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Purine analogs sensitize the multidrug resistant cell line (NCI-H460/R) to doxorubicin

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Multidrug resistance (MDR) is a significant factor that limits the efficacy of classic chemotherapeutics in lung cancer. We used the resistant cell line NCI-H460/R and its counterpart NCI-H460 to investigate the potential of purine analogs to overcome MDR. We observed that two purine analogs, sulfinosine (SF) and 8-Cl-cAMP, exerted dose dependent effects on cell growth of both parental and resistant cell lines. SF and 8-Cl-cAMP significantly decreased *mdr1* expression in NCI-H460/R cells. When a low concentration (1 μM) of SF and 8-Cl-cAMP was combined with doxorubicin (DOX), the drugs demonstrated synergistic growth inhibitiory effects in both cell lines. Pretreatment with SF and 8-Cl-cAMP improved the sensitivity to DOX more than verapamil (VER). The observed increased accumulation of DOX after the treatment with SF and 8-Cl-cAMP was consistent with results obtained with VER. Our results show that SF and 8-Cl-cAMP modulate MDR in NCI-H460/R, especially when applied before DOX administration. Along with the exhibited potential for MDR reversal, purine analogs in combination with DOX represent valuable agents with a potential for improving chemotherapy.

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Phase 2 study of pemetrexed and cisplatin plus either enzastaurin or placebo in chemonaive patients with advanced NSCLC

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Background: Enzastaurin (ENZ), an oral serine/threonine kinase inhibitor, has the potential to be used in combination with chemotherapeutic agents. Previous clinical studies in combination with pemetrexed have shown additive antitumor activity (Nakajima et al, JCO 2006) and a tolerable safety profile (Hanauske et al, JCO 2006).
Materials and Methods: This study enrolled chemonaive patients (pts) with stage IIIb/IV NSCLC and performance status 0−1, and was conducted in two parts: Part 1 was an open-label safety lead-in, evaluating safety of 2 cohorts (Coh): Coh1 had ENZ 250 mg BID daily, while Coh2 had 500 mg BID, both in combination with 500 mg/m^2 pemetrexed and 75 mg/m^2 cisplatin (P/C) in a 3-week cycle. Part 2 was a multicenter, double-blind, randomized study comparing the combination of P/C with ENZ (500 mg daily) or placebo in nonsquamous NSCLC pts. Primary endpoint was PFS.
Results: Between 09/07 and 08/08 a total of 13 pts were enrolled in part 1 (9 in Coh1, 4 in Coh2). Only 22 pts were enrolled in part 2 because of early closure of the trial. All were Caucasian, 16 female, 19 male, mean age 59 yrs, 74% PS 1. Histology diagnosed as 77% adeno/8% large/15% squamous cell in part 1 and 64% adeno/23% large/14% NOS in part 2. In study part 1, one patient (Coh1) discontinued before completing cycle 1 due to a drug-related serious adverse event (SAE) (paralytic ileus) and was replaced. One patient in Coh2 discontinued due to a drug-related adverse event (myalgia). Overall 3 pts (23%) experienced a possibly drug-related SAE (paralytic ileus, increased blood amylase, pulmonary embolism), all in Coh 1. Best overall response was 8 PR (1 not confirmed), 2 SD and 2 PD. In part 2, one patient discontinued due to a drug-related adverse event (hypertension) in the ENZ arm. Two pts (9%) experienced at least one possibly drug-related SAE, both in the placebo arm (duodenal ulcer and candidiasis, tachyarrhytmia). The most common drug-related non-hematological CTC grade 3/4 toxicity was grade 3 myalgia (one in Coh1 and one in Coh2). The most common, expected CTC grade 3/4 lab toxicity was neutropenia (two in Coh1 and one in Coh2, and two in the placebo arm).
Conclusions: The combination regimen of ENZ and P/C was well tolerated. Although the combination treatment showed good activity in this study, the trial was closed early based on the interim analysis of two other pivotal NSCLC studies, which showed no improved outcome by adding ENZ to chemotherapy.
Study H6Q-MC-S021 sponsored by Eli Lilly

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Subset analysis of a phase III trial comparing two platinum-based doublets: i.v./Oral vinorelbine (NVB) vs docetaxel (DTX): impact of histology on response and survival in advanced Non-Small Cell Lung Cancer (NSCLC)

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Introduction: Histology gains predominance in scientific communications on NSCLC. Following a large phase III trial comparing two reference platinum-based doublets as first-line chemotherapy in advanced NSCLC, we performed a retrospective analysis in order to evaluate the impact of histology on the efficacy parameters.
Materials and Methods: From February 2004 to January 2006, 381 patients with unresectable or metastatic NSCLC from 42 investigational centers in 19 countries were randomly assigned and treated by either a cisplatin-based doublet with iv/oral NVB on day 1.8 (NVB Arm, 190 pts) or DTX on day 1 (DTX Arm, 191 pts), both combinations delivered every 3 weeks for a maximum of 6 cycles. Time to Treatment Failure (TTF) was the primary endpoint. Patients characteristics in both arms were balanced for age, sex, disease extent, and PS. Histological types at diagnosis in NVB/DTX arms (%): Squamous 65(34.2)/64(35.5); Adenocarcinoma (ADK) 79 (41.6)/75 (39.3); Large cell 8 (4.2)/18 (9.4); BAC 2 (1.1)/0 (0); Giant Cell 1 (0.5)/1 (0.5); Unknown 35 (18.4)/33 (17.3). An exploratory analysis on OR, TTF and OS was performed taking into account the Squamous, Adenocarcinoma and other histology of patients included in both arms.
Results: Overall, both arms reported similar results in terms of OR (NVB 27.4% [95% CI 21.2−34.2]; DTX 27.2% [95% CI 21−34.2]) (p = 0.97), TTF (NVB 3.22 months [95% CI 2.96−4.24]; DTX 4.11 months [95% CI 3.45−4.50]) (p = 0.20), and OS (NVB 9.9 months [95% CI 8.41−11.6]; DTX 9.8 months [95% CI 8.80−11.5]) (p = 0.58). OR (%) by histology (NVB/DTX): ADK 29.1/22.7; other 26.1/30.2. Considering ADK and Squamous, TTF and OS are reported in the following table:

	NVB Arm		DTX Arm	
	Squamous	Adenocarcinoma	Squamous	Adenocarcinoma
TTF (months)	3.22	3.05	4.22	3.94
95% CI	2.76−4.63	2.33−4.27	3.81−4.57	2.23−6.08
OS (months)	8.87	11.73	9.82	11.60
95% CI	6.44−12.81	8.67−16.46	8.41−12.19	9.72−15.74

Conclusion: Adenocarcinoma seems in relation with a better response to chemotherapy but it is not the only criterion that can determine on its own a therapeutic strategy. Third generation platinum-based doublets are effective in all histological subtypes of advanced NSCLC, as confirmed in this trial with NVBo + CDDP.

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Pemetrexed in combination with cisplatin or carboplatin in the first line therapy of locally advanced or metastatic non-small cell lung cancer: a randomized, two-arm, parallel, open-label, multicentric phase 2 study

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Background: Pemetrexed (P) single agent has shown to be effective and safe in 2nd line treatment (Tx) and in combination with platinum compounds in 1st line Tx of patients (pts) with advanced non-small cell lung cancer (NSCLC). P single agent was approved for 2nd line Tx and, combined with cisplatin (Cis), 1st line for pts with other than predominantly squamous histology. This study H3E-SB-S109 evaluated P+Cis and P+carboplatin (Car) in 1st line Tx of stage IIIb/IV NSCLC.
Material and Methods: 130 pts with cytol./histol. confirmed NSCLC stage IIIb or IV were planned to be random. to P (500 mg/m^2)+Cis (75 mg/m^2) or P (500 mg/m^2)+Car (AUC6) d1 q3 wks, for up to 6 cycles. Primary outcome was 6 mo progression-free survival (PFS) rate [estimate based

on exponential distribution]. Independently, for each Tx arm, the H_0 6 mo PFS rate $\leqslant$ 25% was tested. RECIST evaluation was performed q6 wks. Secondary outcomes included objective response rate (ORR) and tolerability.
Results: Of 133 pts random. at 15 sites, 130 received Tx (97.7%; P+Cis/P+Car: 65/65). All pts treated were included into the efficacy analyses; 14 pts (10.5%; 5/9) had stage IIIb, 119 (89.5%; 61/58) stage IV tumor (65%/71% male; median age 64/63yrs). Tx groups were balanced (squamous histology 18.5%/20.0%, non-squamous histology 81.5%/80.0%, bone-mets 21.5%/16.9%, brain-mets 3.1%/1.5%). 6 mo PFS rate (P+Cis/P+Car [95% CI]) was 52.8% [40.3;65.3]/39.3% [27.8;50.8]. In the subgroups, the 6 mo PFS rate for pts with squamous hist. was 34.9% [9.4;60.4]/42.0% [16.8;67.3], for pts with non-squamous hist. 57.6% [43.7;71.5]/38.5% [25.6;51.5]. 43.1% /50.8% of pts received all 6 Tx-cycles. Median dose intensity for P (+Cis/+Car [25th, 75th perc.] was 98.2% [92.0;100.0]/98.6 [91.6;99.7]; for Cis 97.8% [91.6;99.8], Car 96.3 [83.1;99.5]. ORR was 32.3% [21.2;45.1; N = 21/65] /20% [11.1;31.8; N = 13/65]. Possibly study drug related, treatment emergent adverse events (TEAE) occurred in 84.6% of pts in either Tx arm; at least 1 serious related TEAE in 16.9%/23.1%. 13 deaths (3/10) occurred; 1/2 due to study drug tox, 0/3 (2 cardiac failures) due to other AEs.
Conclusions: Both regimens showed efficacy according to study hypothesis. Overall, P+Cis revealed more favorable results, especially in the non-squamous histologies.

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Phase I trial of gemcitabine/carboplatin(GC), followed by pemetrexed/gemcitabine (PG) in chemonaïve patients (pts) with advanced NSCLC

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Background: We performed a Ph I study to establish maximum tolerated dose (MTD) of sequential doublet chemotherapy with GC, followed by PG in chemonaive patients with stage IIIB/IV NSCLC.
Materials and Methods: The starting dose for eligible pts were G(1000 mg/m^2) and C (AUC 4) on Day1, followed by P (500 mg/m^2) with dex/Vit B12/folate supplementation) and G (1000 mg/m^2) on Day14 in a 28 day cycle. Cohorts of 3 pts were expanded to 6, if a dose-limiting toxicity (DLT) was observed. Six dose escalations with a maximum of 6 cycles per patient were planned. Dose adjustments were allowed according to pre-specified criteria. DLTs were recorded if in cylce 1 of chemotherapy: pts had Gr 4 neutropaenia lasting $\geqslant$7 days of febrile neutropaenia, Gr 4/3 thrombocytopaenia (with bleeding), Gr $\geqslant$3 non-haematological toxicity, or if treatment could not be restarted due to unresolved toxicities. At each dose level (DL), if 3/6 pts had any DLT or if 2/6 patients had the same DLT, then that DL was to be considered the MTD.
Results: Of 21 pts entered, 15 (safety population) received $\geqslant$1 cycle of chemotherapy, 6 pts either failed screening or decided not to proceed with treatment. Tumour could be assessed in 13 pts (efficacy population). Three dose levels were administered: DL1:G(1000)/C(AUC4) and G(1000)/P(500), DL2:G(1000)/C(AUC5) and G(1000)/P(500) and DL3:G(1200)/C(AUC5) and G(1200)/P(500). No pts met the pre-defined DLT criteria for MTD. Of 6 patients in DL1, 1/6 pts in the first cohort had a serious AE ischaemic foot, which was not related to study drugs. Of 6 pts who received DL2, 2 DLTs were seen (1 each with $\geqslant$Gr3 ALT and raised creatinine). For DL3, 1/3 had a transient ischaemic attack, which resolved after 2 days. Two pts died due to progressive disease. A partial response was recorded in 2 pts (1 each in DL1 and DL2) and stable disease in 7 pts (2 in DL1, 4 in DL2 and 1 in DL3). The study was closed before MTD was reached because: i) EMEA had issued a new restricted license for pemetrexed in adv NSCLC; ii) high doses of PG combination was shown to have an acceptable risk/benefit profile in other tumours; iii) no further clinical benefit was expected by increasing the dose any further.
Conclusion: Although MTD was not established, an acceptable safety profile was demonstrated. Antitumour activity was seen in 9 pts. Pemetrexed, carboplatin and gemcitabine are 3 of the most active drugs in NSCLC. This new schedule combining all 3 drugs may be worthy of further evaluation.

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A phase II retrospective trial of Carboplatin (CBDCA) and Alimta in refractory non-small cell lung cancer (NSCLC) with genetic polymorphisms analysis

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Background: Identification of genetic polymorphisms which influence chemotherapy outcome may help towards individually optimized therapy. We investigated the influence of ten single nucleotide polymorphisms (SNPs) of 7 genes (P53 Arg72Pro (G/C); XRCC3 Thr241Met (C/T); XPD Lys751Gln (A/C); ERCC1 Asn118Asn (C/T); GARFT C/G, GARFT C/T, DHFR C/G, DHFR A/G, TS 5′UTR, TS 3′UTR involved with metabolism of CBDCA and Alimta regimen in pts with advanced NSCLC.
Methods: Genomic DNA was extracted from whole blood samples using the QIAamp DNA estraction kit on Biorobot EZ1 (Qiagen). Polymorphisms were detected with TaqMan-probe based assays using the 7300 Real-Time PCR system (Applied Biosystems, Foster City, CA) or PCR followed by RFLP. The results of SNPs were assessed by Cox model for survival/PFS & logistics regression for response/toxicity.
Results: We performed a retrospective analysis in 57 advanced NSCLC pts treated with CBDCA(AUC = 5) + Alimta (500 mg/m^2) after failure of two or three lines of chemotherapy. Median age was 59 years (range 26−79), M/F:63/37%; Adeno/Squa/other Ca:65/20/15%; ECOG PS:0−1/2−3:96/4%. Overall response rate was 38.6%, stable disease 38.6% and disease progression 21.1%. At median follow-up of 7.9 months, 10 pts (17.5%) died, 47 pts (82.5%) are alive. The median progression free survival (PFS) was 7.4 months, the median survival time not reached. P53 Pro72Pro was significantly associated with shorter survival (HR 5.5, 95% CI 1.01−30.5, p = 0.04) when compared to P53 Arg72Arg and P53 Arg72Pro. None of the analyzed polymorphisms was related to response to therapy. No associations were found between the analyzed polymorphisms and toxicity considered either as the maximum observed grade, or as sum of each toxicity pattern grade, probably due to low number of events observed for toxicity within this data set.
Conclusions: P53 Pro72Pro may be associated with shorter survival in pts with advanced NSCLC. Further studies are warranted to validate this finding. Genotype-related differences in common toxicities and in response to therapy were not observed. The small sample size limits interpretation of these data.

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Phase II study with fractionated schedule of docetaxel and cisplatin in patients with advanced non-small cell lung cancer

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Background: Docetaxel and cisplatin combination chemotherapy is one of the established first line chemotherapy for advanced non-small cell lung cancer (NSCLC). We evaluated the weekly schedule of docetaxel and ciplatin for the efficacy and tolerability in patients with chemotherapy naive NSCLC.
Material and Method: Patients who participated in this study had Stage IIIB or IV NSCLC with measurable disease, no prior chemotherapy, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0−2. Treatment consisted of docetaxel 40 mg/m^2 and cisplatin 35 mg/m^2 on D1 and D8 every 3 weeks. Patients were evaluated for response every two cycles of treatment.
Result: 35 patients [28 males and 7 females, median age of 61 years old (range 38−68), 31 patients with ECOG PS 0−1 and 4 patients with ECOG PS 2] were enrolled. 57% (20/35) of patients had adenocarcinoma and 74.3% (26/35) had Stage IV disease. Total 153 cycles of chemotherapy were administered. Of the 35 patients, 17 (48.6%) achieved partial response; 11(31.4%) showed stable disease; 7(20%) had progressive disease. Median duration of response was 5.3 months (95% CI: 4.2−6.2 months) and median time to disease progression was 7.43 months (95% CI: 6.41−8.45 months) and estimated overall survival at 1 year was 46.6%. The major hematologic toxicity was myelosuppression. Grade 3 or 4 anemia occured in 6 cycles and grade 3 or 4 neutropenia was observed in 4 cycles. Major non-hematologic toxicities were nausea and fatigue. Grade 3 nausea was observed in 3 patients and grade 3 fatigue was found in 2 patients. 3 patients experienced pneumonia and 1 patient had infectious colitis. There was no treatment related death in this study population.