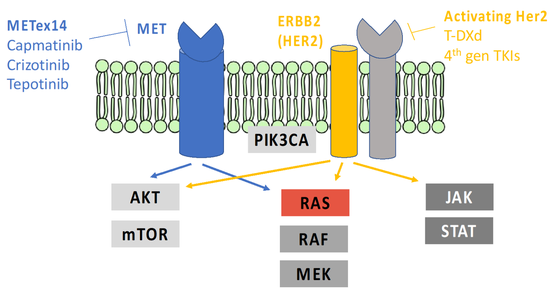
Abstract #9084: Survival associations and driver oncogene overlap for copy-number amplifications of *ERBB2*, *KRAS* and *MET* in Non-small cell lung cancer

Alexander S Watson[a], Harris Krause[b], Andrew Elliott[b], Alex Farrell[b], Stephen V. Liu[c], Patrick Ma[d], Ari VanderWalde[b], George Sledge[b], David Spetzler[b] Erin L Schenk[e], D Ross Camidge[e]

[a]Tom Baker Cancer Centre, Department of Oncology, University of Calgary, Calgary, Alberta [b]Caris Life Sciences, Irving, Texas [c]Georgetown University, Washington, DC
[d]Penn State University, State College, PA [e]University of Colorado Cancer Center, Anschutz Medical Campus, University of Colorado, Aurora, CO

BACKGROUND

- Next-generation sequencing (NGS) is standard of care in metastatic non-small cell lung cancer (NSCLC)
- Targeted therapy has transformed outcomes for driver mutation-positive tumors
- **Copy number amplifications (CNA)** of driver oncogenes are also frequently detected via NGS - interpretation and clinical impact is less clear
- *ERBB2*, *KRAS* and *MET* are oncogenic driver genes with intersecting resistance mechanisms and evolving therapeutic landscapes



- Understanding how CNA of these genes overlap with common driver mutations and impact survival will aid clinical discussion and future research

METHODS

- NGS of DNA (592 genes or WES)/RNA (WTS) performed on 5870 consecutive lung adenocarcinoma tumors submitted to Caris Life Sciences (Phoenix, AZ)
- Driver oncogenes (**Driver+/-**) defined as pathogenic SNVs/indels (*ALK, BRAF, EGFR, ERBB2, KRAS, MET*) or pathogenic fusions (*ALK, NTRK 1/2/3, RET, ROS1*)
- Copy number determined using sequencing depth of exon and average depth of tumor sample
- CNA-H (vs CNA-L) defined separately for *EBBB2*, *KRAS* and *MET*, at CNA threshold where driver gene mutation frequency significantly decreased (Table 1)
- Tumor mutational burden (TMB)-H defined as ≥ 10 mutations per megabase
- Overall survival (OS) calculated as time of collection to last contact (using insurance claims)
- χ^2 test was applied as appropriate ($p < .05$)

RESULTS

CNA are less common with Driver+ NSCLC

ERBB2 CNA	N	Additional oncogenic driver (%)	*p*
Copy Number <4	5598	3759 (67%)	<0.001
Copy Number ≥4 to <6	194	137 (70%)	
Copy Number ≥6	53	12 (23%)	
KRAS CNA	**N**	**Additional oncogenic driver (%)**	***p***
Copy Number <4	5670	3797 (67%)	<0.001
Copy Number ≥4 to <6	117	88 (75%)	
Copy Number ≥6	57	22 (39%)	
MET CNA	**N**	**Additional oncogenic driver (%)**	***p***
Copy Number <4	5723	3868 (68%)	<0.001
Copy Number ≥4 to <6	76	25 (32%)	
Copy Number ≥6	45	14 (33%)	

CNA-High (H) CNA-Low (L)

Table 1: Co-occurring oncogenic driver mutations at different CNA thresholds for *ERBB2*, *KRAS* and *MET*.
*One instance of co-occurring CNA-H genes (*KRAS* and *MET*)

TMB-H distribution by driver positivity, oncogene, and CNA

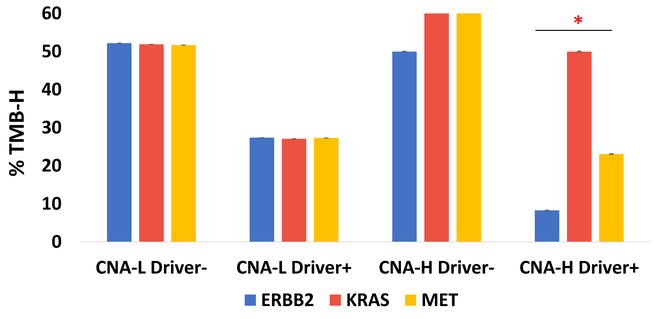


Figure 1: Percentage TMB-High by CNA and driver status (p<0.05)

RESULTS (cont)

CNA-High status associates with decreased OS*

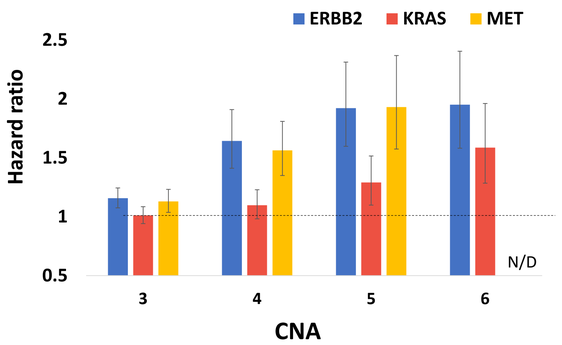


Figure 2: Hazard Ratio (HR) for death by CNA threshold (above vs below threshold). *Overall survival from collection to last contact (insurance data)

CNA-OS association is independent of driver status for *ERBB2* and *MET*, not *KRAS*

ERBB2	HR (CNA-High vs -Low)	Lower CI	Upper CI	*p*
Driver +	1.3	0.9	1.89	0.16
Driver -	1.71	2	2.43	0.003
KRAS	**HR (CNA-High vs -Low)**	**Lower CI**	**Upper CI**	***p***
Driver +	1.5	1.17	1.91	0.001
Driver -	0.92	0.6	1.42	0.669
MET	**HR (CNA-High vs -Low)**	**Lower CI**	**Upper CI**	***p***
Driver +	1.62	1.29	2.02	<0.001
Driver -	1.47	1.14	1.9	0.003

Table 2: Hazard Ratio (HR) for death for CNA-High vs CNA-L stratified by Driver mutation status (higher HR means worse outcomes for CNA-High)

CONCLUSIONS

NSCLC with **high CNA** of *ERBB2*, *KRAS* and *MET* represent **distinct** molecular entities, and are associated with **shorter overall survival**

LIMITATIONS

- Limited demographic information and staging information, therefore potential unmeasured confounders for survival

FUTURE DIRECTIONS

- Standard definitions for functional amplification combining CNA threshold and driver overlap should be prospectively examined in trials of targeted therapies
- *KRAS* CNA-H tumors overlap more with Driver+ population, requires further examination
- More granular investigation of driver/CNA-H overlap, including resistance implications
- Interaction between CNA status and immunotherapy

Correspondence to alexander.watson@ucalgary.ca