

REPORT ASCO 2010 CHICAGO : RESPIRATORY ONCOLOGY

Johan Vansteenkiste / Christophe Doooms, Univ. Hospital Leuven and Leuven Lung Cancer Group

10 MESSAGE HIGHLIGHTS

Early stage non-small cell lung cancer

1. Endosonography (EUS/EBUS) should be the first option for invasive mediastinal staging in resectable NSCLC.
2. Chemoprevention with selenium in resected stage I NSCLC has no effect in preventing second primary tumors.
3. Surgery and adjuvant chemotherapy remains the standard approach for some patients with stage IB and most with II-III NSCLC: (a) neo-adjuvant chemotherapy may be an alternative as there is a persistent long-term benefit for neo-adjuvant chemotherapy compared to surgery alone; (b) adjuvant Gefitinib failed to show survival benefit compared to surgery alone; (c) KRAS mutations might identify a subset of resected stage IB patients that have less benefit from adjuvant chemotherapy.

Locally advanced non-small cell lung cancer

4. Phase II studies of full dose concurrent chemoradiotherapy with platinum and Pemetrexed in irresectable stage III NSCLC provided further support for the ongoing phase III trial comparing concurrent chemoradiotherapy with full dose Cisplatin-Pemetrexed versus full dose Cisplatin-Etoposide (PROCLAIM trial).

Advanced non-small cell lung cancer

5. A phase III first-line study in elderly patients showed that a platinum doublet is better than single agent chemotherapy. The study confirmed that elderly but otherwise fit patients should in general have the same treatment as other patients.
6. The fusion oncogene EML4-ALK is a new molecular target. It is expressed in 4% of the patients with lung adenocarcinoma, in general never-smokers with wild-type EGFR status. PF- 02341066, an oral tyrosine kinase inhibitor (TKI) acting on the ALK and MET/HGF receptor tyrosine kinases, resulted in very high response rate in this population.
7. A phase III first-line study (TORCH) compared Erlotinib versus standard doublet chemotherapy as initial therapy in non-selected patients. The study was stopped, because survival was significantly inferior with Erlotinib.
8. A phase III study in heavily pre-treated patients compared Vandetanib (a combined EGFR and VEGF TKI) to Placebo. There was significant delay of disease progression, but the primary endpoint, overall survival was not significantly different.
9. A phase III maintenance study compared observation to either Gemcitabine continuation or Erlotinib consolidation. Original was the well defined relapse therapy with Pemetrexed at the time of progression (one of the deficits in previous maintenance studies) . The primary endpoint progression-free survival was significantly better in both maintenance arms. Overall survival data are not yet mature, but at present non significant.

Other tumors

10. A phase III study compared BSC alone with Picoplatin (a new platinum thought to overcome platinum resistance) in relapsing SCLC. No overall improvement in survival, but a significant difference in subanalysis of truly refractory patients. Heavily criticized by the discussant, as BSC is no longer an appropriate comparator arm.

At the ASCO 2010 meeting, a total of 240 abstracts in the field of respiratory oncology were presented (314 in 2009), 175 posters, 41 poster discussion items, and 17 oral presentations (including two in the plenary session).

For our reports, we classified studies as *RCT* (large randomized controlled trial, i.e. >100 patients per arm), *RCT-small* (often phase 2 RCTs), *RCT-sec* (secondary analyses of previously presented RCTs), or *others* (phase 2 studies, retrospective analyses, surveys, ...). We concentrated on randomized data relevant for the practicing clinician.

As this report is only the 'extract of the abstracts', the reader is referred with the # sign to the respective abstract in J Clin Oncol 28 Suppl, pages 515-572 for more detailed information.

NSCLC – Early stages (stage I-III)

The ASTER study is a randomized trial comparing surgical mediastinal staging alone *versus* endosonography (ES) followed by surgical staging (only in case of a negative staging with ES) in an unselected patient population with resectable (suspected) NSCLC (**#7000, Figure 1**). ES is the combination of esophageal ultrasonography (EUS) and endobronchial ultrasonography (EBUS) The prevalence of malignancy in mediastinal nodes was 49%, without a significant difference in prevalence between both study arms.

Figure 1: #7000: phase III trial on invasive mediastinal staging (ASTER).

Patient setting

Resectable stage I-III (suspected) NSCLC requiring invasive mediastinal staging.

Randomization

Endosonography (EUS-FNA+EBUS-TBNA) followed by surgical staging if ES negative (n=123)

versus

Surgical staging alone (n=118)

Outcome

Primary : detection of N2/3 disease : 50% *vs.* 35% ($P=0.02$)

sensitivity for N2/3 : 94% (95% CI 85-98) *vs.* 80% (95% CI 68-89) ($P=0.04$)

Other: significantly less futile thoracotomies in strategy starting with endosonography.

Safety: similar complication rates between both arms.

Conclusion

Invasive mediastinal nodal staging of lung cancer should start with endosonography.

Starting with ES thus significantly improves the detection of mediastinal nodal metastases. The number of patients having to undergo an additional surgical staging procedure in the ES arm in order to identify an additional patient with mediastinal nodal metastasis was 11. Moreover, although the complication rates were identical between the two study arms, only one complication was attributable to the ES procedure (pneumothorax due to EBUS-TBNA).

A phase III randomized chemoprevention trial of selenium (Se) supplementation in resected stage I NSCLC failed to show an effect on the prevention of second primary cancers or overall second cancers. (**#7004, Figure 2**). Smoking cessation thus remains the only effective prevention action which should be undertaken after curative resection of lung cancer.

Figure 2: #7004: phase III chemoprevention trial in resected stage I.

Patient setting

Resected stage I NSCLC.

Randomization

Selenium yeast 200µg daily PO for 4 years (n=1041)

versus

Placebo yeast daily PO for 4 years (n=520)

Outcome

Primary: second primary tumor incidence: 1.91 cases *vs.* 1.36 cases per 100 person years ($P=0.15$)

Other : PFS at 5yrs 72% *vs.* 78% (NS) and OS at 5yrs 75% *vs.* 80% (NS)

Conclusion

Selenium had no effect on the prevention of second primary lung cancer.

Adjuvant chemotherapy trials already addressed the possible late chemotherapy-related effects (IALT at ASCO 2008; BR.10 at ASCO 2009). The BR.10 adjuvant chemotherapy trial showed a durable 11% long-term survival benefit without late chemotherapy-related toxicities, but the IALT data raised concerns about late chemotherapy-related toxicities. At ASCO 2010, the long-term survival of the French randomized trial (Depierre et al, J Clin Oncol 20:247-253, 2002). comparing neo-adjuvant chemotherapy versus surgery alone was reported (**#7003, Figure 3**).

Figure 3: #7003 : phase III neo-adjuvant chemotherapy trial in stage IB-IIIa.

Patient setting

Operable stage IB-IIIa NSCLC.

Randomization

Neo-adjuvant 2 cycles MIC → surgery → adjuvant 2 cycles MIC if response (n=179)

versus

Surgery alone (n=176)

Outcome

Primary: OS at 10y follow-up : 29% *vs.* 21% (HR 0.82; $P=0.12$).

Other: PFS at 10y follow up: 25% *vs.* 16% (HR 0.78; $P=0.03$). Second primary cancers were not significantly different between both arms.

Conclusion

Although statistically NS, neo-adjuvant chemotherapy was associated with a long-term survival benefit of 8% at 10 years, the magnitude observed at 5years was maintained.

Thus, in concordance with the BR.10 adjuvant trial, the French neo-adjuvant chemotherapy trial did not observe any increase in 10-year non-cancer related death rate nor any difference in second primary cancers between both arms. The occurrence of brain metastases did not differ between both arms, but the rate of bone metastases significantly decreased after neo-adjuvant chemotherapy (5 *vs.* 13%; $P=0.004$).

In 2002 – in the absence of positive adjuvant data for chemotherapy – a trial in completely resected NSCLC with the EGFR-TKI Gefitinib was initiated (**#7005, Figure 4**). In 2005, accrual was stopped early with 503/1160 patients enrolled as Gefitinib demonstrated compared to placebo (1) no significant improvement in survival in advanced disease (ISEL; second line Gefitinib) and (2) worse survival in locally advanced disease (SWOG0023; maintenance Gefitinib after chemoradiotherapy).

Figure 4: #7005: phase III adjuvant Gefitinib trial (NCIC CTG BR.19).

Patient setting

Completely resected stage IB-IIIa NSCLC.

Randomization

Surgery → adjuvant Gefitinib 250mg daily PO for 2 years (n=251)

versus

Surgery alone → adjuvant placebo 0mg daily PO for 2 years (n=252)

Outcome

Primary: OS: HR 1.23 [0.94-1.64], $P=0.136$, median 5.1 years vs. not reached.

Other : DFS : HR 1.22, $P=0.15$. KRAS and EGFR mutation status were neither prognostic nor predictive of survival.

Conclusion

Adjuvant Gefitinib did not improve survival in completely resected NSCLC.

Exploratory subgroup analyses showed that (1) the presence of an EGFR activating mutation in the placebo arm was not associated with a prolonged survival (HR 1.06; $P=0.66$), and (2) a trend for worse overall survival (HR 1.58; $P=0.16$) in the EGFR mutant patients with Gefitinib compared to placebo. The results of the RADIANT trial (adjuvant Erlotinib in resected stage IB-IIIa NSCLC) are still awaited.

Currently we use clinical ‘high risk’ predictive markers to decide upon adjuvant chemotherapy in early stage NSCLC (e.g. presence of hilar lymph nodes, or presence of a primary tumor ≥ 4.0). However, upon these ‘high-risk’ patients, we want to address who should not receive adjuvant chemotherapy. To address this question, an exploratory analysis on the impact of KRAS mutations was performed for stage IB patients with ≥ 4.0 tumors in CALGB 9633.

Figure 5: #7008: explorative subgroup analysis of CALGB 9633.

Patient setting

77% tumor resection specimens available of completely resected stage IB patients.

Randomization

Surgery → adjuvant Carboplatin-Paclitaxel (n=139/173)

versus

Surgery alone (n=128/171)

Outcome

KRAS not prognostic, but maybe predictive, especially in tumors ≥ 4.0 cm.

Conclusion

KRAS mutant patients may have less benefit from adjuvant chemotherapy.

KRAS mutant and wild type patients had a similar OS on the observation arm (HR 1.28; $P=0.47$). The OS per treatment arm showed that KRAS mutant patients did significantly worse on adjuvant chemotherapy compared to KRAS wild type patients (HR 2.15; $P=0.02$). Overall, this observation suggests that KRAS mutant stage IB patients with a primary tumor ≥ 4.0 cm might less benefit from adjuvant chemotherapy. A meta-analysis is under way to further address this observation.

NSCLC – ADVANCED STAGE - FIRST-LINE THERAPY

Classical options in fit patients are (Cis)platin-based doublets – with Pemetrexed superior to Gemcitabine in non-squamous histology. Adding a monoclonal antibody (Bevacizumab, Cetuximab) results in slight improvements in outcome. First-line Gefitinib can be considered for patients with EGFR mutant tumors. In so-called special populations, a distinction should be made between elderly but otherwise fit patients,

who in general will have the same treatment, versus patients with major co-morbidity and/or low performance status, where an adaptation of the choice is often needed.

In the plenary session, a French Intergroup study in this setting was presented (**#2, Figure 6**).

Figure 6 : #2: Phase III doublet versus single-agent chemotherapy in the elderly NSCLC patients.

Patient setting

Advanced NSCLC, elderly (>70 years) with PS 0-2.

Randomization

Carboplatin AUC=6 every 4 weeks with Paclitaxel 90 mg/m² on days 1, 8, and 15 (n=225)

versus

Single agent chemotherapy (Gemcitabine 1150 mg/m² *or* Vinorelbine 30 mg/m², both days 1 and 8 every 3 weeks) (n=226).

Outcome

Primary: OS: HR 0.60 [0.46-0.78], *P*=0.0001, median 10.4 vs. 6.2 months.

Other: PFS HR 0.55 [0.44-0.70], *P*<0.0001, median 6.3 vs. 3.2 months.

Safety: hematological toxicity significantly more common, 54.1% vs. 17.9%.

Conclusion

Doublet provides a significantly longer survival, making it a new treatment paradigm for PS 0-2 patients above the age of 70.

Based on the OS difference, the study was stopped at the 2nd interim analysis, with 451 of the planned 522 patients. About three quarters of the patients had a PS 0-1. The survival difference thus was not truly a surprise, as several studies and e.g. a European Consensus meeting published in 2005 already stated “platinum-based chemotherapy a viable option for fit patients (Gridelli et al, J Clin Oncol 23:3125-3137, 2005). This study adds to the evidence that age alone is not a reason to withheld the optimal treatment for NSCLC patients.

The other lung presentation in the plenary session was on targeted treatment for tumors harboring the EML4-ALK fusion oncogene (**#3, Figure 7**).

Figure 7 : #3: Phase II extension study with PF-02341066 in ALK positive NSCLC.

Patient setting

Advanced NSCLC, FISH+ for EML4-ALK fusion oncogene, irrespective of previous therapy

Randomization

None, open phase II study with PF-02341066, an oral TKI acting on the ALK and MET/HGF receptor tyrosine kinases, in a dose of 250 mg twice daily.

Outcome

Primary: disease control rate at 8 weeks of 90% in 50 evaluable patients.

Other: response rate 64%.

Safety: mainly (mild) gastro-intestinal toxicity (nausea, vomiting).

Conclusion

A new example of how molecularly targeted treatment results in very high disease control rate.

Based on the exciting findings with this drug in this niche of NSCLC patients (4% of total, in general never-smokers with adenocarcinoma and wild-type EGFR status), a phase III study is started.

Some other presentations focused on the use of the EGFR-TKI Erlotinib as 1st line treatment in non-molecularly selected patients, one in fit patients (**#7508, Figure 8**), and one in patients unfit for chemotherapy (**#7504, Figure 9**). These phase III trials were based on phase II studies that suggested that 1st line treatment with Erlotinib might be a valid alternative to chemotherapy.

Figure 8 : #7508: Phase III on sequencing of chemotherapy and EGFR-TKI (TORCH).

Patient setting

Advanced NSCLC.

Randomization

1st line Erlotinib 150 mg/day followed at progression by Cisplatin-Gemcitabine (n=380)

versus

1st line Cisplatin-Gemcitabine followed at progression by Erlotinib 150 mg/day (n=380).

Outcome

Primary: OS at interim analysis was inferior, HR 1.40 [1.13-1.73], $P=0.002$, median 10.1 vs. 7.7 months. Study was stopped by monitoring committee, ongoing Erlotinib patients were crossed over to chemotherapy.

Safety: no new findings, known toxicities for both treatments.

Conclusion

First-line chemotherapy remains the standard of care in unselected NSCLC patients.

This study was designed to prove non-inferiority, but failed to do so, and was stopped after inclusion of 760 of the planned 900 patients. The data thus confirm with Erlotinib what we have learned from the IPASS study: EGFR-TKI is not an option for 1st line therapy in unselected NSCLC patients.

Another study on the 1st line use of EGFR-TKI in special populations was reported from the UK (**#7504, Figure 9**).

Figure 9 : #7504: Phase III on 1st line Erlotinib for poor PS patients.

Patient setting

Advanced NSCLC in poor PS (2-3) or PS 0-1 unfit for chemotherapy.

Randomization

BSC + 1st line Erlotinib 150 mg/day until PD (n=350)

versus

BSC + 1st line Placebo until PD (n=320).

Outcome

Primary: OS: HR 0.98 [0.82-1.15], $P=0.77$.

Other: PFS HR 0.86 [0.74-1.01], $P=0.07$. Pre-specified subgroup analyses showed significantly longer OS for females only: HR 0.75 [0.57-0.99], $P=0.04$, median 5.3 vs. 4.3 months.

Safety: as expected, increased grade $\frac{3}{4}$ rash and diarrhea with Erlotinib.

Conclusion

Overall, Erlotinib did not improve OS, but there was a clear effect for females.

The gender driven effect in this study is not easy to understand. In the Forest plot, gender had a significant interaction test for OS activity, and this was independent from histology or even EGFR status. Whether 1st line Erlotinib should now be considered in females in this setting remains an option question, and in relation with the clinical relevance of the one month median survival difference in this study.

In two phase III trials, new platinum doublets were compared with Carboplatin-Paclitaxel. No outcome improvement was documented, just differences in toxicity, unlikely to have impact in European settings:

- Carboplatin + S1 (an oral prodrug of 5-FU mainly developed in Japan, #7530)
- Carboplatin + nab-Paclitaxel (#7511).

Several initially promising agents did not fulfill expectations in further testing:

- Figitumumab (CP-751871, a monoclonal antibody targeting the IGF-IR) in a phase III in combination with Carboplatin-Paclitaxel: study stopped for futility (#7500),
- Mapatumumab (apoptosis agent, agonist monoclonal antibody for TRAIL-R1) in a phase II randomized study with Carboplatin-Paclitaxel (#7501),
- NOV-002 (a glutathione pathway regulator) did not give any benefit when combined with Carboplatin-Paclitaxel (#7007)

Interesting early findings were reported on agents that may be useful in EGFR-mutation positive patients experiencing disease progression while on Gefitinib or Erlotinib. PF299804 (an irreversible EGFR/HER2/HER4 TKI) resulted in better PFS than Erlotinib in a phase II comparison relapsing NSCLC (#7523). ARQ 197-209 (a C-MET TKI) added to Erlotinib did the same in comparison with Erlotinib alone (#7502).

NSCLC – ADVANCED STAGE – MAINTENANCE THERAPY

The classical approach to patients achieving disease control after four to six cycles of 1st line platinum doublet based chemotherapy is close follow-up with indication of relapse therapy at the time of progression. Recent important “maintenance” studies at ASCO 2008-2009, one with consolidation Pemetrexed, and one with consolidation Erlotinib have challenged this treatment paradigm.

Three presentations at ASCO 2010 were presented. One was the OS outcome in the ATLAS study (maintenance Erlotinib versus Placebo after doublet chemotherapy with Bevacizumab), it was negative, HR 0.90 [0.74-1.09], $P=0.27$ (#7526).

One new result looked at continuation of Gemcitabine after Carboplatin-Gemcitabine as 1st line (**#7506, Figure 10**).

Figure 10: #7506: phase III continuation of Gemcitabine after Carboplatin-Gemcitabine.

Patient setting

Advanced NSCLC in disease control (response, stable) after 4 cy of Carboplatin-Gemcitabine.

Randomization

BSC + continuation Gemcitabine 1000 mg/m² days 1-8 every 3 weeks (n=128)

versus

BSC alone (n=127).

Outcome

Primary: OS: HR=0.97 [0.72-1.30], $P=0.84$, median 8.0 (Gem) vs. 9.3 months (BSC alone).

Other: PFS median 3.9 (Gem) vs. 3.8 months (BSC).

Safety: well tolerated, more hematological toxicity.

Conclusion

Gemcitabine continuation failed to improve OS.

A very nicely designed study from France looked at maintenance with either Gemcitabine or Erlotinib (**#7507, Figure 11**). Its original aspect was that the well predefined relapse therapy with Pemetrexed at the time of progression (one of the caveats in the previous studies) . It should be understood that it was a 3-arm study designed to compare each maintenance arm with the standard, not for comparison between the two different drugs.

Figure 11 : #7507 : phase III Gemcitabine continuation or Erlotinib consolidation.

Patient setting

Advanced NSCLC in disease control (response, stable) after 4 cy of Cisplatin-Gemcitabine.

Randomization

BSC + continuation Gemcitabine 1250 mg/m² days 1-8 every 3 weeks (n=154)

versus

BSC + consolidation Erlotinib 150 mg/day (n=155)

both versus

BSC alone (n=155).

Outcome

Primary: PFS for Gemcitabine: HR 0.51 [0.39-0.66], median 3.7 vs. 2.1 months

PFS for Erlotinib: HR 0.83 [0.73-0.94], median 2.8 vs. 2.1 months.

Other: 2nd line therapy well balanced with Pemetrexed in 60% / 63% / 76% of the patients. OS data are still immature, but at present not significant.

Safety: grade $\frac{3}{4}$ adverse events more common with Gem (27%) / Erlo (14%) vs. observation (2%).

Conclusion

Primary endpoint of progression-free survival was met in both arms. Effect with Gemcitabine was mainly seen in responders to 1st line.

NSCLC – ADVANCED STAGE – RELAPSE THERAPY

Classical options are Docetaxel or Pemetrexed single agent chemotherapy (the latter only for patients with non-squamous histology), or Erlotinib (based on a phase III study where Erlotinib was better than placebo in 3rd line therapy or in 2nd line patients unfit for chemotherapy). Despite one global phase III trial that showed that Gefitinib was non-inferior to Docetaxel in the overall 2nd line population, this drug did not get approval for targeted use in patients with EGFR activating mutations only.

Several trials looked at combination therapy to improve outcome in this setting, until now with limited results. At ASCO 2009, two large phase III trials with Vandetanib (oral tyrosine kinase inhibitor active in the EGFR and VEGF axis) were reported, one in combination with Docetaxel (ZODIAC), and one in combination with Pemetrexed (ZEAL). The primary endpoint (PFS) was positive in ZODIAC only, and significant benefits in response rate and symptom control were reported for both trials.

At ASCO 2010, the biomarker data on 570 samples of the ZODIAC study were reported (#7516). Analyses were EGFR protein expression by immunohistochemistry (EGFR-IHC, 88% positive), EGFR gene copy number by fluorescent in situ hybridization (EGFR-FISH, 35% positive), and EGFR and KRAS gene mutation by ARMS assay (EGFR-MUT 14%; KRAS-MUT 13%). Consistent trends toward improved PFS, OS, and response rate were seen for patients with positive EGFR-FISH or EGFR-MUT, with no difference for EGFR-IHC or KRAS-MUT.

Additionally, the phase III study with Vandetanib in patients failing after prior chemotherapy and EGFR-TKI was presented (#7525, **Figure 12**). The study did not meet its primary objective of demonstrating an OS benefit with Vandetanib vs. Placebo in patients with advanced NSCLC who had previously failed chemotherapy and received treatment with an EGFR TKI, although PFS was better with Vandetanib vs. Placebo.

Figure 12: #7525: Phase III comparing Vandetanib to Placebo.

Patient setting

Advanced NSCLC with progression after one/two chemotherapies and EGFR-TKI.

Randomization (2:1)

Vandetanib 300 mg/d until progression (n=617)

versus

Placebo until progression (n=307).

Outcome

Primary: OS: HR 0.95 [0.81-1.11], $P=0.527$, median 8.5 vs. 7.8 months.

Other: response rate 2.6% vs. 0.7% ($P=0.028$). Disease control rate at 6 weeks 30% vs. 16% ($P<0.0001$).

PFS HR 0.63 [0.54-0.74] ($P<0.0001$).

Safety: diarrhea (46% vs. 11%), rash (42% vs. 11%) and hypertension (26% vs. 3%).

Conclusion

Primary endpoint of OS not reached, but better disease control and PFS with Vandetanib.

New strategies for better combination treatment for relapsing patients are eagerly awaited, and the use of Vandetanib seems to be a small step in that direction. Whether the overall data with this agent will suffice for registration remains uncertain.

OTHER TUMORS (SCLC – MESOTHELIOMA)

The 1st line chemotherapy for SCLC is a platinum compound plus Etoposide. At relapse, a distinction is often made between refractory patients (i.e. PD during platinum), resistant relapse (i.e. 2-3 months after stopping 1st line), or sensitive relapse (>2-3 months) For sensitive relapse, both Topotecan as well rechallenged with the initial regimen are options. The others are difficult to treat, Topotecan can be an option, while Amrubicin is in clinical development in that setting.

The only phase III presentation at this ASCO was on the use of Picoplatin in relapsed patients (**#5002, Figure 13**). Picoplatin is a new platinum compound designed to overcome platinum resistance, with less neurotoxicity/nephrotoxicity. The study was criticized by the discussant, as “best supportive care” is not an appropriate comparator arm in patients relapsing <6 months after the end of their initial treatment.

Figure 13: #7002: Phase III comparing Picoplatin to Best Supportive Care.

Patient setting

SCLC non-responsive or relapsing less than 6 months after platinum 1st line therapy.

Randomization (2:1)

Picoplatin 150 mg/m² every 3 weeks (n=268)

versus

Best Supportive Care alone (n=133).

Outcome

Primary: OS: HR 0.80, $P=0.09$, median 21 vs. 20 weeks.

Subanalysis refractory patients: HR 0.72 [0.54-0.95], $P=0.017$, median 21 vs. 18 weeks.

Other: PFS HR 0.80 ($P=0.03$), median 9 vs. 7 weeks.

Safety: mild, grade $\frac{3}{4}$ AEs were 10%, mostly thrombocytopenia (44%), anemia (29%), neutropenia (18%), asthenia (11%). Febrile neutropenia occurred in 1%.

Conclusion

Primary endpoint of OS not met. On subanalysis, refractory patients had significant improvement in survival with Picoplatin.

For your calendar: ASCO 2011 : June 3-7, 2011, McCormick Place, Chicago.