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NSCLC TARGETED THERAPY AND CIRCULATING BIOMARKERS

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DISCLOSURE SLIDE

- Consulting or advisory role:
    - Astra-Zeneca, Boehringer-Ingelheim, BMS, Celgene, Novartis, Pfizer, Roche

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

- Brigatinib Efficacy and Safety in Patients With Anaplastic Lymphoma Kinase–Positive (ALK+) Non–Small Cell Lung Cancer (NSCLC) in a phase 1/2 Trial. ***Dr. Rosell R. et al.*** Abstract 1330

SQUIRE[1]: NECITUMUMAB IN 1ST-LINE SQUAMOUS NSCLC

- CDDP/Gem + Necitumumab in stage IV Squamous NSCLC p[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

[1]***SQU****amous NSCLC treatment with the* ***I****nhibitor of EGF* ***RE****ceptor)*

[2]*Thatcher N et al. Lancet Oncology 2015*

SQUIRE OUTCOMES IN PATIENTS WITH EGFR-EXPRESSING TUMORS: RESULTS

- 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-expressing 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

- **FLEX** *(Pirker R, Lancet 2009; O´Byrne K, Lancet Oncology 2011; Pirker R, Lancet Oncology 2012)*
  - 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 necitumuab 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 p with advanced SCC NSCLC
- The selection of patients based on EGFR H-score > 200 (≈ 30% of p) or FISH + (51% available, 208 p +) 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 m (11.7 vs. 10 m)
  - Median PFS increased by 2 wk (5.7 vs. 5.5 m)

- **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 p.
- Combination of immune therapy and necitumumab may expand the potential for using it in unselected population.

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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%
- Intracraneal (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*".

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 asses 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