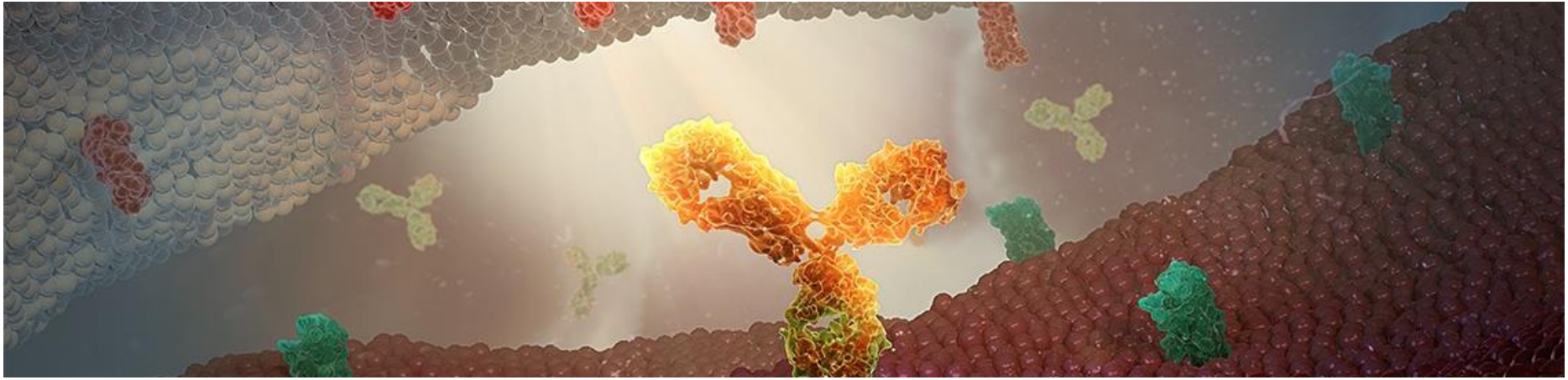
Clinical development of AZD9291 in non-small cell lung cancer

Rachael Lawrance (AstraZeneca)

PSI One Day Meeting:

The Innovative, Challenging and Diversified World of Respiratory Disease

13 Nov 2015



Overview

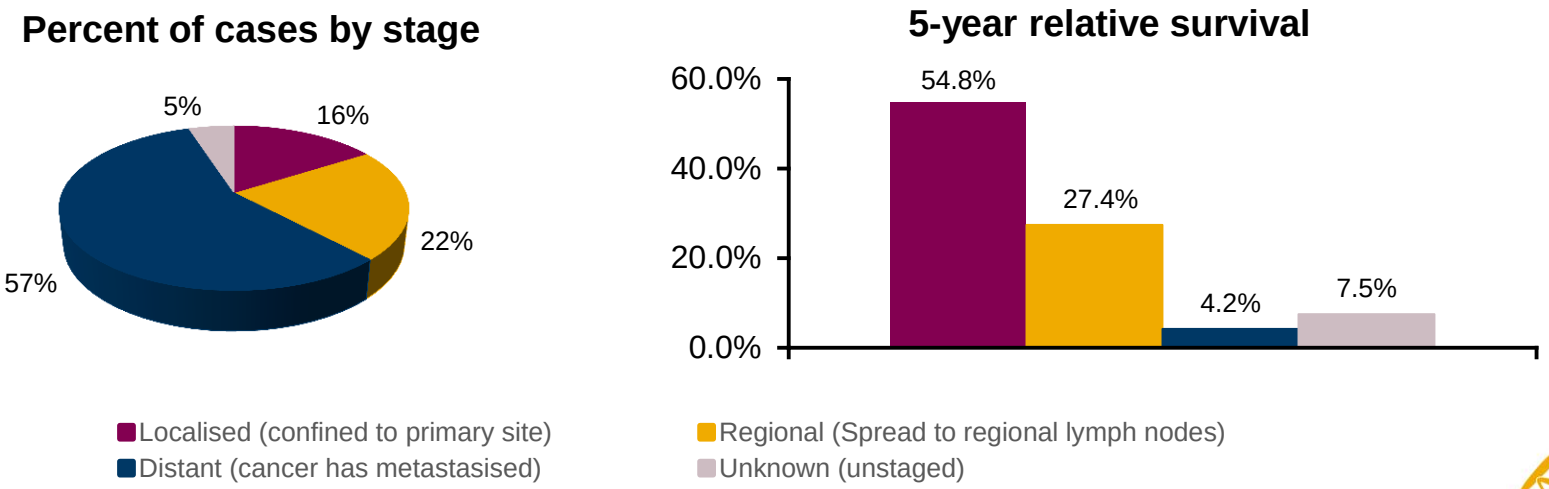
- Overview of non-small cell lung cancer
- Role of molecularly-targeted drugs in oncology
- Oncology endpoints & study design considerations
  - ORR, PFS
  - OS
  - Diagnostic
- AZD9291 example of a novel molecularly targeted NSCLC treatment: rapid drug & companion-diagnostic development programme

Lung Cancer

Overview of lung cancer

- Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths worldwide[1]
- In 2012, there were an estimated 1.8 million new cases and 1.59 million deaths per year globally[1]
- The highest incident rates are in North America, Europe and East Asia[1]
- In the US, approximately 60% of patients are diagnosed with metastatic lung cancer; the 5-year survival rate is 4%[2]

Lung cancer diagnosis and 5-year survival by stage, 2005–2011[1]



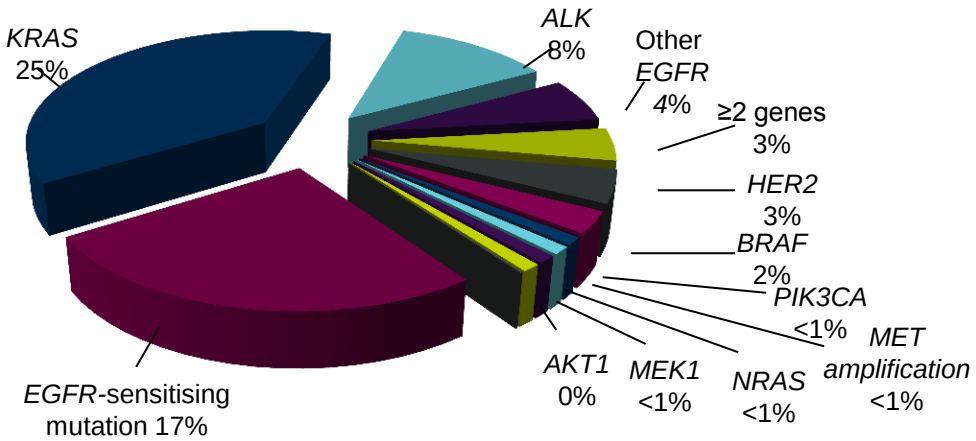
1. GLOBOCAN 2012. http://globocan.iarc.fr; 2. SEER Cancer Statistics Factsheets: Lung and Bronchus Cancer. 2015.

Molecularly-targeted therapies

Lung Cancer is subdivided into key types: Non small cell lung cancer (NSCLC) & Small cell lung cancer

Within NSCLS, adenocarcinoma is the most common subtype (~40% of all NSCLC) and mainly occurs in former or non-smokers NSCLC patients

There has been a paradigm shift in knowledge about oncogenic drivers in lung cancer – leading to molecularly-targeted therapies playing a key role in treatment pathways for patients: EGFRm and ALK being key pathways targeted



Tumours from 733 patients were tested for 10 oncogenic drivers; 64% of patients were positive for one or more genes as detailed in the pie chart

Oncogenic drivers associated with lung cancer[1]

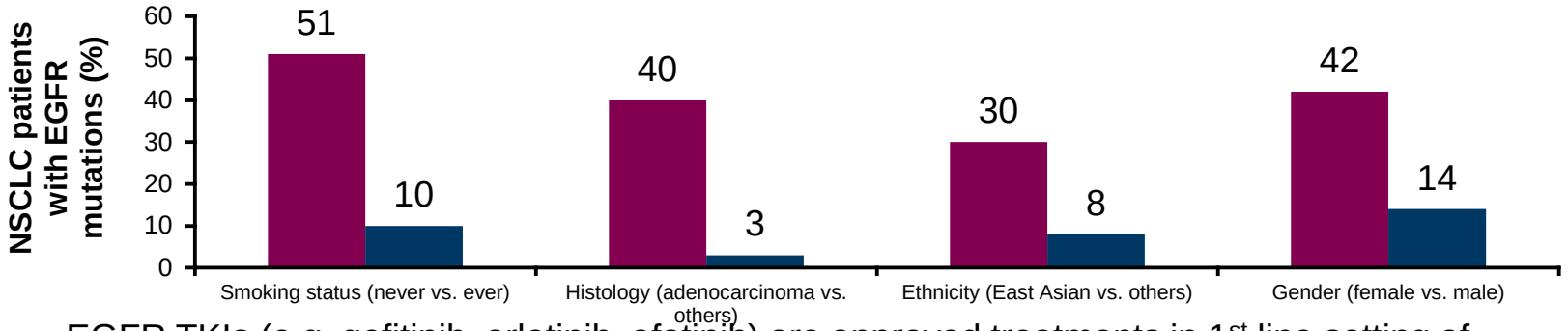
- Several oncogenic drivers associated with the development of lung cancer have been identified , including EGFR-sensitising activating mutations[1]
- EGFR tyrosine kinase activation indirectly inhibits apoptosis and promotes tumour cell survival through signal transduction pathways[2]

NB: the frequency of the different genetic aberrations varies based on patients characteristics e.g. smoking status, gender, race.

1. Kris MG, et al. JAMA 2014;311:1998–2006;
2. Herbst RS & Bunn Jr, PA. Clin Cancer Res 2003;9:5813–5824.

Molecularly-targeted therapies: Example EGFR TKI

- EGFRm tumours are more frequent in never smokers, females, those with adenocarcinoma histology and East Asian patients[1-5]
- Approximately 30–50% of advanced NSCLC patients in Asian populations and approximately 15% (7 - 3%) in Western populations will have tumours that are EGFRm[1-5]

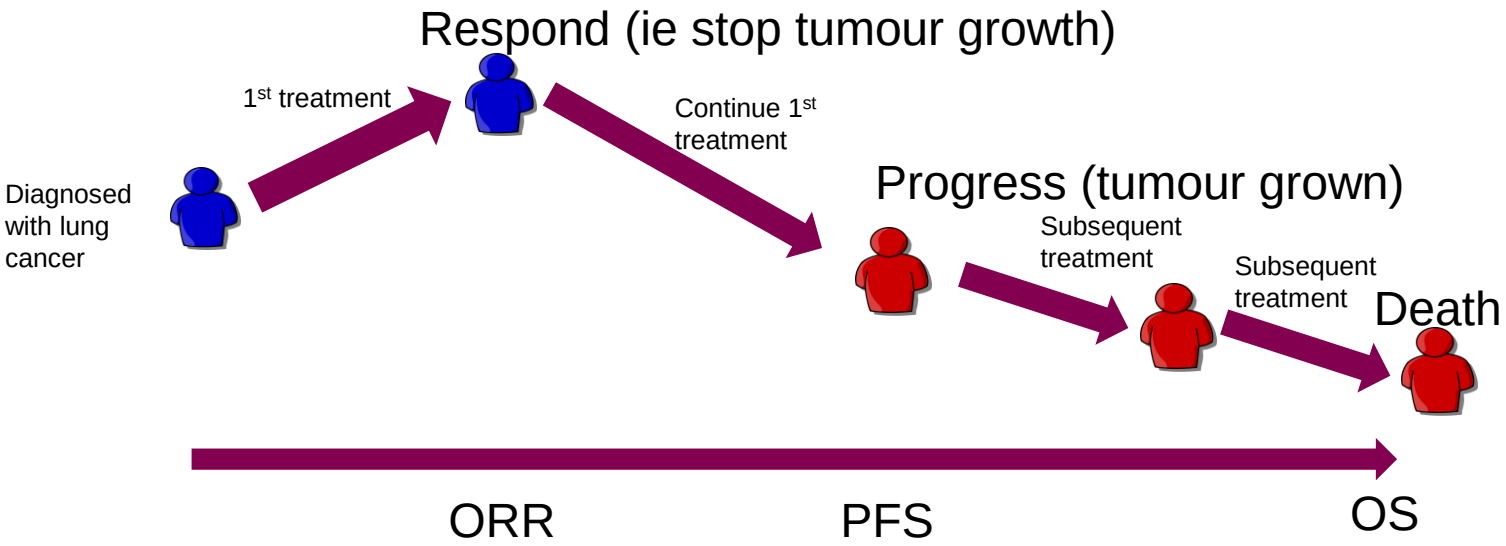


- EGFR TKIs (e.g. gefitinib, erlotinib, afatinib) are approved treatments in 1st line setting of EGFR m NSCLC
- Most NSCLC disease cases treated with a currently approved first-line EGFR-TKI develop resistance – leading to a large area of unmet medical need in EGFRm patients with aquired resistance

1. Shigematsu H, et al. J Natl Cancer Inst 2005;97:339–346; 2. Rosell R, et al. Lancet Oncol 2012;13:239–246; 3. Shi Y, et al. J Thorac Oncol14;9:154–162;
4. D'Angelo SP, et al. J Clin Oncol 2011;29:2066–2070; 5. Sekine I, et al. Br J Cancer 2008;99:1757–1762.

Oncology Clinical Trial Endpoints & Study Design

Oncology endpoints - challenges

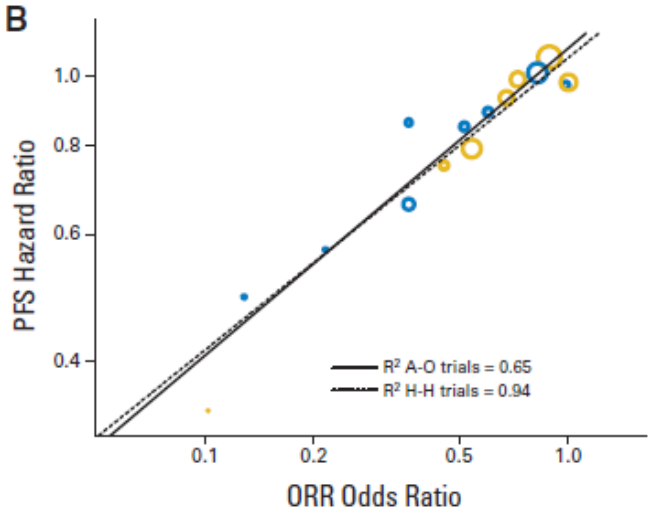


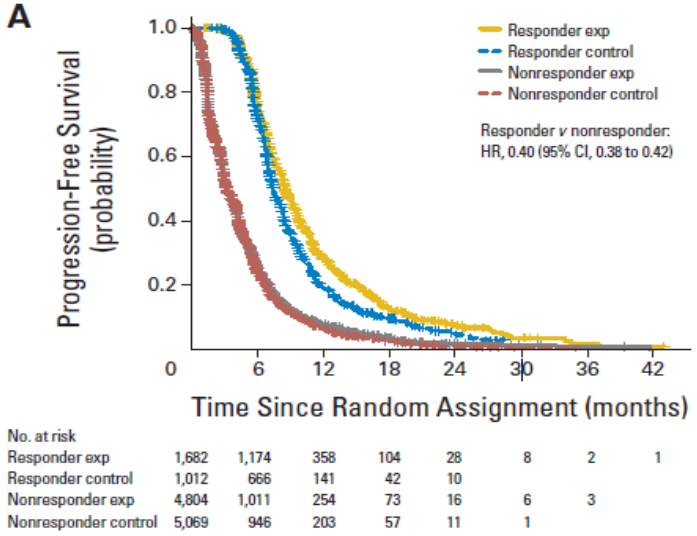
- In oncology, overall survival (OS) is regarded as the optimal clinical endpoint
- Due to challenges in assessing OS, PFS (progression free survival) is used as a surrogate endpoint
  - Depending on the disease prognosis, and the magnitude of benefit this can be accepted by regulatory authorities to demonstrate clinical efficacy
- The use of objective response rate (ORR) is also becoming an acceptable surrogate, particularly in targeted therapies, where high ORRs are seen or in areas of unmet medical need

Relationship between ORR/PFS and OS in NSCLC Blumenthal JCO 2015 (FDA)

- Exploring trial-level and patient-level associations between ORR, PFS and OS
- FDA used 14 trials (N=12567 pats) submitted since 2003 (RCT with >150 pts only)
- Trial-level analysis: weighted linear regression model used to assess the association between treatment effects on ORR, PFS and OS; treatment effects were estimated from cox PH model or logistic regression
- Patient-level responder analysis: (irrespective of treatment) using Cox PH model
    - Burzkowski method to estimate patient-level associations
    - Landmark analyses at different timepoints

Relationship between ORR/PFS and OS in NSCLC





At a trial-level

- ORR and PFS associated
- ORR and OS less clear association
- PFS and OS less clear association

At a responder level

- Responders are associated with better PFS
- Responders also associated with better OS
- Effects consistent over time

Study design considerations – in NSCLC

- Primary endpoint
  - OS or PFS preferable
  - ORR now becoming an acceptable surrogate endpoint in registration studies in molecularly targeted disease areas
  - ORR/PFS by RECIST can be assessed by investigator or by blinded independent central review (BICR)
  - BICR provides an independent review of the radiological data and can be useful as primary endpoint in single arm trials and for ORR endpoints.
    - Need to consider agreement between independent & central review in study design

Study design considerations – in NSCLC

- RCT vs Single Arm trials
  - RCT may be increasingly difficult to conduct whilst maintaining clinical equipoise if strong phase I ORR data etc.
  - ORR can be reliably assessed in single arm trials and as ORR (measured by RECIST criteria) is well established as there are many studies which may be considered as adequate controls to present ORR in context

- Sample sizing in single arm trials: consider precision of ORR estimate, evalubility of ORR across subgroups (regulatory and biologically plausible), and AEs (e.g. sufficient power to detect rare AEs)

- It is also important to understand OS benefits if possible for patients and also of particular interest to Payer/reimbursement submissions
  - Pre-plan adjusted analysis of OS, especially in the case of expectation that “cross-over” to similar therapies likely to confound OS in a RCT

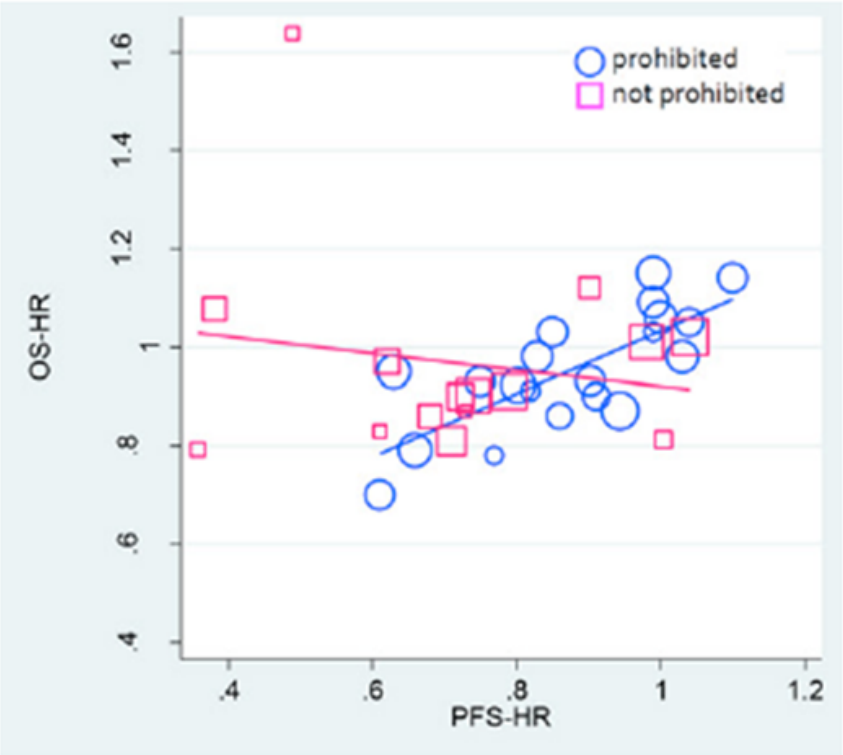
Overall Survival

- Even with a primary endpoint of ORR or PFS, it is also important to understand OS benefits if possible for patients and also of particular interest to Payer/reimbursement submissions

  – Overall survival analysis in future studies likely to be confounded by "cross-over" of treatments once effective targeted therapies are approved
  – Challenge across oncology about how to assess overall survival benefits in clinical trials

- Statistical Methods have been developed which could be useful for adjusted analysis of OS – ideally collect as much information as possible in clinical trial to make analysis most beneficial
  – Pre-plan adjusted analysis of OS, especially in the case of expectation that "cross-over" to similar therapies likely to confound OS in a RCT

Overall Survival – potential confounding problem



Switch prohibited (n=20)
R^2=0.5341

Switch allowed (n=15)
R^2=0.0027

Interaction p=0.019

Hotta et al: Progression-free survival and overall survival in phase III trials of molecular-targeted agents in advanced non-small-cell lung cancer. Lung Cancer 79 (2013) 20– 26

Adjusted OS methods

Statistical methods can be applied to model adjusted OS estimates, however they all make assumptions:

- Naïve and “Complex” methods - No one method yet identified as “best”
- IPCW and RPSFTM methods are key complex methods
  - IPCW (Inverse probability censored weighted)
    - Models the patients on the control arm for those who “switch” and those who do not – uses both baseline and time-varying covariates
    - Uses a time-dependent Cox model; Analysis provides an adjusted HR and KM
    - Important to collect as many factors as possible that may influence treatment decisions; Cannot be used if all patients in control arm switch
  - RPSFTM (Rank preserving structure failure time model)
    - Maintains randomisation, adjust post-switch times, assumes constant treatment effect over time
    - No change in power (ITT p-value maintained)
- Consider collection of as much data as possible in trials

Watkins et al Adjusting overall survival for treatment switches: commonly used methods and practical application Pharm Stats 2013

Diagnostic Considerations

- Patient population
  - Prospective or retrospective biomarker identification?

- For drugs where a prospective diagnostic test (e.g. EGFR mutation test) is used to select the patients in the study, study designs must consider how patients will be selected from the general population

- In US, drug must be approved with a co-diagnostic test for use
- In Europe and rest of world, an approved diagnostic test must be available

EXAMPLE: On July 13, 2015, the U. S. Food and Drug Administration approved gefitinib (IRESSA) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations ***as detected by an FDA-approved test.***

Co-Diagnostic Approval (US)

- In US the CDRH division (medical devices) evaluate the diagnostic test. They evaluate the test characteristics and also “clinical utility” – demonstration of clinical efficacy by the test
- The test used in the study may not be the “final” marketed version, or may use a different type of sample (e.g. tissue or plasma), therefore a “bridging study” may be needed to evaluate clinical efficacy in the marketed version of the test:
  - Important to consider this aspect in the study/programme design to collect all data needed (e.g. detailed demographics data on all screened patients to allow assessment of PPA and NPA)
  - “Bridging” of drug efficacy may addressed by modelling/simulation

Example Question: What is drug efficacy in marketed test ?

- *Patients tested using test in trial (TT); bridge to the marketed test (MT): analyse the drug efficacy in overall MT positive patients where the (TT-, PT+) patients were not treated and hence use imputation for the missing clinical outcomes. For these (TT-, PT+) patients, consider a range of drug efficacy to examine robustness of the analyses.*

AZD9291

AZD9291 Clinical Programme (pre-treated patients)

- 60% of patients who progress on EGFT TKI have T790M resistance mutation
- AZD9291 targets EGFRm and EGFR T790M mutation

AURA[1] NCT01802632	**Phase I: dose escalation and expansion , single arm** Primary endpoint: safety, preliminary efficacy
	Phase II: Assessment of efficacy and tolerability of AZD9291 80 mg QD in T790M NSCLC[2] n=175 **Primary endpoint: ORR**
AURA2[4] NCT02094261	**Phase II:** Assessment of efficacy and tolerability of AZD9291 80 mg QD in T790M NSCLC[2] n=175 **Primary endpoint: ORR**
AURA3[5] NCT02151981	**Randomised comparative Phase III (N=~410)[6]** Efficacy and safety of AZD9291 vs. platinum-based doublet chemotherapy in patients with T790M, advanced/metastatic NSCLC who have progressed following prior therapy with an EGFR-TKI[6] **Primary endpoint: PFS**

1. NCT01802632. www.clinicaltrials.gov;
2. Jänne PA, et al. Ann Oncol 2015;26:(suppl 1 abstract LBA3);
3. Jänne PA, et al. New Engl J Med 2015;372:1689–1699;
4. NCT02094261. www.clinicaltrials.gov;
5. NCT02151981. www.clinicaltrials.gov;
6. Wu YL, et al. Ann Oncol 2015;26:(suppl 1 abstract 140TiP).

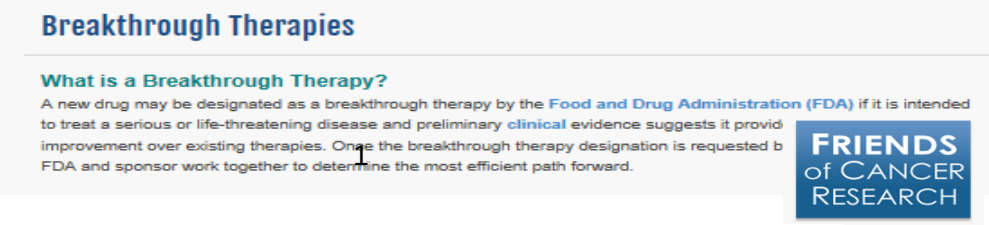
AURA Phase II Registration Studies

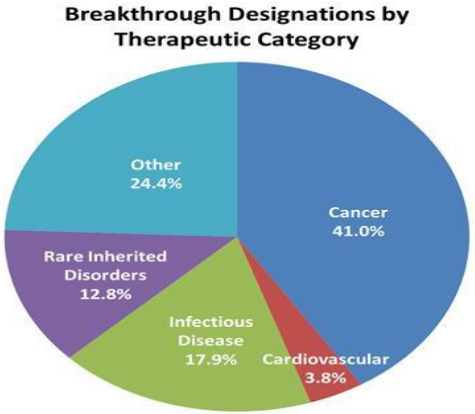
- 2 identical single arm studies
- ORR primary endpoint by BICR (ORR & 95% CI)
  - Duration of response (DoR) (KM plot & estimates)
  - Depth of response (change in tumour size) (mean and waterfall plot)
  - PFS (KM plot & estimates)
  - Investigator assessment of ORR, DoR, PFS

- Sample size n=175, to include n=50 2nd line patients and n=125 ≥3rd line
  - Sized to give adequate precision e.g.95% CI +/-8% for ORR
  - And considering the safety profile (using binomial distribution assumptions:
  - chance of observing at least 1 rare event (if true event frequency 1%)
  - If observed 0 events, 95% confidence that the true rate <2.5%

- Also considered replication across trials, and use of pooled data for evaluation of efficacy and safety outcomes in subgroups
- Also required companion-diagnostic development programme

AZD9291 Development Programme





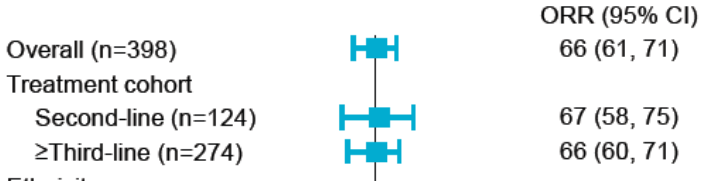
Reprinted with permission from Friends of Cancer Research. Breakthrough therapies. http://www.focr.org/breakthrough-therapies

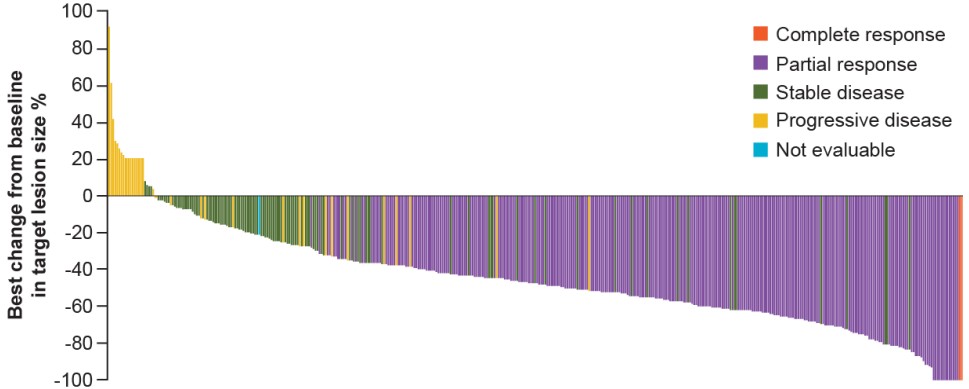
- On 16 April 2014, AZD9291 was granted Breakthrough Therapy Designation by the FDA, for the treatment of patients with metastatic, EGFR T790M mutation-positive NSCLC, whose NSCLC has progressed during treatment with an FDA-approved, EGFR-TKI[2]
- This was granted on the basis of early clinical data from the Phase I (AURA) study in patients with T790M disease[2,3]
- AZD9291 is currently under priority review by FDA, accelerated assessment by EMEA and priority review by PMDA
- Companion-diagnostic submission (PMA) made to FDA in parallel with NDA; cobas EGFR mutation test including T790M mutation achieve CE mark in Europe (September 2015).

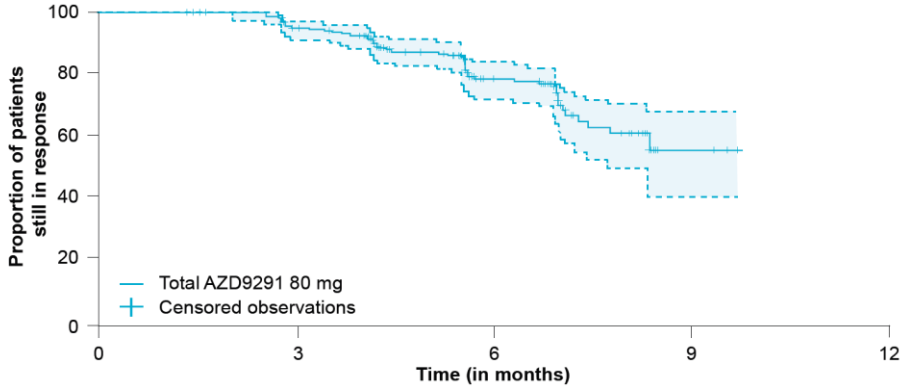
1. Friends of Cancer Research. Breakthrough therapies. http://www.focr.org/breakthrough-therapies (accessed 07 July 2015);
2. http://www.astrazeneca.com/Media/Press-releases/Article/20140423--first-quarter-results-2014;
3. http://www.onclive.com/conference-coverage/asco-2014/AZD9291-Shows-Robust-Activity-in-Resistant-EGFR-positive-NSCLC;
4. http://www.astrazeneca.com/Media/Press-releases/Article/AstraZeneca-strategy-on-track-to-deliver-sustainable-growth-and-value-through-innovation.

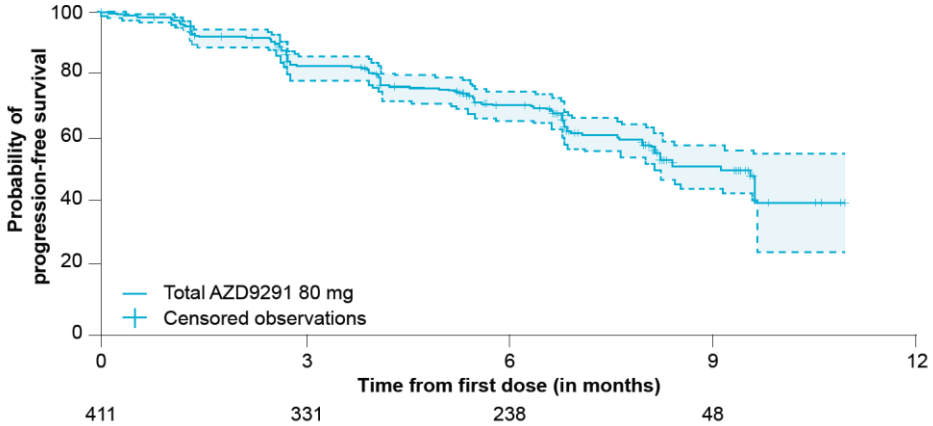
AURA Phase II Studies: Single-arm study efficacy presentations

ORR: 66.1% (95% CI 61.2, 70.7%)









By blinded independent central review. Patients with confirmed objective response (n=263), maturity 23%. Blue dotted lines represent 95% CI
CI, confidence interval; NC, not calculated

Conclusions

Summary

- Lung cancer is the leading cause of cancer related death worlwide
- Molecularly targeted therapies increasingly important for patients
- Clinical trial designs require optimised endpoints to demonstrate that new agents provide quantifiable benefit to patients
  - Regulatory authorities recognising this need (eg. “Breakthrough therapies”)
- Important study design aspects include:
  - Endpoint ORR/PFS/OS
  - Single arm vs RCT
  - Overall survival analysis
  - Co-diagnostic development
- AZD9291: an example development programme in NSCLC