NSCLC TARGETED THERAPY AND CIRCULATING BIOMARKERS

Pilar Garrido MD PhD

Medical Oncology Department
University Hospital Ramón y Cajal,
Madrid
DISCLOSURE SLIDE

- Consulting or advisory role:
  - Astra-Zeneca, Boehringer-Ingelheim, BMS, Celgene, Novartis, Pfizer, Roche
Subgroup analyses of patients with epidermal growth factor receptor (EGFR)-expressing tumors in SQUIRE: a randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin plus necitumumab versus gemcitabine-cisplatin alone in the first-line treatment of patients with stage IV squamous non-small cell lung cancer (SQ-NSCLC). Dr. Paz Ares L. et al. Abstract 1320

**SQUIRE¹: NECITUMUMAB IN 1ST-LINE SQUAMOUS NSCLC**

- CDDP/Gem + Necitumumab in stage IV Squamous NSCLC \(^2\)
- No restriction by EGFR expression
- Positive results for primary endpoint (N 1093)
  - OS (HR 0.84; p: 0.01; median OS 11.5 vs. 9.9 m)
- Availability of tissue for biomarkers analysis mandatory

¹SQUamous NSCLC treatment with the Inhibitor of EGF REceptor)  
²Thatcher N et al. Lancet Oncology 2015
EGFR protein expression evaluated by IHC (Dako EGFR PharmDx kit) in a central lab, assessed independently by two pathologists

Two subsets: EGFR>0 and EGFR=0 tumors

Results of the exploratory analysis

- EGFR IHC Staining = 0% in only 5% of tested (47 patients)
- OS Gem-Cis + Neci vs. Gem-Cis
  - HR 0.79; p=0.002;
  - Median OS: 11.7m vs. 10.0 m. (↑ 1.7 m)
- Similar efficacy outcomes by subgroup analysis
- Safety profile no differences
SQUIRE OUTCOMES IN PATIENTS WITH EGFR-EXPRESSING TUMORS: CONCLUSIONS

- The results (efficacy and safety) in the sub-population of patients with EGFR-expressiong tumors (N 982) were consistent with the SQUIRE ITT (N 1093).

- Benefit was not apparent for the small subgroup of patients (N 47) with non-EGFR-expressing tumors.
BIOMARKERS LINKED TO THE EGFR SIGNALLING PATHWAY IN NSCLC.

- There are several potential biomarkers linked to the EGFR signalling pathway.

- EGFR protein expression is commonly seen in SCC-NSCLC (60 - 83%) and Non-SCC NSCLC (≈ 50%) but the clinical relevance of the selection of treatment based on it, is uncertain.

- So far EGFR mutation is the only validated therapeutic target in NSCLC
  - Predictive role to select EGFR TKI therapy.
PREDICTIVE BIOMARKERS FOR CETUXIMAB IN STAGE IV NSCLC

  - CDDP/Vinorelbine + Cetuximab N: 1125 p; 34 % Squamous (377 p)
  - IHC evidence of **EGFR expression mandatory** (77% of screened)
  - Treatment benefit detected in unselected population according to histology

- **BMS 099** *(Lynch T, JCO 2010; Khambata S, JCO 2010)*
  - Carboplatin/Taxane + Cetuximab. N: 676 p; 20% Sq (132 p)
  - No restriction by histology or EGFR expression (11.5% negative)
  - Tissue available for less than 30% of p

- **SWOG 0819** *(Herbst R, WCLC 2015)*
  - Carboplatin/Paclitaxel or Carboplatin/Paclitaxel/Bevacizumab + Cetuximab
  - **Tumor tissue available mandatory.** N: 1313 p
  - Co-primary endpoint PFS in FISH +. N: 400
  - Exploratory analysis in SCC FISH + N: 111
CETUXIMAB IN NSCLC: PREDICTIVE BIOMARKERS IN STAGE III

- **RTOG 0324**: Phase II of cetuximab in combination with chemoradiation (Blumenschein GR, JCO 2011; Komaki R, Radiother Oncol 2014)
  - 51/93 p evaluable for EGFR protein expression, quick score and FISH

**RTOG 0617**: Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab (Bradley J, Lancet Oncology 2015)
  - 203/544 p with usable samples
NECITUMUMAB IN STAGE IV NSCLC

- **SQUIRE** (*Thatcher N, Lancet Oncology 2015*)
  - CDDP/Gem + Necitumumab
  - Squamous histology (N 1093)
  - **Availability of tissue mandatory** but no restriction by EGFR expression

- **INSPIRE** (*Paz-Ares L, Lancet Oncology 2015*)
  - CDDP/Pem ± Necitumumab
  - Non-SCC histology (N: 633)
  - **Availability of tissue mandatory**
RETROSPECTIVE RESULTS OF PREDICTIVE BIOMARKERS

- Benefit from cetuximab was not associated with:
  - KRAS or EGFR mutation status in FLEX; S0819 results pending
  - PTEN expression (FLEX study)
  - EGFR protein expression IHC status (+/-) in BMS 099, RTOG 0324,
PREDICTIVE ROLE OF EGFR COPY NUMBER

- Benefit from cetuximab based on EGFR gene copy numbers **negative** in FLEX, BMS099, RTOG 0324, S0819.

  - Exploratory positive results in a post-hoc exploratory analysis in 111 SCC FISH+ in S0819 trial. *(Herbst R, WCLC 2015)*
    - OS HR 0.56. p: 0.005
    - median OS 11.8 m vs. 6.4 m

- **Negative** results from necitumumab in SQUIRE trial *(Hirsch F, WCLC 2015)*
  - 51% of ITT tumor samples with valid FISH; N: 208 p FISH +
  - OS HR 0.70; p: 0.066 (m OS 12.6 m vs. 9.2)
  - Interaction test negative (p: 0.57)
PREDICTIVE ROLE OF EGFR PROTEIN EXPRESSION BY H-SCORE

- **Cetuximab:**
  - FLEX Treatment interaction value + (p= 0.044).
    - 345 evaluable p (31%) scored as high expression (144 SCC-NSCLC p)
    - OS HR 0.73; p: 0.011
    - Median OS 12 m vs. 9.6 m for H-score >200
  - Results in S0819 pending

- **Necitumab:**
  - SQUIRE and INSPIRE: Interaction test negative (OS and PFS)
    - 38% H-score > 200 in 374 evaluable p in SQUIRE trial and 41% in INSPIRE study.

  Similar treatment effect in OS (HR 0.75) for high expression in SQUIRE as in FLEX trial but not significant (p: 0.24).

*EGFR IHC score: product of the percentage of cancer cells positive for EGFR protein on the cell surface X the overall intensity of staining (ranging from 0 to 3+), producing a number from 0 to 300
DIFFERENT METHODS FOR EVALUATION OF EGFR EXPRESSION LEAD TO DIFFERENT RESULTS.

- Difficult interpretation of results
  - Small samples sizes
  - Different methods for evaluation of EGFR expression
  - Sensitivity limitations of the IHC assay
  - Post-hoc and subgroups analyses
- Relevance of
  - Prospective biomarkers studies
  - Standardization of EGFR protein detection methods
  - External validation
  - Reproducibility of results

The identification of predictive biomarkers is key to increase the clinical benefit-risk ratio
CAN WE SELECT PATIENTS TO RECEIVE NECITUMUMAB?

- The addition of Necitumumab to CDDP/Gem improves overall survival in unselected patients with advanced SCC NSCLC.
- The selection of patients based on EGFR H-score > 200 (≈ 30% of patients) or FISH + (51% available, 208 patients +) was not predictive of efficacy.
- The selection of patients based on EGFR-expression > 0 (95% of total population) was consistent with the SQUIRE ITT population:
  - Median OS increased by 1.7 months (11.7 vs. 10.0 months)
  - Median PFS increased by 2 weeks (5.7 vs. 5.5 months)

- Lack of clearly defined predictive markers to optimize patient selection is one of the main limitations for the use of Necitumumab.
FUTURE DIRECTIONS?

- Genomic profiles highlight the heterogeneity of NSCLC genome
- SCC is the tumor with the second highest amount of somatic mutations providing a plausible explanation about heterogeneity of treatment responses
- Antibodies targeting PD-1-PDL-1 checkpoint are showing remarkable benefits in lung cancer.
- Combination of immune therapy and necitumumab may expand the potential for using it in unselected population.
ABSTRACTS TO DISCUSS

- Subgroup analyses of patients with epidermal growth factor receptor (EGFR)-expressing tumors in SQUIRE: a randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin plus necitumumab versus gemcitabine-cisplatin alone in the first-line treatment of patients with stage IV squamous non-small cell lung cancer (SQ-NSCLC). Dr. Paz Ares L. et al. Abstract 1320

EFFICACY OF BRIGATINIB IN ALK + NSCLC

- 10-fold more potent inhibitor of ALK than crizotinib
- Activity across all known crizotinib resistant ALK mutations
- Phase I/II (N: 137). ALK+ NSCLC: 79. 90% crizotinib pretreated
- Pretreated (N:70)
  - ORR 71% (95% CI 59 -82%)
  - Median time on treatment 12 m (0.03 -35.5 +)
  - Median PFS 13.4 m, 1-y OS 81% and projected 2-y 71%
- Intracranial (measurable 15 p and non measurable 31 p)
  - 50/79 brain met (15 p evaluable)
  - ORR 53% (35% in evaluable)
  - Median DOR 18.9 m. PFS 15.6 m.
SAFETY OF BRIGATINIB

- More common AEs: Nausea (53%), fatigue (43%), and diarrhea (41%),
- TEAEs G ≥3: increased lipase (9%), dyspnea (7%), pneumonia (6%), hypertension (5%), and hypoxia (5%).
- Dose reduction 14%
- Discontinuation due to AEs 9%

**Early-Onset Pulmonary Events** in 11/137 (8%)

- Dyspnea, hypoxia, pneumonia, and/or pneumonitis,
- EOPE incidence rates were numerically lower with lower starting doses
  - 14% p at 180 mg / 2% at 90 mg
  - No EOPEs reported after dose escalation 90 ->180 mg (n=32)
  - Randomized study ongoing 90 mg vs 90 ->180 mg
NEXT-GENERATION ALK-i IN PRETREATED PATIENTS

- **Ceritinib**
  - ASCEND I *(Kim D, Lancet Oncology 2016)*
    - N: 163/246 ALK-i pretreated
    - RR 56%, median DOR 8.3 m; PFS 7 m. OS 16.7 m
    - Treatment-related G3-4 AEs: 51%. Interstitial lung disease 4%
    - 62% at least one dose reduction, 11% discontinuation.

- **Alectinib**
  - Phase II *(Ou I, JCO 2016)*
    - N 138, RR 50%, median duration of response 11.2 m; PFS 8.9 m
    - G3-4 5%; 21% dose reduction; 8% discontinuation
  - Phase II *(Shaw A, Lancet Oncology 2016)*
    - N 87 ALK-i pretreated; ORR 48 %; median DOR 13.5 m; PFS 8.1 m
    - G3-4 6%; 16% dose reduction; 2% discontinuation for AEs
    - No Interstitial lung disease
DIFFERENT MECHANISMS OF RESISTANCE TO ALK INHIBITORS

- Most patients relapse within the first year of crizotinib treatment.
- High frequency of brain metastasis, reflecting poor CSF penetration.
- Extra-cranial relapses mediated by different mechanisms:
  - ALK-dominant
    - 1/3 due to amplification of the ALK fusion gene or secondary mutation within the ALK tyrosine kinase domain
    - Different activity of next-generation ALK-i
      - ALK-V1180L-resistant to alectinib but sensitive to ceritinib.
      - ALK-G1123S resistant to ceritinib but sensitive to alectinib
      - ALK-G1202R and F1174C mutations resistance to both
  - ALK-non dominant resistance
    - Mediated by activation of alternative signaling pathways, including the EGF pathway, IGF pathway, and SRC
CNS METASTASIS

- Heterogeneous population
- Remain a significant challenge
- Crucial to improve survival
- Few clinical trials despite high frequency in ALK +:
  - 20-35% basal
  - Up to 60% during crizotinib treatment
- Next generation ALK-i increased activity
CNS EFFICACY OF CRIZOTINIB

- **PROFILE 1014** *(Solomon B, JCO 2016)*
  - 79/343 p (23%) RT treated BM at baseline
  - IC DCR 85% at 12 weeks and 56% at 24 weeks
  - IC-PFS tBM: HR, 0.40; p < .001; median, 9.0 v 4.0 m

- **Pooled analysis of PROFILE 1005 and 1007** *(Costa JCO 2015)*
  - 31% (275/888) asymptomatic brain metastases
  - In 109 p previously untreated: IC DCR 56% and median IC PFS 7 m
  - In 166 p previously RT treated: IC DCR 62% and median IC PFS 13.2 m
  - “Progression of preexisting or development of new intracranial lesions while receiving therapy was a common manifestation of acquired resistance to crizotinib”.

---

EUROPEAN LUNG CANCER CONFERENCE 2016
CNS ACTIVITY OF NEXT GENERATION ALK-I

- 60% p enrolled onto second-line clinical trials have baseline BM

- **Ceritinib**
  - Retrospectively assessed
  - ASCEND 1 (246), ASCEND 2 (N 140), ASCEND 3 (N 124)
  - ORR 61% (36 p), 45% (20 p), 20% (10 p)
  - ASCEND 7 recruiting

- **Alectinib**
  - Phase II (*Ou I, JCO 2016*)
    - 84/138 BM baseline
    - ORR by IRC 50%. CNS disease control 83%.
    - Median DOR 10.3m. PFS 8.9 m.
    - Accumulative CNS progression rate 24.8% at 12 m
OPEN QUESTIONS ABOUT CNS MANAGEMENT

- What is the role, best technique and timing of RT?
- Are the current criteria to assess CNS response adequate?
  - Incidence of pseudoprogression is expected to increase
  - Relevant before removing treatment
- Are the molecular determinants of ALK-i resistant the same in CNS and extra-cranial disease?
STRATEGIC STUDIES ON THERAPEUTIC SEQUENCES ARE NEEDED

- Ongoing debate regarding the context in which second generation should be applied.
- No randomized studies comparing next-generation ALKi in the setting of crizotinib resistance.
- Sequencing/resensitization
- Relevance of serial genotyping in ALK dominant resistance
- Role of combination strategies (CT, immunotherapy, local therapies..) in ALK independent resistances
  - Toxicity profile matters