A4- Charles Ryan et al. Phase I of AZD2171 in prostatic cancer. AZD2171, inhibit VEGF receptor. N=24, dose ranged 1 to 30 mg po qd. Linear PK, mean effective half time 20 h. One CR > 6 mo+ and one reduction in PSA of 30%. Recommended dose 20 mg/d. Further study recommended.

A10- Seunqwon Kim et al. Sorafenib (BAY43-9006) inhibit growth and angiogenesis in orthotopic anaplastic thyroid carcinoma (ATC) xenografts in nude mice. It has been demonstrated that 20-30% of ATC present BRAFV599E mutation, which can be inhibited by sorafenib. IC_{50} –2 to 5 uM inhibited growth and at –6 to 7 uM induced apoptosis. 80 mg/kg sorafenib demonstrated tumor reduction of 93%, and 84% decrease in microvessel density. Prolongation of survival also was observed. Effect likely also due to PDGFR and VEGFR2 inhibition.

A41- Bo Hansen et al. SPC2996, a short antisense oligonucleotide BCL-2 mRNA inhibitor in the treatment of CLL. Tested in cell culture and nude mice model, inhibition found at 1 nM concentration. More resistant to endonuclease degradation than phosphorothioates and siRNA. Downregulation of BCL-2 was demonstrated. Phase I on going.

A49- Robert Amato et al. Phase II of Thalidomide (starting 200 and up to 400 at 48h, then qd) + IL2 (starting one week later at 7 mlu/m^2 days 1-5, weeks 1-4 resting weeks 5 & 6) +GM-CSF (250 mcg/m^2 same schedule as IL2) in previously untreated progressive metastatic RCC. N=31. Results: 3CR, 8 PR, 6 NC, 7 PD and 7 non evaluable. (OR=45%)Somnolence, constipation, skin rash, flu-like, fluid retention, hypotension, hypothyroidism, neuropathy and bradycardia. After 6 cycles, continue with Thalidomide single agent therapy.

A65- John Tedesco et al. Development of Lu^{177} -MOAb 7E11 against PSMA conjugated via DOTA bifunctional chelating agent (GYC-DTPA, approved by the FDA) in prostatic cancer: preclinical studies. Localized in the tumor (LNCaP xenograft) up to 2.2% of the injected dose. Purity of conjugate 98%. No toxicity was found. Ready for Phase I and localization studies in humans.

A107- Josep Tabernero et al. Combined Cetuximab and Gefitinib, compared to single agents, in CRC, H&NC and NSCLC expressing EGFR. No PK interacitrons found. Doses used were Cetuximab as recommended, and Gefitinib escalated up to 500 mg qd. Skin biopsies to evaluate targets ( EGFR, MAPK, AKT, Ki67 and p27 indicated better inhibition and reduction in proliferation. Responses: 1CR, 4PR, 3SD>6wk for the combination, and only 1 PR and 1 SD for single agents…

A111- Keneshia K Turner et al. Found that tumor death by loosing anchorage to extracellular matrix (anoikis) is dependent on the expression of Integrin-alfa5. This is upregulated when breast cancer express ErbB2/Neu or Ras. Inhibition of Integrin alfa5 by siRNA oligos inhibited tumor growth and colony formation. New target for therapy?
A114- Robert L Yauch et al. Studied genes (other than EGFR) in a panel of NSCLC lines and found a lack of response to erlotinib in tumors with a multigene signature of and epithelial to mesenchymal transition (EMT), which can be identified by E-Cadherin, vimentin immunohistochemistry studies in biopsies. When these findings were correlated with clinical results in a NSCLC trial it was found that 75% of resistant patients had strong E-Cadherin expression. Igt might help to further identify patients resistant to erlotinib if validated in a prospective study.

A120- Stuart Thomson et al. Confirmed that EMT predicts loss of response to erlotinib in NSCLC cell lines and xenografts.

A203- Jeffrey Eng et al. Thymitaq (inhibitor of Thymidylate synthase, which enters the cell without active carrier and it is not polyglutamylated) in combination with 5FU high dose-short iv infusion to get the maximum PK-PD advantage in mouse xenografts. Thymitaq 100 mg/kg x 5 d was active and it demonstrated synergism for the sequence of 5FU followed by Thymitaq in 5FU and MTX resistant cell lines.

*A232- Sandrine Faivre et al. Imatinib 800 mg/d in salivary gland adenoid cystic carcinoma overexpressing KIT. This was the case in 87% of 45 patient’s biopsies. A Phase II study was the started and now there are 1 PR and 2 SD in the first 7 evaluable patients.

A236- Max E Scheulen et al. Phase II first line sorafenib in pancreatic cancer (by the Central European Society for Anticancer Drug Research). Sorafenib 400 mg bid po continuously. There were 9 SD> 12 wk and 1 PR, out of 36 patients.

A238- Hans Prenen et al In vitro activity of multi-targeted TKI Sunitinib Malate (SU11248) against GIST resistant to imatinib indicated activity for the KIT v65a or KIT t6701 mutations, but not the PDGFR-alfa d842v mutation.

A252- Jose Baselga et al. Confirm preliminary evidences that ZD6474 inhibit EGFR and VEGFR in skin biopsies of patients with breast cancer, as a surrogate target evaluation point.

A263- Robert Amato et al. Phase II of IFN alfa + Iressa or Gleevec in metastatic RCC. Doses were IFN 3 mu tiw first wk and then 6 mu tiw thereafter, and Iressa 500 mg/d or Gleevec 600 mg/d in a non randomised selection. Response was 2 PR, 1 mR, and 1 SD out of 8 patients for IFN/Iressa and 1 mR out of 4 patients for IFN/Gleevec.

A268- Fred R Hirsch et al ISEL Trial: molecular analysis of EGFR copy number, EGFR expression and Akt activation status in NSCLC treated with Gefitinib or placebo. EGFR FISH positive patients (31%) exhibited better RR (16.2% vs 3.2%) and longer median OS (8.3 mo vs 4.3 mo) or median TTF (4.5 mo vs 2.4 mo) (HR=0.61 for the FISH positive group when comparing Gefitinib and Placebo groups). Results were not significantly correlated with EGFR expression status or Akt activation.

A269- Brian Holloway et al. ISEL study investigated the presence of EGFR mutations 12%, k ras mutations (8%) and B-Raf mutations (none) in important series of randomised gefitinib to placebo Phase III study. Clinical outcome results not given in the abstract.
B5- Ghassan Abu-Alfa et al. Phase II of Sorafenib (BAY43-9006) in patients with advanced HCC. N=137, treated with Sorafenib 400 mg bid. Patients with higher staining pattern of perk had longer TTP. A 50 proteomic pattern identified responders.

B46- Takayuki Ikezoe et al. SU11248 inhibits growth of GIST (Demetri et al Proc ACSCO 2005;23:abst 4000,9001) with activating mutation of exon 11 of KIT, and it is potentiated by blocking the PI3-K/Akt/mTOR signalling.

B52- Letizia Porcelli et al. Synergism of the combination of Iressa and mTOR inhibitor Rapamycin in pancreatic cancer cell lines, given sequentially, Iressa first.


B105- Nadine Tchen et al. Combination of Irofulven and LOHP is active in prostatic cancer resistant to TXT. Phase I study: MRD LOHP 80 mg/m2 & IRO 0.40 mg/kg. 1 CR,, 1 PR and 4 SD out of 15 patients treated at the MRD. Toxicity was as expected, myelotoxicity and neuropathy, mild and 2 mild visual disturbances.

B106- JA Bonner. Cetuximab improved survival of H&N cancer in the Phase III trial comparing CTX+RT vs RT alone. M F-up 45 mo.N=424. Locoregional control was 24.4 mo vs 14.9 mo, and the local failure rate was reduced (HR=0.68). 3 y OS favored also the combination (56% vs 45%).

B110- Stephen Welch et al. Phase II of Sorafenib 400 mg/bid continuously combined to Gemcitabine 1000 mg/m2 wkly x 7 wk q 8 wkin ovarian cancer. N=25, recurrent, up to 2 lines of therapy. Results: 1 PR+ 8 SD + 5 NE at the time of study abstract.

B113- C M Rocha-Lima et al. Phase I trial of Talotrexin (PT-523) analog of MTX with increased binding to DHFR more active than MTX in models and cell lines, tested in NSCLC, after 2 +/- target therapy chemotherapy lines.. DLT not reached, > 108 mg/m2, having observed already 1 PR and 4 SD without toxicity (out of 9 patients). Active!

B119- W Fiedler et al. Phase I SU014813, VEGFR-1, VEGFR-2, PDGFR, KIT and FLT-3 TKI at nanomolar concentrations. Study doses 25 up to 250 mg po qd x 4 wk q 5 wk. MTD 200 mg qd 4/1 schedule. Linear PK found. 1 CR (RCC), 7 PR (biliary, thyroid, STS, Thymus, CRC, NSCLC) and 9 SD out of 49 patients. Promising, daily doses of 100-150 mg lead to target plasma level 100 ng/ml.

*B164- PN Munster et al. PK/PD analysis of valproic acid combined to epirubicin. Histone deacetylase inhibitors potentiate topo II inhibitors. VPA given as a loading dose followed by 6 oral doses given bid, and EPI on day 3, repeated q 3 wks. Highest doses were VPA 90 mg/kg/d + EPI 100 mg/m2. No added toxicity found, but somnolence, ataxia and confusion. At highest VPA dose average peak 1.6 mM (228 ug/ml) and trough levels 1.3 mM (178 ug/ml). N=31 prior therapy and anthracyclines, evaluable 28 (breast, melanoma, sarcoma, lung, gyn, etc). OR 4 + 3 mR + 12 SD>12 wk (benefit 68%). Outstanding results...
**B169- B Leyland-Jones et al (J Baselga). Herceptin 6 mgKkg d 1, 8 & 15 and then q 3 wk achieves rapidly steady state levels (4 wk) as compared with standard dosing (24 wks. Desirable to enhance the chemotherapy effect.

*B181- V M Ribera et al Activity Biomarkers of AP2357 (rapamycin analog that inhibits mTOR, PI3K/Akt signalling pathways) in a Phase II in sarcoma patients showing a relationship with low levels of PTEN and a decrease of VEGF in responders (representing approximately a half of the 36 analysed patients).

B219- K Mross et al. Phase I single dose study of STKI Polo-like kinase 1 (PLK-1), with BI-2536. DLT was >2 neutropenia and MTD was considered at 200 mg. Other toxic events were N, fatigue, anorexia. 1 PR occurred in a patient with H&N cancer.

B237- L Vincent et al. Combretastatin A4 Phosphate mechanism of action is due to microtubule binding and induction of apoptosis in a HL60 mouse leukaemia.

B246- F Y Lee et al. BV+Ixabepilone (BMS247550) is better than BV+TXL in an in vitro model of tissue growth and endothelial inhibition.

*B248- S Wells et al. Zactima (ZD6474) a TKI of VEGF, EGFR and RET was studied in medullary thyroid carcinoma. N=10. Results: 3 PR and 7 SD; decrease in calcitonin in all patients (median 80% reduction) and CEA in 8/10 (median 65% reduction).

*B268- H Calvert et al. AG014699 (PolyADP-ribose inhibitor, PARP, involved in base excision repair) combined to temozolomide. PARP inhibitory dose was 12 mg/m2 (74-97% inhibition) and Temozolomide was escalated up to 200 mg/m2 qd x 5 q 4 wks. No DLT found for AG014699. PK of TMZ were nof affected.. N=33. OR: 1CR + 3 PR +2 SD in 17 patients with melanoma and 1 PR in desmoid tumor.


C81- R Heller et al. Phase I trial of intratumoral plasmid IL-12 electrogene therapy in melanoma. Electroporation treatments done days 1, 5 & 8. Plasmid escalated 0.6 to 12 mg. Most patients had >4 lesions treated. Biopsies demonstrated increase in IL-12 in the tumors but not in the serum. Response in 4/6 patients were observed. Non toxic except for local pain.

C84- G R Blumenschein et al. Phase II sorafenib, 400 mg bid in NSCLC. N=54. Results: 30 SD + 15 mR, MPFS for SD 166 d. Toxicity: diarrhea, hand/foort syndrome, fatigue and nausea.

C86- S Fuessel et al. Vaccination of hormone refractory prostatic cancer patients HLA-A2 with autologous monocytes obtained through apheresis loaded with a peptide mixture (PSA, PSMA, surviving, prostein, trp p8). N=8. Each vaccine consisted in 1x10e7 DC id and iv q o wk. Results: 4 had PSA decline + 1 PR of PSA + 3 SD. Elispot indicated CTL specific for surviving, prostein and PSMA.
C90- LH Camacho et al. ZIO-101 (novel organic arsenic molecule) Phase I study. Less toxic organic derivative which achieves x 15 intracellular concentration at equimolar AS concentrations. On going at 78 mg/m2/d x 5 d and increments of 40%. Already a CR in brain mets from RCC!.

C91- R Amato. Bortezomib and Thalidomide in RCC. On going. N=10. 2 SD only…

C96- G Kelly et al Phenoxidiol (targets the sphingosine kinase Akt signalling) inducing apoptosis. N=26 hormone refractory prostatic cancer. Phenoxidiol at 200-400 mg/d x 3 wk q mo x 6, delayed progression (26-48 wks) and caused 3 PSA responses as compared to 20-80 mg dose levels.

C108- Sabrina Prici et al. KIT\textsuperscript{670x} mutation in GIST (homologous to the PDGFRalfa\textsuperscript{674} of idiopathic hypereosinofllic syndrome and to the BCR-ABL\textsuperscript{1315} in CML). In all three cases T is substituted by I (isoleucine). Functional mutagenesis studies and computational modelling indicated that fo all the allowed aminoacids derived from the exchange of each base of the DNA triplet codifying for T at the position 670 of KIT only Isoleucine is bound to be naturally selected as a resistant mutation of imatinib treated GIST.

C272- SP Chawla et al. Phase II trial in sarcoma with AP23573, mTOR inhibitor, 12.5 mg iv qd x 5 q 2 wks. N=82. Results: 3 PR in osteosarcoma and 1 PR in MFH, & SD leiomyo, lipo and other types). Clinical benefit (include SD> 16 wk) 35% (28/78). 19 patients PFS >6 mo.

C273- GJ Peters et al. PD of Gemcitabine in glioblastoma multiforme. GEM 500-1000 mg/m2 given before the operation. GEM and metabolites were measured in tissue biopsies demonstrating a good concentration in tumor tissue. Phosphorylated compound was not measured because of tissue degradation. Interesting for RT combination studies.