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NSCLC Harboring EGFR Exon 20 Insertions after the Regulatory C-helix of Kinase Domain Responds Poorly to Known EGFR inhibitors

Int J Cancer, 2016;139(1):171-6.
Yang M., Xu X., Ning J., Wery J-P., Li Q-X.

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Publication Overview

- Anecdotal clinical observations suggest NSCLC with exon 20 insertions respond poorly to EGFR TKIs
- Lack of patient-derived models to evaluate new treatments
- CrownBio developed 2 PDX NSCLC models with differing exon 20 insertions
- Confirmed poor response in these models to known EGFR inhibitors:
  - cetuximab
  - EGFR TKIs
- Models may be used to facilitate discovery of new therapies targeting NSCLC with exon 20 insertions

EGFR Genetic Alterations in NSCLC

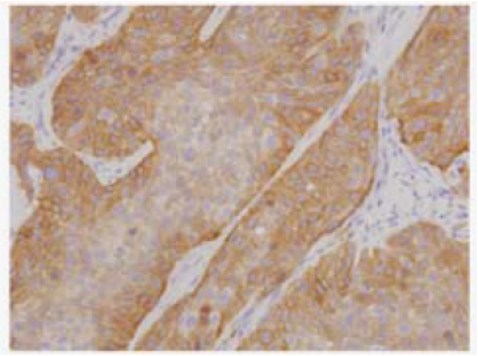
- Activating EGFR mutations found in ~15% of NSCLC cases
- Includes:
  - classic exon 19 in frame deletion (45%)
  - exon 21 L858R (40%)
  - exon 18 T790M & noncanonical G719X (3%)
  - exon 20 insertions (5-10%)
- All important drug targets in NSCLC
- Patients with classic EGFR mutations usually respond to EGFR TKIs
  - gefitinib, erlotinib, afatinib, osimertinib, rociletinib
- And respond to mAb cetuximab
- Efficacy of agents on NSCLC harboring noncanonical EGFR mutations less clear

EGFR Exon 20 Insertions

- Majority located close to end of regulatory C-helix domain
- Generally associated with resistance to existing TKIs
- Basis of *de novo* resistance poorly understood
- Lack of patient derived or GEMM models with relevant insertions major obstacle to developing new treatments
- CrownBio has established 2 NSCLC PDX models
  - LU0387 and LU3075
  - derived from patient tumor tissue
  - with 2 different exon 20 insertions
  - both insertions follow C-helix domain
  - used to evaluate response to EGFR TKIs

PDX Development

- LU0387: ADC, 9 base insertion at 2319
- LU3075: SCC, 9 base insertion at 2316
- Both insertions map within the loop following regulatory helix-C of EGFR kinase domain
- Identified by transcriptome sequencing
- Mutation confirmed by hotspot mutation analysis
- Both models display higher levels of EGFR protein at cancer cell surface
  - LU0387 2.5+
  - LU3075 2+ (shown)



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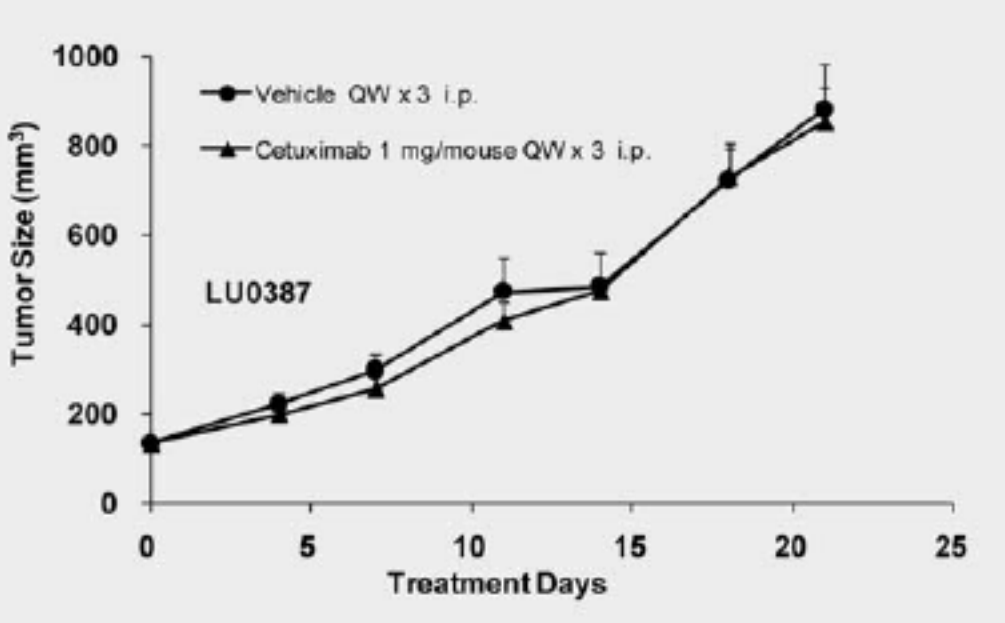
PDX with Exon 20 Mutations Do Not Respond to Cetuximab

- NSCLC PDX with classic EGFR mutations respond to cetuximab
- LU0387 and LU3075 resistant to cetuximab
- Suggests fundamental differences between classic and noncanonical EGFR mutants
  - structurally
  - biochemically



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PDX with Exon 20 Mutations Respond Poorly to Existing TKIs

- Classic EGFR mutants generally sensitive to EGFR TKIs
- PDX with EGFR exon 20 insertion have poor response to 1st, 2nd, 3rd generation TKIs

Mutations	PDX-ID	Cetuximab 40 mg/kg[7]	Erlotinib 50 mg/kg	Gefitnib 100 mg/kg	Afatinib 15 mg/kg	Osimertinib 10 mg/kg	Rociletinib 30 mg/kg
WT	LU0357	5	57	25	NT	NT	NT
L858R[1]	LU0858#	+++	+++	+++	NT	NT	NT
L858R/T790M	LU1868	−6	84	85.7	35	NT	−11
exon-19-Del	LU1235	−12	−7	−17.6	NT	NT	NT
exon-18 G719A	LU1903[2]	–	–	NT	NT	NT	NT
exon-20-Ins	LU0387	96.5	42.9	92	56.4	50.9	92.6
exon-20-Ins	LU3075	80	83.0	87.3	50.6	53.2	48.4

Responses are measured as $\%\Delta T/\Delta C$.[7] LU0858, 1868 and 1235 have been described previously.[7]
[1]Model with two oncogenic drivers: EGFR L858R and cMET amplification. When cMET is inhibited, LU0858 is sensitive to EGFR inhibitors (+++).[7]
[2]Model with c-met amplification. In this model combination of a c-MET inhibitor and a EGFR inhibitor does not result in detectable antitumor activity (–).

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PDX-Derived Cell Lines Show Poor *In Vitro* Response

- Primary cell lines derived from LU0387 and LU3075
- *In vitro* drug response profiles partially predictive of *in vivo* drug sensitivity

		LU0387		LU3075	
No.	Testing articles	Absolute IC_{50} (μM)	%Maximal inhibition	Absolute IC_{50} (μM)	%Maximal inhibition
1st trial	Osimertinib	3.298	92.84	1.591	99.87
2nd trial	Osimertinib	5.721	72.52	2.57	99.77
1st trial	Rociletinib	2.636	77.01	2.095	93.46
2nd trial	Rociletinib	3.442	67.70	2.501	90.24
1st trial	Afatinib	10.823	44.91	1.23	99.43
2nd trial	Afatinib	>10	41.75	1.816	99.37
1st trial	Gefitinib	>10	46.06	4.369	73.14
2nd trial	Gefitinib	>10	38.00	6.790	63.83
1st trial	Erlotinib	11.621	48.36	9.665	50.71
2nd trial	Erlotinib	>10	40.56	>10	37.16
1st trial	Cetuximab	–	13.26	–	21.13
2nd trial	Cetuximab	–	21.5	–	19.04

–: no effect.

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Publication Summary

- Lack of patient-derived models is hindering research in NSCLC with exon 20 deletions
- CrownBio developed 2 PDX NSCLC models with differing exon 20 insertions (LU0387, LU3075)
- In contrast to classical EGFR mutations, we confirmed poor response to known EGFR inhibitors:
  - cetuximab
  - EGFR TKIs
- Poor response maintained in PDX-derived cell lines
- Models may be used to facilitate discovery of new therapies targeting NSCLC with exon 20 insertions
- Read more: **Yang M. *et al.* Int J Cancer, 2016;139(1):171-6**

Connect with CrownBio

- Contact us at **busdev@crownbio.com** for full details on our PDX models and NSCLC resources
- Explore CrownBio PDX models through HuBase™ our free-to-access, online database
- Or investigate
  - CDX models via XenoBase®
  - mouse cancer cell lines (including syngeneics) in MuBase®
  - accessible from **www.crownbio.com**
  - one stop search for PDX, CDX, syngeneics with Onco*Express*™ at **oncoexpress.crownbio.com**