RET-MAP: An international multi-center study on clinicopathologic features and treatment response in patients with NSCLC and *RET* fusions

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Background

- Molecular drugs targeting mutated/rearranged oncogene drivers – standard recognized Rx in pts with adv NSCLC
- Activating *RET* fusions are found in 1-2% of NSCLC, mostly adenocarcinoma
- These fusions result in ligand-independent constitutive activation of the RET pathway and increased oncogenic signaling
- Initially multikinase inhibitors and recently selective RET inhibitors have shown good anti tumor efficacy

- It is exactly a decade since RET has been designated as an activating driver oncogene in NSCLC
- And since it very uncommon, this population subgroup has not been well characterised

Aim

- To evaluate and report
  - real-life data on patients affected by RET+ NSCLC
  - clinical and biological characteristics,
  - response to different treatment modalities, and
  - survival

Methods

- Retrospective multi-center study including patients from 19 European centres with:
  - Any stage *RET*+ NSCLC
  - Known molecular profile by DNA/RNA sequencing and/or FISH analyses
- Clinical, pathological, biological features and treatment outcomes (assessed by investigators) including surgery, chemotherapy (CT), immunotherapy (ICI), CT-ICI, multityrosine kinase inhibitors (MTKi) and RET inhibitors (RETi) were evaluated

Results

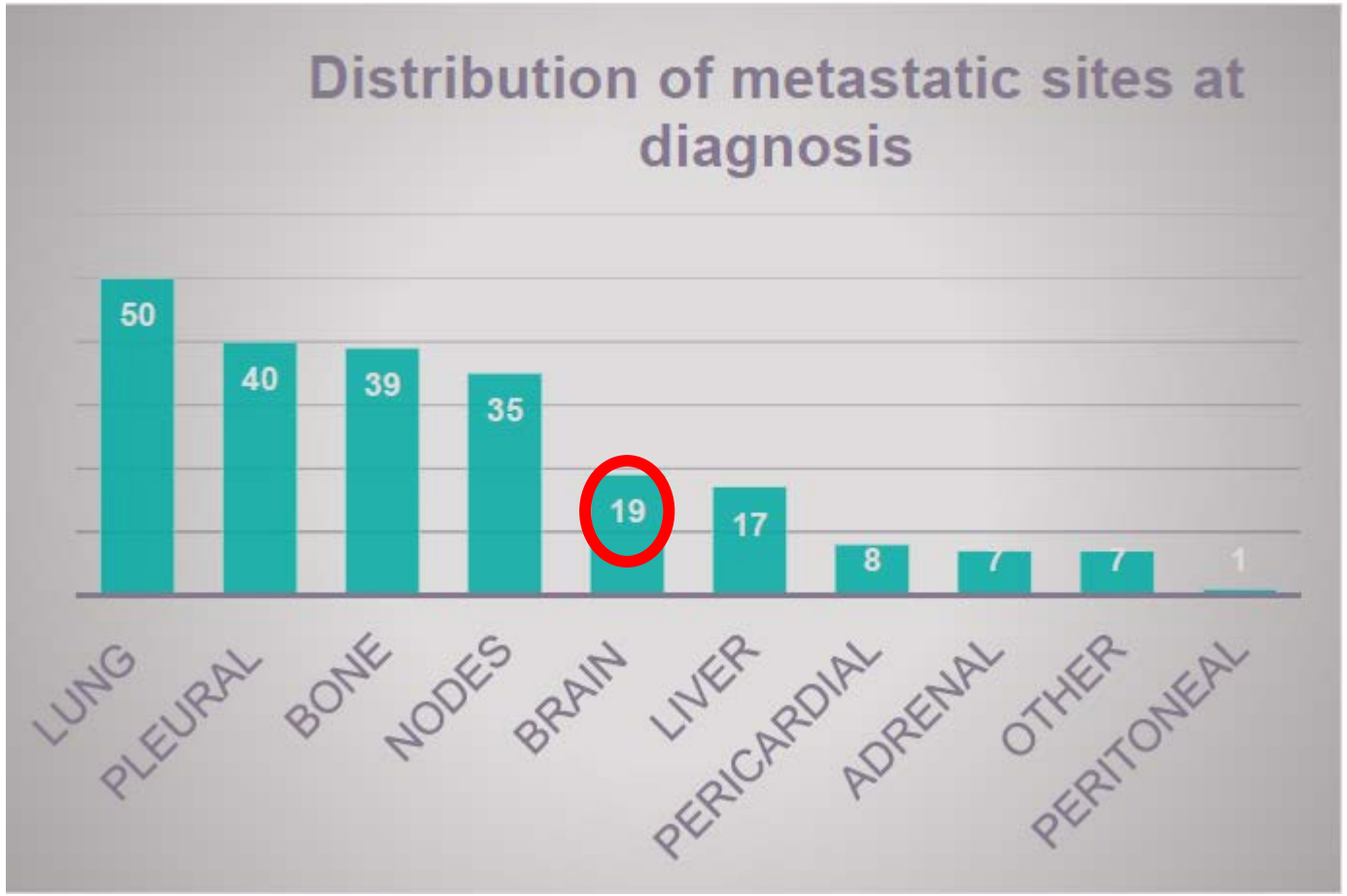
45% pts have history of smoking

Patients' characteristics	N = 149
Median age (range)	61.9 (53-69.6)
Female sex (%)	87 (58.4)
Smoking history (%)	67 (45)
Adenocarcinoma histology (%)	138 (92.5)
Median number of lines (IQR)	2 (1-3)

Metastatic sites at Diagnosis

- 67% were metastatic

30% Brain mets at last follow up



RET fusion partners and PD-L1, TMB

Fusion partners

- **KIF5B-71%**
- **CCDC6-20%**
- **Others-19%**

mPD-L1(n=101)
5%

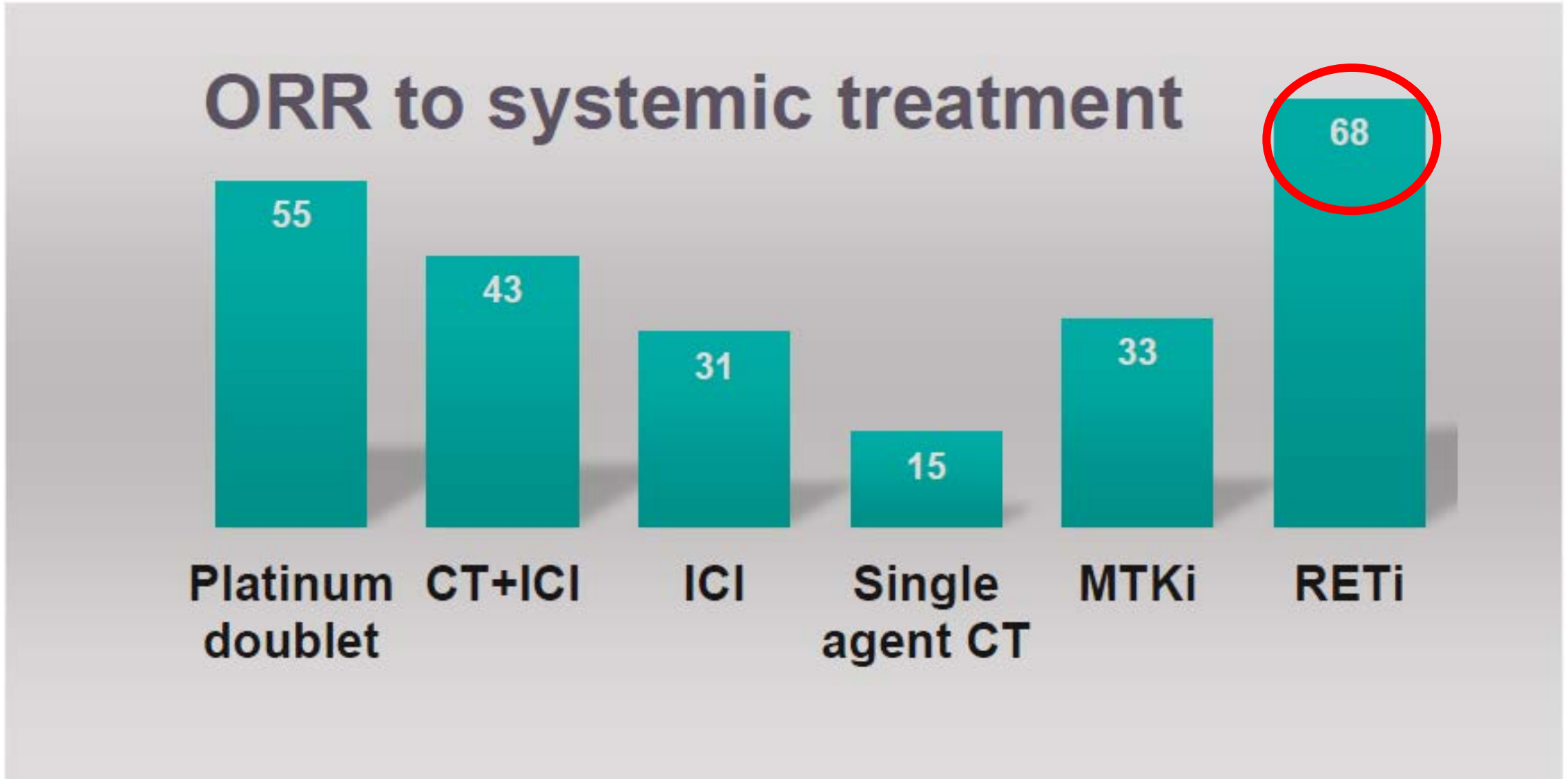
mTMB (n=18)
3.5 mut/mB

Most frequent
Co-mutation
Tp53(21%)

Efficacy of treatment

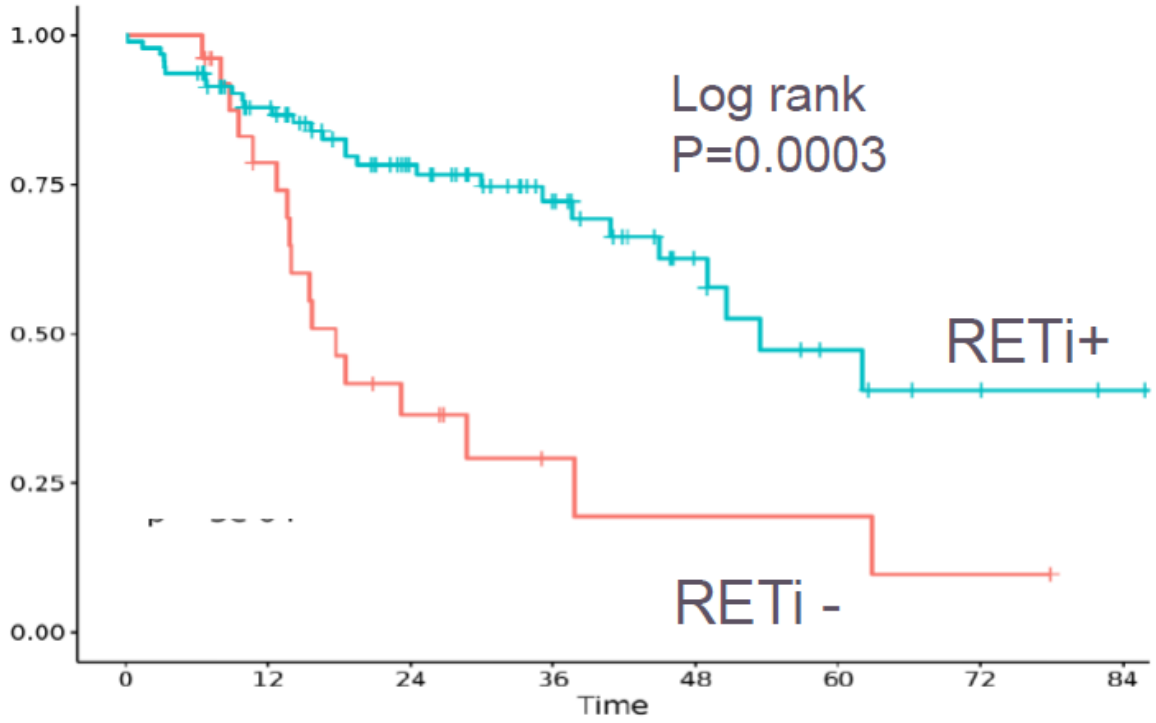
Treatment	N (%)	mPFS (95% CI)	mDOR (95% CI)
RET inhibitors (RETi)	100 (67.1)	18.9 (13.4-33.5)	21.1 (14.9-NA)
Chemo-immunotherapy (CT-ICI)	23 (15.4)	9.43 (3.88-18.7)	8.8 (8.25-NA)
Immunocheckpoint inhibitors (ICI)	35 (23.5)	5.03 (2.99-11)	9.31 (7.69-NA)
Platinum doublet	73 (49)	8.4 (6.18-11.4)	6.11 (5.13-10.9)
Multityrosine-kinase inhibitors (MTKI)	15 (10)	2.83 (1.28-NA)	5.82 (1.84-NA)

RETi have the highest PFS and DOR!

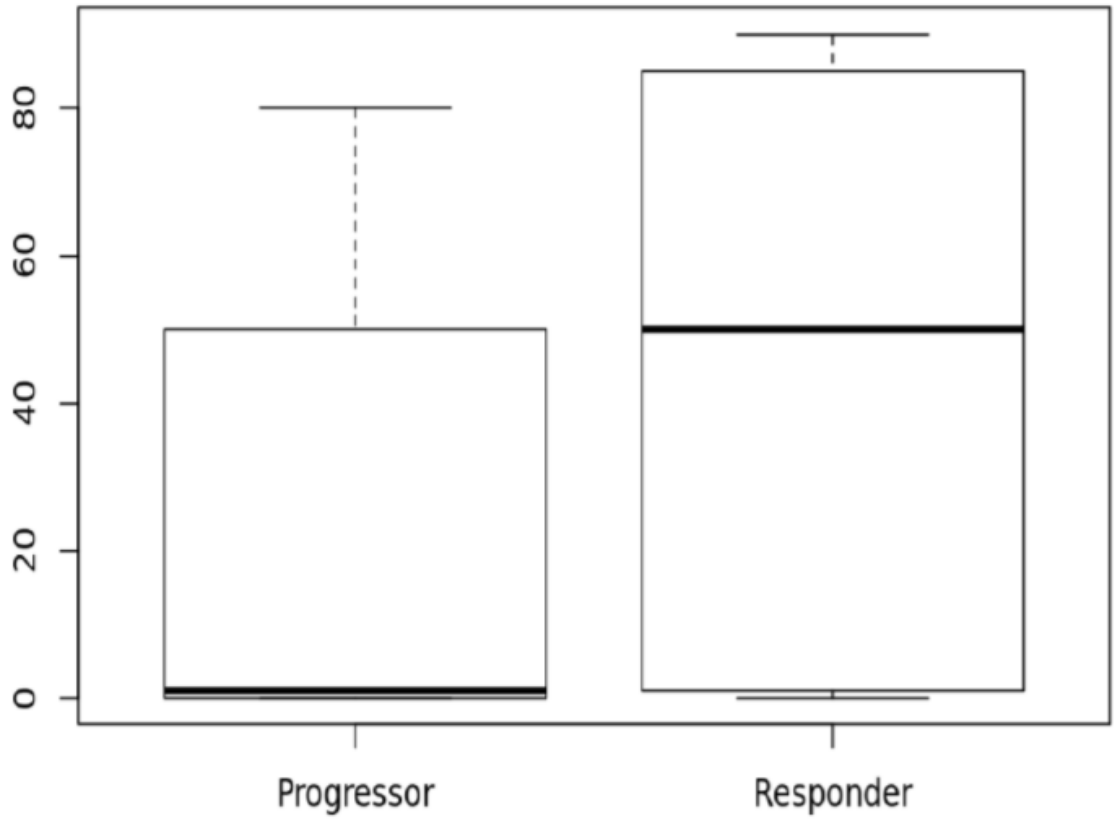

ORR to systemic treatment
55
43
31
15
33
68
Platinum doublet
CT+ICI
ICI
Single agent CT
MTKi
RETi

Overall survival of pts treated or not with RETi:

mOS=53.5 months (CI 95% 49.0-NA) vs 17.7 months (CI 95% 13.8-NA)



- **PD-L1 expression in responders vs non responder to ICI treatment:**
- mPD-L1 50 (0-90) vs 27.50 (0-90) p=0.1



Conclusions

- Pts with *RET*+ NSCLC may have a smoking history and heterogeneous histologies
- RETi treatment improves survival in pretreated pts
- ICI may be effective in selected pts
- The role of predictive biomarkers needs to be further investigated.

My take…

- Selective RET inhibitors have good anti tumor activity with survival benefit, and efficacy which was seen in the trial setting has been replicated in the real world

- Hence, RET testing should be part of standard diagnostic testing of lung adenoca to pass on the maximum benefit to pts

- Multikinase inhibitors should be avoided given their poor activity and high toxicity and emphasis should be laid on using selective RETi

Thank you