograft model and 20mg/kg at DMBA-induced mamary carcinoma rat model.	Preclinical		Unknown
	NMS-1116354 (Compound #4)	2-heteroaryl-pyrrolopyridones	IC50 = 3nM, active in different xenograft tumor mouse model (at 20mg/kg) and in DMBA induced carcinoma rat model. High selectivity against 120 cancer cell lines. Renal toxicity/rapid metabolism and a toxic metabolite in clinical study.	Phase I	Solid and hematolgoic tumors	Suspended in 2011
Roche	Compound #5	pyridothienopyrimidine	Ki of 2nM. High selectivity against 1 kinases.	Preclinical		No further reports
NVS		2-(heteroaryl)-6,7-dihydrothieno[3,2-c]pyridin-4(5H)-one		Preclinical		Unknown
	Compound #6	4-indazolylpyrimidin-2(1H)-one	IC50 = 5nM. Low membrane permeability and metabolic liability. Weak cellular activity.	Preclinical		Unknown
PFE	Compound #7	thienopyrazoles	IC50<1000nM. No kinase selectivity data	Preclinical		Unknown
Sanofi-Aventis	Compound #9	imidazolones		Preclinical		Unknown
RXDX	RXDX-103	Undisclosed	Improved metabolite profile vs. NMS-354	Preclinical		Phase 1 in 1H:16

Source: Company Reports and Leerink Partners

Cdc7 Inhibitors – Chemical Structure



Note: 1) PHA-767491 (IC50 = 10 nM) (NMS); 2) 3-aminopyrimidine analog (IC50 = 7 nM) (NMS); 3) (S)-2-(2-aminopyrimidiny-4-yl)-7-(2-fl uoroethyl)-1,5,6,7-tetrahydropyrrolo[3,2-c]pyridinone (IC50 = 2 nM) (NMS); 4) the pyrrolopyridinone analog (IC50 = 3 nM) (NMS); 5) Tricyclic Cdc7 inhibitor (Roche); 6) indazolylpyrimidin-2(1H)-one inhibitor (NVS); 7, thienopyrazole-base inhibitor (PFE);8, 2-pyrimidyl-5-amidothiophene analog (NVS); 9, imidazolone-based inhibitor (Sanofi -Aventis).
Source: Sawa and Masai, Drug Design, Development and Therapy 2008, 2:255

Challenging Cdc7 development history raises some concerns on PK profile, though unlikely due to Cdc7 as a target, according to the KOLs. Among a handful of compounds in initial development, only two entered clinical studies. BMY/EXEL's Cdc7 program (BMS-863233) entered two Phase I studies for both hematologic malignancies and solid tumors. However, both trials were suspended due to "an unfavorable pharmacological profile observed in phase 1 clinical evaluation", according to EXEL 10K filing. Independently, NMS-354 was advanced into 3 Phase I trials in 2009 and dosed in 48 patients. However, the trials were terminated due to rapid metabolism and a toxic metabolite, resulting in mainly renal toxicity. A high level of toxic metabolite was not observed in animal studies, according to management. Although these two drugs appear to have different chemical scaffolds (benzofuropyrimidinone for BMS-863233 and 2-heteroaryl-pyrrolopyridones for NMS-354), both of them appear to have issues with PK profile.

However, according to the KOLs, PK issues are unlikely a result of Cdc7 as a target, but more likely due to chemical structure.

RXDX-103 – Positives and Negatives

Positive considerations for RXDX-103

- **NMS as the leader in the Cdc7 drug development could provide important insight for RXDX-103.** Along with scientific discovery and drug development for Cdc7, NMS has made numerous groundbreaking findings to help shape current understanding of the underlying science for Cdc7. NMS is also among a handful companies that have gained initial understanding of clinical development for Cdc7 inhibitors. As a leader in the Cdc7 field, NMS could provide important insights to aid in future development for RXDX-103.

- **Improved metabolic profile vs. 1st-generation Cdc7 inhibitors; potential to become a first- and best-in-class drug candidate.** RXDX-103 is an improved version of NMS-P354, NMS' first-generation Cdc7 inhibitor. According to management, metabolic profile has been improved 10X in animal studies (monkeys). If preclinical data hold in clinic, RXDX-103 could emerge as the first and potentially the best Cdc7 inhibitor targeting a broad market potential in multiple cancer indications.

- **Opportunities for combination therapy widely open.** Since RXDX-103 targets the initiation of DNA replication, combination with an elongation inhibitor should provide synergist activity. The majority of current chemotherapy, including antimetabolites, topoisomerase inhibitors and alkylating agents, are addressing the elongation step of DNA replication; therefore, there are numerous combination choices for RXDX-103. As a cell cycle inhibitor with broader inhibition, RXDX-103 could also be combined with other compounds addressing a specific target. Interesting, a study in cell culture showed synergistic apoptosis when combining treatments with rituximab and Cdc7 gene silencing, suggesting potential combination therapy in diffused large B-cell lymphoma (DLBCL, Hou et al., J Cancer Res Clin Oncol 2012, 138:2027).

- **Companion diagnostic leverages RXDX's technology platform and increases probability of positive outcome.** A high Cdc7 expression level has been observed in multiple cancer types including breast, ovarian and colorectal cancer. Broad evidence also supports high level Mcm2 and other molecules as potential biomarkers for future clinical development.

Negative considerations for RXDX-103

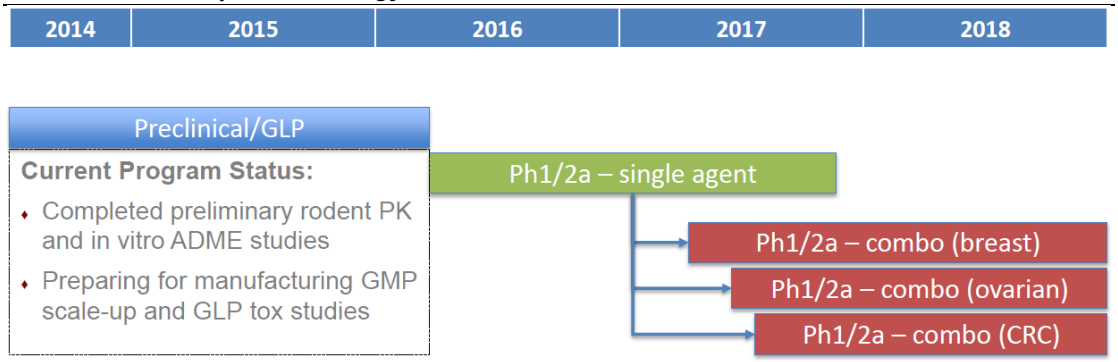
- **Cdc7 appears to be a great target but has yet shown to be drugable as indicated by multiple prior failures.** Scientific discoveries and numerous studies showed that Cdc7 inhibition leads to apoptosis in tumor cells but spares normal tissues or at results in death of normal cells to a lesser degree, supporting it as a good target for cancer therapy. However, the only two attempts for clinical trials failed to proceed due to unfavorable PK profile. Although it is still unclear if this could due to Cdc7 as a target, the KOLs considered it more likely as a result of chemical scaffold.

- **The real de-risking event will be human PK data.** Although animal data support an improved metabolic profile, it is unclear if 10X improvement (we assume 10X reduction in toxic metabolite) would be sufficient to generate an acceptable safety profile in humans.

- **Preclinical safety profile still requires finalization.** RXDX-103 is in preclinical development and is still conducting GLP toxicology studies. Questions could still remain on preclinical safety profile.

- **Long time to reach clinic.** RXDX-103 is still in preclinical stage and it will need substantial time to move into clinic (1H:16 first-in-human study).

RXDX-103 Development Strategy

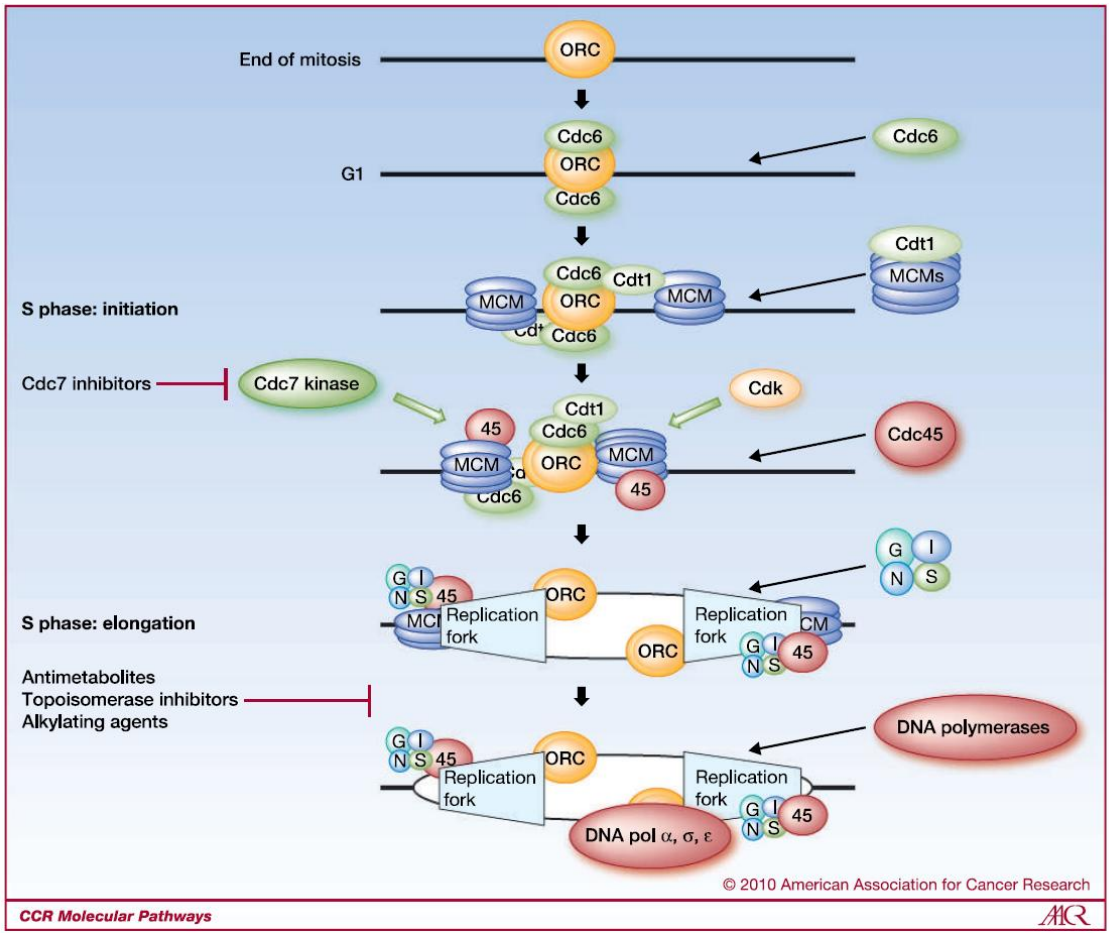


Source: Company Reports

Cdc7 as a Target for Cancer Therapy

Cdc7 inhibition leads to blockade of DNA replication and induces apoptosis in tumor cells but less cell death in normal tissues. Cdc7 (cell division cycle 7) is a conserved serine-threonine kinase that is essential for the initiation of DNA replication. Cdc7 phosphorylates Mcm2 (minichromosome maintenance protein 2) is a component of the DNA replicative helicase. Knockout of Cdc7 genes in mice led to early embryo death, while conditional knockout resulted in the arrest of DNA synthesis, accumulation of DNA damage and eventual p53-dependent cell death (Kim et al., EMBO J 2002, 21:2168). Different from other DNA replication inhibitors, Cdc7 inhibition of DNA replication triggers Chk1-dependent pathway, which leads to apoptosis in cancer cells (dysfunctional checkpoint pathway) but only results in cell cycle S-phase arrest in normal cells (functional replication checkpoint pathway), which could resume replication if Cdc7 inhibition is removed. Therefore, Cdc7 has double functions in both DNA replication and DNA damage response (reviewed in Montagnoli et al., 2010, 16:4503).

DNA Replication in Eukaryotic Cells – Cdc7 Inhibition Results in S Phase Blockade

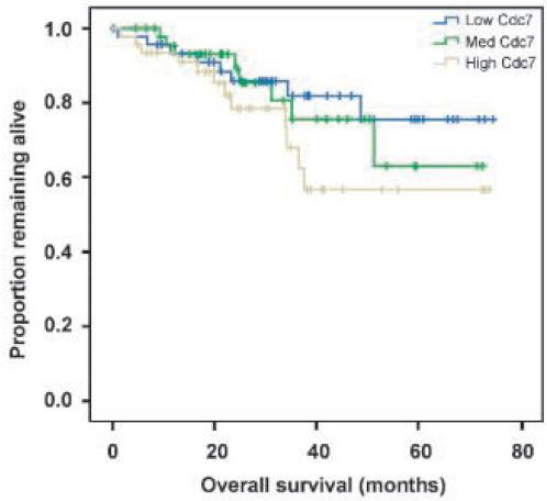


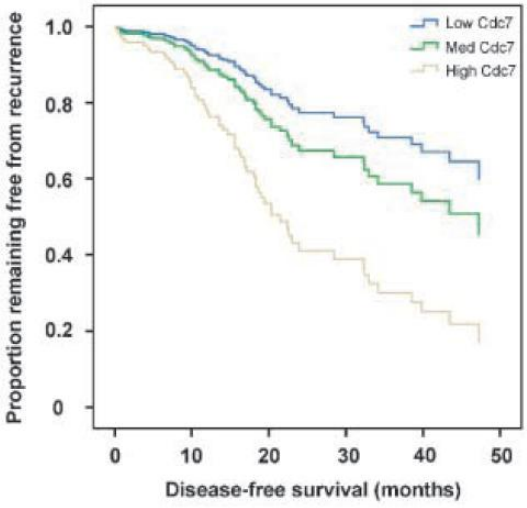
Source: Montagnoli et al., 2010, 16:4503

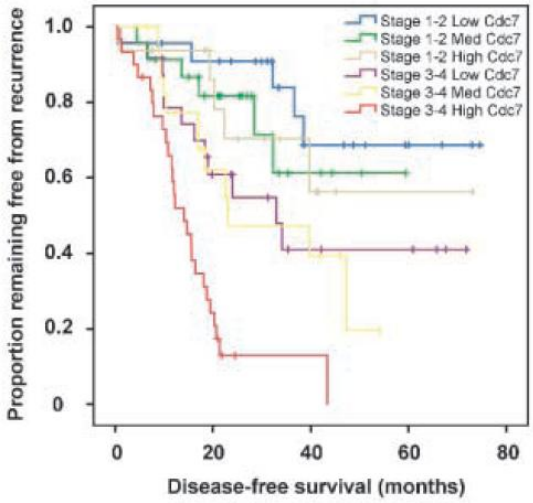
Over expression of Cdc7 has been observed in many tumor types and is correlated with p53 loss. Cdc7 expression level appears very low in normal tissues and cell lines, but increases significantly in ~50% of 62 human tumor cell lines that were examined in a study (Bonte et al., Neoplasia 2008, 10:920). This observation was confirmed in primary breast, colon, and lung tumors. Further analysis showed high correlation between high Cdc7 expression and p53 (tumor suppressor) loss in breast cancer and cell lines tested.

Cdc7 may serve as a predictor for survival based on data from a broad range of cancer types. In a study conducted in 143 human ovarian cancer tissues and 5 normal ovary, increased Cdc7 level was significantly associated with arrested tumor differentiation ($p=0.004$), advanced clinical stage ($p=0.01$), genomic instability ($p<0.001$) and accelerated cell cycle progression. Multivariate analysis further showed that Cdc7 increase was highly associated with overall survival (OS) and disease-free survival DFS), and this correlation increased for Stage 3 and 4 ovarian tumors (Kulkarni et al., Clin Cancer Res 2009, 15:2417). Independently, studies conducted in skin tumor suggests that Cdc7 was overexpressed in malignant melanoma vs. benign melanocytic nevi, and Dbf4 (Cdc7 activator) overexpression was associated with lower relapse-free survival (Clarke et al., J Cutan Pathol 2009, 36:433; Nambiar et al., Carcinogenesis 2007, 28:2501). In DLBCL (diffused large B-cell lymphoma), several studies showed that high expression of Cdc7 was associated with poor prognosis (Hou et al., Med Oncol 2012, 29:3498). In breast cancer, high expression level was significantly associated with high tumor grade, HR (hormone receptor) negative status and amplification of HER2 and c-myc genes (Choschzick et al., Hum Pathol 2010, 41:358).

Cdc7 Expression Level Is Associated with Survival in Ovarian Cancers







Source: Kulkarni et al., Clin Cancer Res 2009, 15:2417

Drug Development for RET Inhibitors Evolving Rapidly; Initial Evidence of Activity Has Been Established

A broad range of drugs have putative activity against RET. Several approved drugs as well as a few drugs in development showed activity against RET. IC50 of these compounds were within nM range in various cell lines bearing either RET rearrangement or mutations.

RET Inhibitors Activity in Cell Lines

RET Inhibitor	Company	IC50 (nM) - Cell Lines (lung cancer)			
		KIF5B-RET	CCDC6-RET	RET^{C634R}	RET^{M918T}
Cometriq (cabozantinib)	EXEL	292	8	226	100
Sutent (sunitinib)	PFE	570	370 (thyroid)	299	312
Iclusig (ponatinib)	ARIA	11		2	3
Caprelsa (vandetanib)	AZN	773	370	448	357
Nexavar (sorafenib)	AMGN	861		>1000	372
Lenvantinib	Eisai				
RXDX-104	RXDX		19	14	39
MGCD516	Mirati				

Source: Company Reports, Gozgit et al., AACR 2013, #2084

Initial activity was observed in two drugs that do not appear to be most potent RET inhibitors. Among the drugs that have putative RET activity, Sutent and Nexavar have been tested in thousands of patients with NSCLC; however, none of the 4 studies identified a single KIF5B-RET fusion in the patients who had a disease response. Recently, the first targeted therapy with Cometriq showed initial promising clinical evidence of activity (Drilon et al., Cancer Disc 2013, 3:630). In a Phase II trial (NCT01639508), Cometriq was evaluated in patients harboring RET fusion proteins. The study is a single-arm Simon two-stage trial with ORR as a primary endpoint, and progression-free survival (PFS) and OS as major secondary endpoints. Data from the first 3 patients showed 2 confirmed partial responses (PRs) and 1 prolonged stable disease (SD). All 3 patients remain progression free on treatment. A case study also showed that Caprelsa had a response in 1 patient carrying KIF5B-RET fusion protein. Both drugs had IC50 within hundred nM range. Initial data support RET as a new treatment paradigm for NSCLC.

Total Reported Activities In RET+ Tumors

Patient	RET fusion	RET Inhibitor	Company	Ethnicity	Sex	Age	Pathologic Diagnosis	Smoking History	Response (% decrease)	Reference
1	TRIM33-RET	Cometriq (cabozantinib)	EXEL	Caucasian	Female	41	Papillary adenocarcinoma	Never-smoker	PR (66%)	Drilon et al, Cancer Disc 2013, 3:630
2	KIF5B-RET	Cometriq (cabozantinib)	EXEL	African-American	Female	75	Poorly differentiated adenocarcinoma	Never-smoker	PR (32%)	
3	KIF5B-RET	Cometriq (cabozantinib)	EXEL	Caucasian	Female	68	Mixed subtype adenocarcinoma	Never-smoker	SD	
4	KIF5B-RET	Caprelsa (vandetanib)	AZN	Caucasian	Male	58	Poorly differentiated adenocarcinoma	Former smoker	Decrease in size	Gautschi et al, J Thorac Oncol 2013, 8:e43

Source: See "Reference"

Ongoing Clinical Trials in RET+ Cancers

RET Inhibitor	Company	Phase	RET+ Caner	Study Design	Primary Endpoint	Enrollment (#)	Study Start	Primary Completion	Reference
Cometriq (cabozantinib)	EXEL	II	Lung cancer	Open-label, single arm	Response rate	25	Jul-12	Jul-15	NCT01639508
Caprelsa (vandetanib)	AZN	II	Lung cancer	Open-label, single arm	Response rate	17	Feb-13		UMIN000010095
		II	Lung cancer	Open-label, single arm	Response rate	17	Apr-13	Sep-15	NCT01823068
		Observational	Medullary thyroid cancer	Open-label, single arm	Response rate	80	Feb-14	Oct-16	NCT01945762
Lenvantinib	Eisai	II	Lung cancer	Open-label, single arm	Response rate	20	Apr-13	Sep-14	NCT01877083
Iclusig (ponatinib)	ARIA	II	Lung cancer	Open-label, single arm	Response rate	20	Jun-13	Jun-15	NCT01813734
		II	Medullary thyroid cancer	Open-label, single arm	Response rate	48	Mar-13	Mar-16	NCT01838642

Source: Company Reports and ClinicalTrial.gov

Some Development Questions for RET Inhibitors

RET is an emerging target with a lot of unknowns. Following the initial case report of RET in lung cancer in 2011, RET development has evolved rapidly. However, the natural history of the patients is still unknown, and only limited information is available on RET. For example, it is still unclear if RET+ patients have more indolent disease, since baseline disease burden appears low (reviewed by Gainor and Shaw, Cancer Disc 2013, 3:604). However, the KOLs disagree with this hypothesis since this is not supported by preclinical data and there has been no clear evidence clinically. Given the low incidence of RET gene alteration, clinical development could be challenging, though a KOL noted that a single-arm study may be sufficient to lead to a regulatory approval given precedence of drug development in ALK+ lung cancer patients.

Most drugs are "Dirty" RET inhibitors. Approved drugs that have putative RET activity appear to have better activity against targets other than RET. For example, Iclusig has potent activity in nM range against a range of kinases including ABL, RET, PDGFR, and FGFR. Similarly, though Cometriq has potent activity against RET and MET, the activity against VEGFR2 appears to be ~100X more potent. This raises the questions as to whether these drugs could be dosed up without reaching limiting toxicity against other more potent targets.

RET Tyrosine Kinase Inhibitors Target Many Other Pathways

Drug	Company	Other targets	Status	Ongoing studies	NCT identifier*
Cabozantinib	Exelixis	• VEGFR2 • MET	Approved for medullary thyroid cancer (MTC)	Phase II for RET-rearranged NSCLC	01639508
				Phase II for refractory differentiated thyroid cancer	01811212
Vandetanib	AstraZeneca	• VEGFR • EGFR	Approved for MTC	Phase II for RET-rearranged NSCLC	01823068
Ponatinib	Ariad	• BCR–ABL • FGFR1 • PDGFR • FLT3 • VEGFR2 • KIT	Approved for resistant CML and Ph+ ALL	Phase II for RET-rearranged NSCLC	01813734
				Phase II for selected NSCLC, including RET-rearranged NSCLC	01935336
Sunitinib	Pfizer	• VEGFR • PDGFR • KIT • FLT3 • CSF1R	Approved for renal cell carcinoma and imatinib-resistant GIST	Phase II for never-smokers with lung adenocarcinoma, including RET-rearranged NSCLC	01829217
				Phase II for refractory differentiated thyroid cancer and MTC	00381641
Sorafenib	Bayer/Onyx	• VEGFR • BRAF • CRAF • KIT	Approved for advanced renal cell carcinoma and hepatocellular carcinoma	Phase II for younger patients with select cancers, including recurrent thyroid cancer	01502410

Source: Shaw et al., Nat Rev Cancer 2013, 13:772

Iclusig and Cometriq Kinase Activity Against Key Cancer Targets

Iclusig Activity

Kinase	IC50 (nM)	Kinase	IC50 (nM)
ABL	0.4	RET	0.16
ABL^{T315I}	2	KIT	13
FLT3	12.6	PDGFRα	1
FGFR1	2	PDGFRβ	8
FGFR2	2	VEGFR2	2
FGFR3	18	TIE2	14
FGFR4	8	CSF1R	9

Cometriq Activity

Kinase	IC_{50} (nM)
VEGFR2	0.035
MET	1.8
RET	4.5

Source: Gozgit et al., AACR 2013, #2084; Company reports

Most drugs in development appear to have safety issues. Four out of 5 approved drugs (Cometriq, Sutent, Iclusig and Caprelsa) have boxed warning for their primary indications. Toxicity concern likely may increase for targeting RET where these drugs appear less potent.

RET Inhibitors – Development Stage

RET Inhibitor	Company	RET Status	Note	Safety
Cometriq (cabozantinib)	EXEL	Phase II	Approved for medullary thyroid cancer	Boxed warning on perforations and fistulas, and hemaorrhage
Sutent (sunitinib)	PFE	Phase II	Approved for GIST, RCC, pNET	Boxed warning on hepatotoxicity
Iclusig (ponatinib)	ARIA	Phase II	Approved for CML or Ph+ ALL	Boxed warning on vascular occlusion, heart failure and hepatotoxicity
Caprelsa (vandetanib)	AZN	Phase II	Approved for medullary thyroid cancer	Boxed warning on QT prolongation, torsades de pointes and sudden death
Nexavar (sorafenib)	AMGN	Phase II	Approved for HCC, RCC, thyroid carcinoma	
Lenvantinib	Eisai	Phase II		
RXDX-104	RXDX	Preclinical		
MGCD516	Mirati	Preclinical		

Note: GIST - gastrointestinal stromal tumor; RCC - renal cell carcinoma; pNET - pancreatic neuroendocrine tumors; CML - chronic myelogenous leukemia; Ph+ ALL - Philadelphia positive acute lymphoblastic leukemia; HCC - hepatocellular carcinoma
Source: Company Reports

RXDX-104 – Positives and Negatives

Positive considerations for RXDX-104

- **High potency against RET.** In various cell lines bearing RET rearrangement or mutations, IC50 for RXDX-104 were in low-double-digit nM range. As a comparison, IC50 for most other drugs were in the range of hundred nM. Compared to other drugs in development, RXDX-104 is among the most potent RET inhibitors.

- **RXDX-104 appears to be a cleaner RET inhibitor.** Most of currently approved drugs were developed initially as an inhibitor against a different target. The MEDACorp KOLs raised the concerns on these drugs as RET inhibitors since they have higher activity against other targets. In contrast, RXDX-104 appears to be a cleaner RET inhibitor, which provides the possibility to dose higher without hitting dose-limiting toxicity.

- **Despite a significant lag in development, improvement in safety profile should be sufficient to support market potential, according to the KOLs.** Given that each of the RET inhibitors in development bears some level of toxicity concern, a drug with an improved safety profile with comparable activity should have a competitive advantage and likely will be used over these more toxic drugs.

Negative considerations for RXDX-104

- **Initial clinical activity may set a high bar for drug development targeting RET.** Although small numbers, initial data from Cometriq showed 2 PRs and 1 SD in all 3 identified lung cancer patients carrying RET fusion proteins. If this magnitude of activity holds in larger trials, the efficacy bar for new drugs could be pretty high.

- **Activity against KIF5B-RET is unclear.** KIF5B-RET fusion protein represents ~90% of RET fusion rearrangement in lung cancer and is important commercially. There were no data on KIF5B-RET cell lines based on RXDX's presentation, and it is unclear if RXDX-104 has activity against KIF5B-RET.

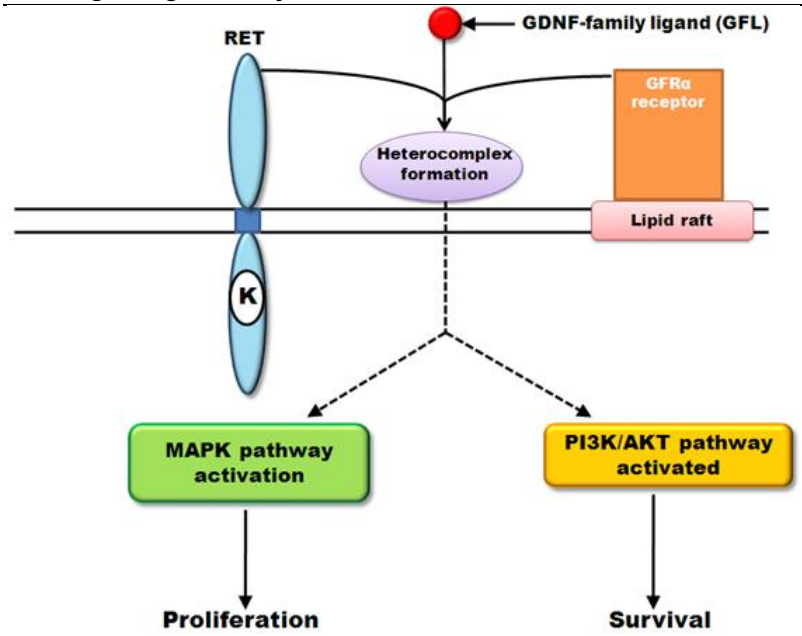
- **Early in development, significant lag vs. competitors.** RXDX-104 is in early stage of development. The company still haven't made the decision on the lead candidate (to be made in early 2015), and likely the first-in-human study may occur at the earliest in 1H:16. As a comparison, all other drugs are already in Phase II development and there will be significant development lag for RXDX-104.

- **Limited information available.** Beyond cell line and xenograft mouse data, there is limited information available, including PK and toxicity profile.

RET Is a Newly Emerged Target

RET belongs to the receptor tyrosine kinase family. The RET (rearranged during transfection) gene belongs to receptor tyrosine kinase (RTK) family and plays a crucial role in neural crest development. Binding of its ligand GDNF (glial cell line derived neurotrophic factor) induces RET receptor phosphorylation and activation, which then phosphorylates its substrates, resulting in activation of multiple pathways including MAPK pathway and PI3K/AKT pathway.

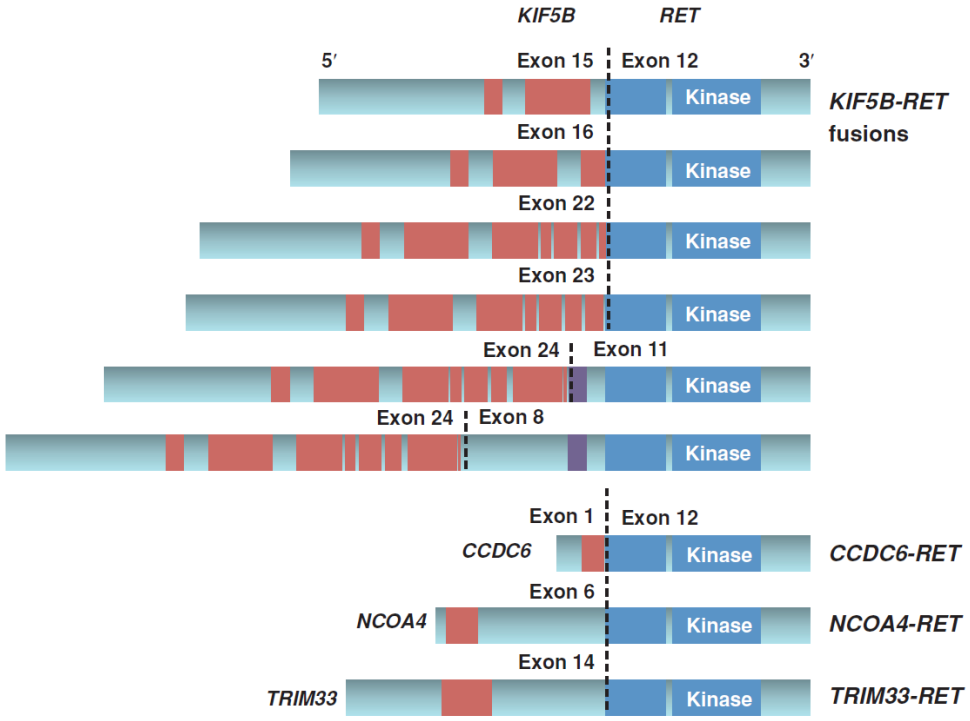
RET Signaling Pathway



Source: MyCancerGenome.org

Genomic alterations in RET are found in several cancer types. RET fusion has been found with a range of genes and characterized most extensively in papillary thyroid carcinoma (~35%), and this incidence could increase to 60-80% when exposed to radiation (Bounacer et al., Oncogene 1997, 15:1263). RET "gain of function" mutations (both germ line and sporadic), on the other hand, have been found in medullary thyroid carcinomas, which result in constitutive activation of RET kinase and tumor growth (Alberti et al., J Cell Physiol 2003, 195:168). The RET fusion was initially reported in NSCLC in 2011 (Ju et al., Genome Res 2012, 22:436).

RET Fusions Reported in the Literature



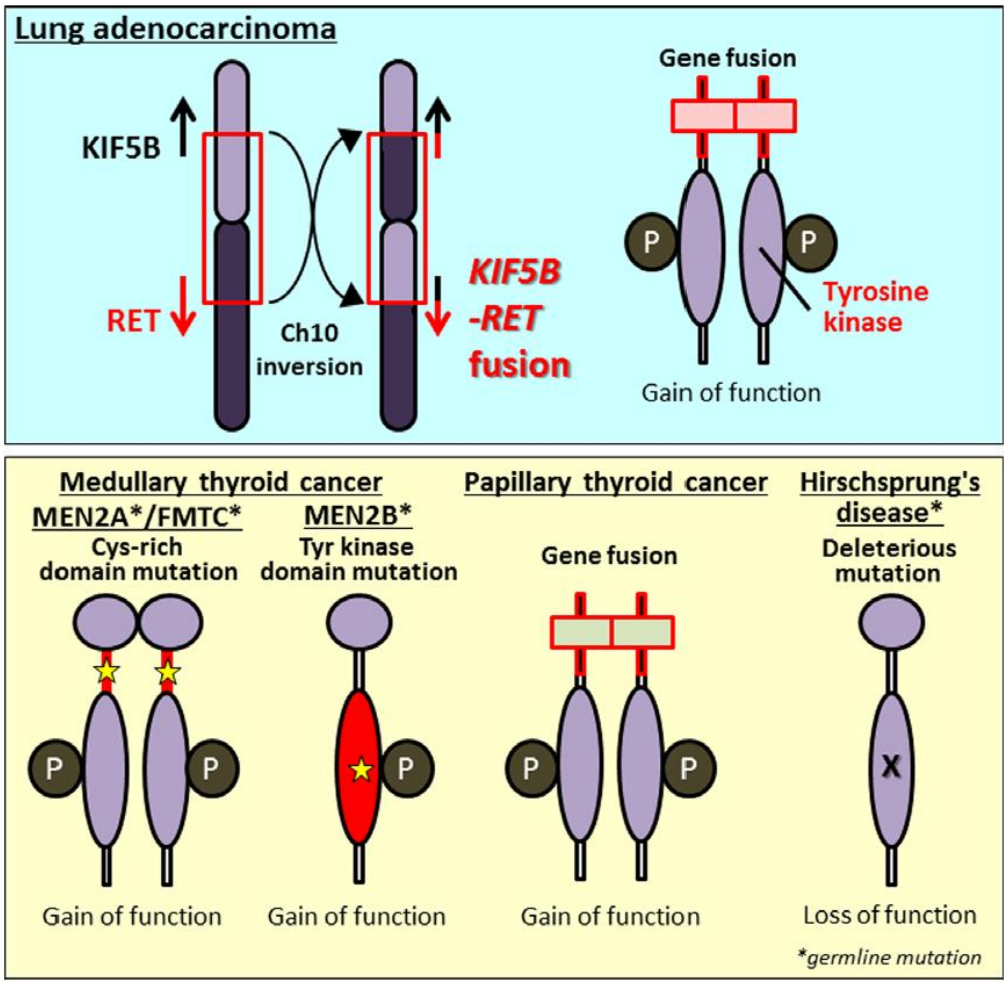
Source: Drilon et al., Cancer Dis 2013, 3:630

RET Rearrangements In Epithelial Cancers

Kinase (location)	Malignancy	Rearrangement partners	Location of partners	Type of rearrangement	Frequency*
RET (10q11.2)	NSCLC	*KIF5B*	10p11.22	Pericentric inversion	1–2%
		CCDC6	10q21	Paracentric inversion	
		NCOA4	10q11.2	Paracentric inversion	
		TRIM33	1p13.1	Interchromosomal	
	Papillary thyroid cancer	*CCDC6*	10q21	Paracentric inversion	~35%‡
		PRKAR1A	17q24.2	Interchromosomal	
		GOLGA5	14q32.12	Interchromosomal	
		NCOA4	10q11.2	Paracentric inversion	
		RAB6IP2	12p13.3	Interchromosomal	
		MBD1	18q21	Interchromosomal	
		TRIM24	7q32-q34	Interchromosomal	
		KTN1	14q22.1	Interchromosomal	
		TRIM33	1p13.1	Interchromosomal	
		TRIM27	6p22	Interchromosomal	
		HOOK3	8p11.21	Interchromosomal	

Source: Shaw et al., Nat Rev Cancer 2013, 13:772

RET Fusions in Lung, Thyroid Carcinoma and Others



Source: Kohno et al., Cancer Sci 2013, 104:1396

RET fusion occurs in 1-2% of NSCLC. Following the first case report, RET fusions have been identified in 1-2% of lung adenocarcinomas, mostly in non-smokers (Kohno et al., Takeuchi et al., Lipton et al., Nat Med 2012, 18:375-384). Sequencing of 319 Japanese lung adenocarcinoma specimens suggested KIF5B-RET in frame fusion variants in 1.9% of samples, and these fusion variants are driver mutations specific to lung adenocarcinoma (Kohno et al., Nat Med 2012, 18:375). An independent research identified KIF5B-RET and coiled-coil domain containing 6(CCDC6)-RET in 1% of 1,529 lung cancers (Takeuchi et al., Nat Med 2012, 18:378-381). Eleven KIF5B-RET gene fusions were identified after screening 561 lung adenocarcinomas, representing 1.9% of incidence (Lipson et al., Nat Med 2012, 18: 382-384). These data suggest that RET occurs in 1-2% of unselected NSCLC patients. KIF5B is the most common fusion partner for RET, representing 90% of rearrangements reported to date. The remaining 10% includes CCDC6 and NCOA4.

Summary of KIF5B-RET Fusions in Lung Cancer

Study	Identification and verification method(s)	Ethnicity (n)	Percentage positive for KIF5B-RET	Variants identified
Kohno *et al.*	Whole-transcriptome sequencing[a]	Japanese (30)	3.3	K15;R12, K16;R12, K23;R12, K24;R8
	RT-PCR and Sanger sequencing	Japanese (289)	1.7	
		American (80)	1.3	
		Norwegian (34)	0.0	
	Total	**433**	**1.6**	
Lipson *et al.*	Targeted capture and resequencing[a]	Not specified (24)	4.2	K15;R11, K15;R12, K16;R12, K22;R12
	RT-PCR	Caucasian (121)	0.8	
		Korean (347)	2.2	
		Japanese (58)		
	RET IHC and RT-PCR	Caucasian (92)	1.1	
		African American (5)	0.0	
		Unknown (20)	0.0	
	Total	**667**	**1.8**	
Takeuchi *et al.*	IHC and FISH screen[a]	Japanese (1529)	**0.9**	K15;R12, K16;R12, K22;R12, K23;R12, K24;R11
Ju *et al.*	Whole-genome and whole-transcriptome sequencing[a]	Korean (1)	100.0	K15;R12, K16;R12, K23;R12
	Whole-transcriptome sequencing (screen)	Korean (5)	20.0	
	RT-PCR	Korean (15)	6.7	
	Total	**21**	**14.3**	
	Total	**2,650**	**1.3**	

Source: Pao et al., Nat Med 2012, 18:349

RXDX – Upcoming Events

Timing	Event
RXDX-101 (Pan-Trk, ROS1, ALK inhibitor)	
2H:14	Phase I update from the Italian trial
3Q:14	Initiation of STARTRK-1 Phase I/II dose escalation study with continuous dosing
	Basket Trial expansion cohorts in TrkA, TrkB, TrkC, ROS1, ALK
ASCO 2015	STARTRK data
RXDX-103 (Cdc7 inhibitor)	
Early '16	Initiating Phase I study
RXDX-104 (RET inhibitor)	
2015	Define a candidate
2016	Initiating Phase I study
Spark-1 (Rx/Dx novel target)	
2015	IND candidate

Source: Company Reports

RXDX – Pipeline

Stage of Development	Current Status/Upcoming Developments
RXDX-101 (Pan-Trk, ROS1, ALK inhibitor)	
Phase I	Phase I dose escalation study of intermittent dosing in Italy with 20-30 pts in each of ALK, ROS1 or TrkA alterations.
STARTRK-1	Global Phase I/II dose escalation study in US, EU and Asia with continuous dosing in 6-24 pts with Trk, ROS, or ALK alterations to be initiated in 3Q:14
	Basket trial expansion cohorts at RP2D with 15-20 pts in each cohort with TrkA, TrkB, TrkC, ROS1 or ALK alterations
STARTRK-2	Pivotal registration trials in most promising tumor types and targets based on ORR and other clinical observations
RXDX-102 (Pan-Trk inhibitor)	
Preclinical	Back-up to RXDX-101
RXDX-103 (Cdc7 inhibitor)	
Preclinical	Enter clinical in 2016
RXDX-104 (RET inhibitor)	
Preclinical	Define candidate in 2015, enter clinical in 2016
Spark-1 Rx/Dx program	
Discovery	IND candidate in 2015
Spark-2 Rx/Dx program	
Discovery	
Spark-3 Rx/Dx program	
Discovery	

Source: Company Reports

VALUATION

Our $14 price target is derived from a probability-weighted DCF analysis. We project US launch for RXDX-101 in NSCLC (both ROS1+ and TrkA re-arrangement, 50% probability) in 2018, and EU launch in 2019. We assume full internal commercialization in both the US and EU with 8% sales royalty to Nerviano. We include $100M cash in 1Q:14 following the recent IPO and assign $40M valuation to the pipeline. We assign no terminal value to RXDX-101. We believe a 10% discount rate is appropriate given probability-weighted sales estimates.

RISK TO VALUATION

- RXDX-101 is at an early stage with limited clinical efficacy data in patients with ROS1 and ALK genetic alteration.
- Although some preclinical data showed RXDX-101 activity against crizotinib resistant cell lines, activity in crizotinib resistant patients is still unknown.
- New toxicity may emerge under the modified continuous dosing regimen in STARTRK Phase I/IIa study.
- Underlying market opportunity for Trk remains to be clarified.
- Competitive landscape remains widely open, and other competitors could emerge rapidly.
- Even with good efficacy as a monotherapy, RXDX-101 may need to be combined with other agents to be competitive.
- Financing risk – Current cash will only support operations into 2016, and RXDX will likely require an additional capital raise before turning profitable.

RXDX - Income Statement ($000, except per share value)	2012A	2013A	Mar-14A	Jun-14E	Sep-14E	Dec-14E	2014E	2015E	2016E	2017E	2018E	2019E
RXDX-101 sales - US							0	0	0	0	8,471	58,747
% to RXDX							*92%*	*92%*	*92%*	*92%*	*92%*	*92%*
RXDX-101 sales - Ex-US							0	0	0	0	0	21,173
% to RXDX							*92%*	*92%*	*92%*	*92%*	*92%*	*92%*
Total revenue	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**7,793**	**73,526**
COGS	0	0	0	0	0	0	0	0	0	0	678	6,394
R&D	708	10,171	2,183	3,056	4,584	5,272	15,095	30,274	43,897	54,871	54,871	53,225
SG&A	548	3,731	1,756	2,107	2,739	3,013	9,616	15,383	16,921	33,843	50,764	55,841
Total expenses	**1,256**	**13,902**	**3,939**	**5,163**	**7,324**	**8,285**	**24,711**	**45,657**	**60,818**	**88,714**	**106,313**	**115,459**
Operating Income	**(1,256)**	**(13,902)**	**(3,939)**	**(5,163)**	**(7,324)**	**(8,285)**	**(24,711)**	**(45,657)**	**(60,818)**	**(88,714)**	**(98,520)**	**(41,933)**
Other income (expenses)	0	(106)	(163)	0	0	0	(163)	0	0	0	0	0
Interest income (expenses)	(23)	(204)										
Tax	1	2	5	0	0	0	5	0				
Net income to common shares	**(1,280)**	**(14,214)**	**(4,107)**	**(5,163)**	**(7,324)**	**(8,285)**	**(24,879)**	**(45,657)**	**(60,818)**	**(88,714)**	**(98,520)**	**(41,933)**
EPS - basic	**(2.00)**	**(3.83)**	**(0.28)**	**(0.26)**	**(0.37)**	**(0.41)**	**(1.35)**	**(1.81)**	**(2.00)**	**(2.19)**	**(2.03)**	**(0.86)**
EPS - dilutive	**(2.00)**	**(3.83)**	**(0.28)**	**(0.26)**	**(0.37)**	**(0.41)**	**(1.35)**	**(1.81)**	**(2.00)**	**(2.19)**	**(2.03)**	**(0.86)**
Basic shares	640	3,712	14,501	19,580	19,775	19,973	18,457	25,237	30,456	40,486	48,527	48,576
Dilutive shares	640	3,712	16,186	21,268	21,467	21,668	20,147	26,940	32,167	42,199	50,241	50,291

Sources: Company Reports, Leerink Partners

Disclosures Appendix

Analyst Certification

I, Gena Wang, Ph.D., CFA, certify that the views expressed in this report accurately reflect my views and that no part of my compensation was, is, or will be directly related to the specific recommendation or views contained in this report.

Distribution of Ratings/Investment Banking Services (IB) as of 06/30/14				
			IB Serv./Past 12 Mos.	
Rating	Count	Percent	Count	Percent
BUY [OP]	138	69.00	50	36.20
HOLD [MP]	62	31.00	2	3.20
SELL [UP]	0	0.00	0	0.00

Explanation of Ratings

Outperform (Buy): We expect this stock to outperform its benchmark over the next 12 months.

Market Perform (Hold/Neutral): We expect this stock to perform in line with its benchmark over the next 12 months.

Underperform (Sell): We expect this stock to underperform its benchmark over the next 12 months.The degree of outperformance or underperformance required to warrant an Outperform or an Underperform rating should be commensurate with the risk profile of the company.

For the purposes of these definitions the relevant benchmark will be the S&P 600® Health Care Index for issuers with a market capitalization of less than $2 billion and the S&P 500® Health Care Index for issuers with a market capitalization over $2 billion.

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