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Gemcitabine Plus Oral Vinorelbine as Salvage Therapy Treatment for Patients With Advanced Non-small-cell Lung Cancer and Squamous Histology − a Galician Lung Cancer Group Study (GGCP042/09) Grupo Galego De Cancro De Pulmón (GGCP)

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Background: Until recently, histology had not been consistently described as a prognostic or predictive variable in advanced NSCLC studies. In this new scenario, patients with squamous histology (SCC) remain with limited treatment options, particularly in the 2nd line setting, where docetaxel and erlotinib are the only approved agents. Compared to single agent chemotherapy (CT) in second line, doublet CT seems more toxic without modest improvement in overall survival (OS), but some combinations have achieved encouraging results. Combination CT with third-generation, non-platinum agents [i.e., gemcitabine (G), vinorelbine (V)] might play a role as salvage therapy. The aim of this study is to evaluate the activity and tolerance of G in combination with oral V in pretreated patients with SCC-advanced NSCLC.
Material and Methods: 24 pre-treated patients (p) with NSCLC of stage IIIB/IV and SCC histology were treated with G (1.250 mg/m^2 i.v.) plus V (60 mg/m^2 p.o.) on days 1 and 8, of each 21-day cycle, up to 6 cycles, unless disease progression or unacceptable toxicity. Baseline characteristics: median age: 61 yrs. (range: 50−82); 96% male; 79% stage IV; 92% performance status ECOG 0−1. The primary end point was progression-free survival (PFS).
Results: The most common non-hematologic toxicities were grade 1−2 asthenia (45.8%; only 1 p grade 3), anorexia (25%), and grade 1−2 nausea/vomiting (12.5%/25%). Half of the p experienced grade 1−2 anaemia. Neutropenia occurred in 38% of the p (13% grade 3−4), but only 1 patient experienced febrile neutropenia. 6 p (25%) developed serious adverse events leading to hospitalization. Median of administered cycles vas 4 (range: 1−6), with a mean dose intensity of 93.4% for both drugs. There were two deaths due to massive haemoptysis (8.3%).
Among evaluable p (63%), response rates were 13.3% and an additional 60% controlled the disease. Median PFS was 3.8 months (95% CI: 1.8−5.8); and median OS was 6.9 (95% CI 1.0–12.8).
Conclusions: Compared to historical controls, the combination of i.v. G plus oral V as salvage therapy of patients with SCC advanced NSCLC seems to be as effective as single agents, with an encouraging disease-control rate. Although the combination is relatively well tolerated, it is associated to a higher incidence of haematological adverse events, with 40% of patients developing neutropenia (13% severe). Non-hematologic toxicities were manageable. The combination of GV is an effective regimen in 2nd-line therapy, but the safety profile of the available options should be considered when deciding the optimal therapy in this setting.

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Effectiveness of Bevacizumab (BV) Maintenance in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Treated in US Community Practices

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Background: BV has demonstrated safety and efficacy when combined with first-line (1L) chemotherapy (CT) and continued as monotherapy to progression (PD) for patients with nonsquamous (ns) advanced NSCLC. In recent analyses of US treatment (tx) patterns, BV is often discontinued after induction CT, and not continued until PD as per the US label.
Methods: A retrospective analysis of data from US community practices (Cancer Clinics of Excellence) was conducted to understand patterns of BV use with induction CT, continuation of BV maintenance to progression (BTP), and outcomes. Patients with advanced ns NSCLC receiving 1L treatment from 1/1/07 to 12/31/08 were identified. Tx and outcomes data were collected through 6/30/10 or date of death/last follow-up visit. Survival analyses (Kaplan–Meier with log-rank test) estimated OS of patients who received BTP vs. No BTP, among those who were alive and PD-free after completion of induction BV+chemo. As data collection is ongoing, preliminary results are reported.
Results: Among 600 ns NSCLC patients identified, 224 (37%) received BV with 1L CT, 83% of which was a platinum-based CT doublet. Of 224 patients who received 1L BV+CT, 22% (n = 50) continued BTP. Patients in the BTP and No BTP groups were similar in age, histology, stage at diagnosis. The 5 most common reasons for patients not receiving BTP: unresolved tx-related toxicity (12%), lack of tx response (14%), plans to use BV in future tx (9%), switched to other tx (9%), poor ECOG performance status (7%). Of those who were alive and PD-free at completion of induction chemo, median OS was longer in the BTP cohort (n = 37) vs. the No BTP cohort (n = 71) (23.3 vs 14.7 months, respectively, p = 0.012). Incidence of BV-related toxicities was consistent with reports from clinical trials. Further analysis of the final dataset will be conducted.

Table: Baseline characteristics

	BTP (n = 50)	No BTP (n = 174)
Female (%)	60	52
Median age (y)	68	69
Adenocarcinoma (%)	70	72
Stage at Dx (%)		
I−II	10	8
IIIA	6	6
IIIB	18	15
IV	62	67
Unknown	4	4
ECOG PS (%)		
0	30	14
1	30	35
⩾2	6	14
Unknown	34	37

Conclusions: In this preliminary analysis of treatment in US community practices, longer OS was observed in patients with ns advanced NSCLC receiving BTP relative to No BTP. While additional data is being collected, these results suggest that continued VEGF suppression may be important in ns NSCLC treatment.

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Clinical Responses to EGFR-tyrosine Kinase Inhibitor Retreatment in Non-small Cell Lung Cancer Patients Who Benefited Prior Gefitinib Therapy

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Background: Gefitinib was the first epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) approved for the treatment of advanced non-small cell lung cancer (NSCLC). Few treatment options are available for NSCLC patients who have responded to gefitinib treatment and demonstrated tumour progression. The present study was conducted to evaluate the efficacy and toxicity of the 2nd EGFR-TKI administration.
Materials and Methods: We retrospectively analyzed 11 patients who had obtained a partial response (PR) or stable disease (SD) with gefitinib treatment and were re-treated with EGFR-TKI after failure of the initial gefitinib treatment.
Results: Three patients (27%) were treated with gefitinib as the 2nd EGFR-TKI, and 8 patients (73%) received erlotinib. Only one patient (9%) showed PR, 7 (64%) achieved SD, and 3 (27%) had progressive disease. The disease control rate was 73% (95% CI, 43–91%) and the median progression-free survival was 3.4 months (95% CI, 2−5.2). The median overall survival from the beginning of the 2nd EGFR-TKI and from diagnosis were 7.3 months (95% CI, 2.7−13) and 36.7 months (95% CI, 23.6–43.9), respectively. No statistical differences in PFS or OS were observed between gefitinib and erlotinib as the 2nd EGFR-TKI (PFS, P = 0.23 and OS, P = 0.052).
We further compared the clinical courses of the patients with those of gefitinib responders who were not treated with a 2nd EGFR-TKI following gefitinib failure. We reviewed the medical records at our institute and found 9 patients with backgrounds that were similar to those of the 2nd EGFR-TKI patients (sex, age (<70 years old or ⩾70 years old), histology, and response to gefitinib treatment). No statistical differences in PFS to 1st gefitinib treatment were noted between both groups (9.8 months in the 2nd TKI group and 8.7 months (95% CI, 7.6−9.8) in the control group, P = 0.87). All of the identified control patients had been treated with platinum-doublet chemotherapy before gefitinib but had not received 2nd EGFR-TKI. The OS from the start of the initial gefitinib treatment tended to be longer in patients who received a 2nd EGFR-TKI (median OS, 21.5 months (95% CI, 14.6–

28.4)) compared to those in the control group (median OS, 12.3 months (95% CI, 9.4–15.2), P = 0.07).
The toxicities associated with the 2nd EGFR-TKI were generally acceptable and comparable to those observed for the initial gefitinib therapy.
Conclusions: Our results indicate that a 2nd EGFR-TKI treatment can be an effective treatment option for gefitinib responders.

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Erlotinib as Frontline Treatment for Elderly Patients With Advanced Non-Small-Cell Lung Cancer (NSCLC) and Non-Squamous Histology − Results of a Galician Lung Cancer Group (GGCP044/09 Study) Grupo Galego De Cancro De Pulmón (GGCP)

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Background: NSCLC is primarily a disease of older people with a median age of approximately 70 years at diagnosis. Unfortunately, these patients are often excluded form the clinical trials, or they are underrepresented. Several guidelines point out that elderly patient should receive third-generation single-agent chemotherapy. Erlotinib is an orally available, reversible inhibitor of EGFR TK activity, providing significant survival benefits as monotherapy for the 2nd-line and maintenance treatment of patients with advanced NSCLC, and with a favourable safety profile and convenient administration.
This Galician study aims to evaluate the efficacy and safety of erlotinib as first-line treatment for elderly patients with advanced NSCLC and non-squamous histology.
Material and Methods: Elderly patients, defined as ⩾70 years old, patients with stage IIIB/IV NSCLC and non-squamous histology were included in this study after providing informed consent. Erlotinib was orally administered at a dose of 150 mg daily until disease progression or intolerable toxicity.
Progression-free survival (PFS; primary objective) and overall survival (OS) were measured from time of diagnosis.
Results: A total of 25 patients were enrolled. Patient characteristics were as follows: median age 78 yrs. (ranged 70−85); 52% female; 92% adenocarcinoma (including BAC features); 84% stage IV; 48% PS ECOG 2.
Out of 20 evaluable patients, 5 had PR and 6 SD, for a response rate of 25% and a disease control rate of 55%. The median PFS was 3.9 months (95% CI: 1.4−6.4), and the median OS was 9.9 months. The most common adverse event (AE) was skin rash (36%; 12% grade 3−4) and diarrhoea (24%). 4 patients (14%) needed dose reduction and 2 patients withdrew the treatment due to grade 3 diarrhoea and eye perforation, respectively.
EGFR mutational status was available for 6 patients (24%); two patients (85 and 77 years old) harboured activating mutations: both achieved partial response, and show SLP of 23 and 14 months respectively (both ongoing).
Conclusions: The results suggest that erlotinib monotherapy is an effective and well-tolerated treatment option for elderly patients with advanced NSCLC and non-squamous histology. Response rate is similar to that achieved with chemotherapy in younger people; benefit in PFS is modest, but median OS is acceptable, specially taking into account that half of the patients had an ECOG performance status of 2. *EGFR* mutation testing should be strongly encouraged among elderly patients. Data will be updated, including a higher number of patients.

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Exploratory Predictive Biomarker Assessment in the BMS099 Study of Cetuximab in NSCLC

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Background: The phase III trial BMS099 showed no significant difference in progression-free survival (PFS) and significantly higher response rate (RR) with the addition of cetuximab (C) to 1st-line taxane/carboplatin (TC) in advanced NSCLC. Median overall survival (OS) was longer, with a difference (not significant) of similar magnitude to the significant OS improvement from FLEX (cis/vin±C). Most biomarker analyses to date have shown no association with C benefit, including EGFR mutation, KRAS mutation, and EGFR amplification in both trials (20−30% of the intent to treat [ITT] populations). We analyzed Fcγ receptor (FCGR) polymorphisms in BMS099, in order to identify patients (pts) expected to mount a more potent antibody-dependent cellular cytoxicity (ADCC) response and therefore likely to derive greater benefit from C. We also profiled mRNA expression patterns on tumour samples to identify EGFR-related and novel markers that may correlate with C benefit.
Methods: FCGR2 and FCGR3 genotypes were obtained from 285/676 pts from BMS099 using Taqman Allelic Discrimination assays for H131R and F158V alleles, respectively. Affymetrix expression data for RNA extracted from formalin-fixed, paraffin-embedded tumour tissue was available for 58/676 pts. Associations between FCGR2/3 genotypes, tumour gene expression patterns and clinical efficacy data were analyzed.
Results: No significant association was observed between FCGR genotype and C benefit across endpoints explored; the FCGR3 F/F polymorphism showed a trend for improved PFS with C, conflicting with prior clinical reports (Bibeau F, J Clin Oncol 2009; Zhang W, J Clin Oncol 2007), and with in vitro data (Lopez-Albaitero, Cancer Immunol Immunother 2009) showing more effective ADCC mediation with the V/V genotype. The population evaluable for gene expression patterns was not representative of the ITT (PFS was greater in the TC arm than the C+TC arm). Potential interactions between expression, median PFS and treatment were assessed and filtered for specific correlations with C benefit. No significant interactions were observed between treatment and RR or PFS for the *AREG*, *EREG*,*TGFa* or the *EGFR* genes. Genes were identified that may predict for progression on C, however independent validation is required.
Conclusions: Exploratory biomarker analyses in BMS099 have yielded no predictive biomarker for C; efforts are ongoing to identify pts likely to benefit from anti-EGFR mAb therapy in NSCLC.

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Cumulative Exposure to Bevacizumab (BV) After Induction Therapy (tx) Correlates With Increased Survival in Patients (pts) With Non-small Cell Lung Cancer (NSCLC)

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Background: In E4599, pts with 1st-line advanced NSCLC were treated with maintenance BV until progressive disease or unacceptable toxicity following 6 cycles (18 weeks) of induction phase (IP) chemotherapy (CT) + BV. The use and duration of BV post-IP varies widely in clinical practice. This analysis examines cumulative post-IP BV exposure and overall survival (OS) in pts with NSCLC in the ARIES observational cohort study (OCS), with particular emphasis on incorporating the dynamic time-varying features of treatment patterns seen in the real world.
Methods: ARIES enrolled pts with advanced NSCLC who received 1st-line BV-containing tx. Pts who began BV and CT simultaneously and were progression-free through the completion of 12−18 weeks of CT were included in the analysis. OS was measured from the end of each pt's BV+CT IP. A time-dependent Cox regression model that controls for survival bias towards pts receiving longer exposure to BV was fitted to assess the effect of cumulative BV exposure on OS, controlling for potential confounders.

Cumulative Post-IP BV cycles[a]	Post-IP Follow-up time, days	n (cycles)[b]	n (0)[c]	HR (95% Confidence Limits)
1	21	473[d]	644[d]	0.955 (0.939–0.972)
2	42	380	562	0.913 (0.881–0.945)
3	63	296	499	0.872 (0.828–0.919)
4	84	233	456	0.833 (0.777–0.893)
5	105	189	413	0.796 (0.730–0.868)
6	126	158	375	0.760 (0.685–0.844)
7	147	129	344	0.726 (0.643–0.820)
8	168	113	317	0.694 (0.604–0.797)

[a] A cycle is approximately 21 days of post-IP cumulative exposure.
[b] No. of pts who received the specified number of post-IP BV cycles by follow-up time.
[c] No. of pts having no exposure to BV by follow-up time.
[d] Example: At 21 days post-IP, 473 pts had a total of approximately 21 days of BV exposure while 644 pts had no exposure to BV.

Results: Of 1967 pts in ARIES NSCLC as of February 2011, 1213 were eligible for the analysis. This population was 51% male, 87% Caucasian, and 15% never-smoker. 13% had ECOG PS ⩾2, 71% had adenocarcinomas, and the median age was 65 (32% were age ⩾70). The median OS for pts in the analysis was 13.2 months. Across follow-up, the