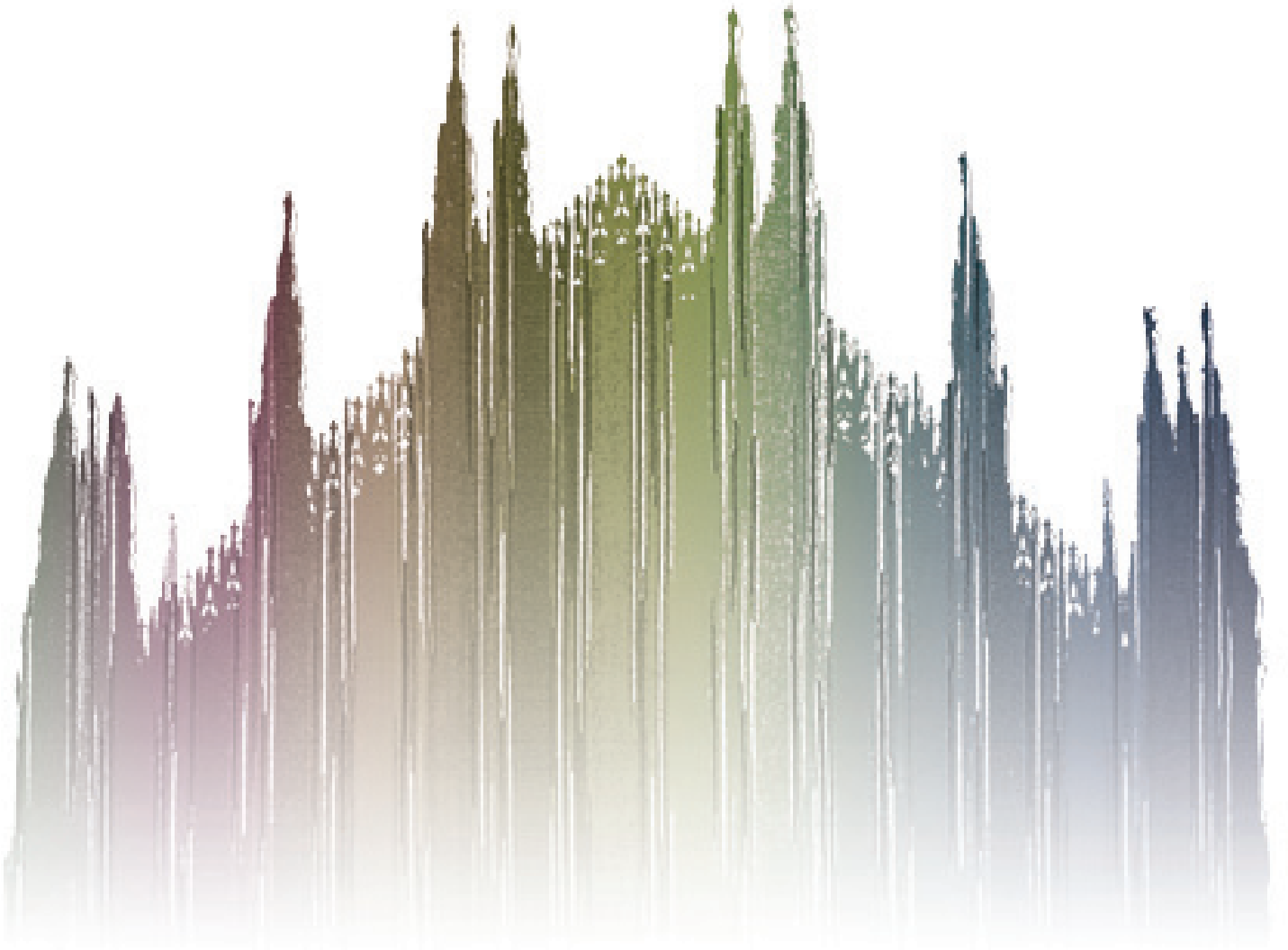
Scientific Meeting Report

Report from the 35th ESMO Congress

Prepared by the ESMO Publishing Working Group*



ESMO congress

8-12 October 2010, Milan, Italy

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For the 35th year, the European Society for Medical Oncology (ESMO)

acted as a " home of a vibrant and growing community encompassing medical oncologists but also other professionals that participate in our multidisciplinary oncology teams," according to ESMO President, David J. Kerr. The Congress took place in Milan, Italy, 8–12 October 2010 and drew 16,000 delegates, breaking all previous attendance records. Over 13,000 oncologists and other professionals in cancer care, 410 media representatives, and nearly 400 cancer patients came from every part of the world, confirming the global nature of the Congress. The scientific program reached new levels of excellence with attention to all human and biological aspects of cancer and the presentation of practice-changing study results, thanks to the efforts of David J. Kerr, ESMO President, Scientific Committee Chair Rolf A. Stahel, Educational Committee Chair Andrés Cervantes, and Chairs of the Scientific Subcommittee tracks.

With the guidance of leading experts, the Scientific Committee assembled a broad based, in-depth program that included state of the art, multidisciplinary educational workshops and symposia, controversy sessions, patient forums and the most recent scientific breakthroughs, which were reflected in the increased number of Presidential and Late Breaking Abstract sessions where new research and fundamental issues came together, forming a comprehensive dialog to shape the practice of oncology. It should be noted that over 63 000 patients have been treated in the randomized studies that were presented in different program tracks. This report reviews and discusses major advances in cancer treatment presented within the Congress scientific program in term of their implications to oncology practice.

Basic science and Translational Research

A meta-analysis of patient data from the COIN trial done by Cheadle et al. showed association between overexpression of a single nucleotide polymorphism (SNP) in the EIF3H promoter and overall survival (OS) in patients with colorectal cancer (CRC). Data from 2,186 CRC patients and 2,176 healthy controls were analyzed; of the 24 SNPs previously identified in genome wide association studies (GWAS), four CRC susceptibility alleles for rs16892766 associated significantly and independently from other prognostic factors, with CRC cases but not controls. Patients with 1 or more of these alleles (AC or CC genotypes) had poorer OS than patients with the AA genotype ($P<0.001$). The group then sequenced EIF3H and found a

putative SP 1 promoter element (rs28649280) expressed only in CRC cases (P=0.022) that associated with decreased OS (P<0.001) and treatment response (P=0.004) (Cheadle, abstract 760).

Practice point and future research opportunities

This study identifies a SNP that associates significantly with treatment response and overall survival in patients with CRC that may be a biomarker for susceptibility and also shed light on the underlying mechanism.

Biomarkers

The quest to identify biomarkers that have prognostic value for patient outcome was carried out in many cancer types, with definitive results in two non-small cell lung cancer (NSCLC) trials.
Tsao et al. conducted an analysis of KRAS mutational status on the pooled data of 1721 NSCLC patients who took part in 4 randomized trials of adjuvant platinum-based chemotherapy (ACT) to determine whether KRAS could be used to predict patient benefit from ACT. KRAS mutation was seen in 303 (19.7%) of patients; on multivariate analysis, age (P=0.0012) and histology (P<0.0001) were significantly associated with mutation. A non-significant trend toward worse OS was seen in patients with KRAS mutation (P=0.09); a significant predictive value for OS according to KRAS status was seen only in the non-squamous non-adenocarcinoma group (P=0.05). There was no difference in disease free survival (DFS) between wild type and mutant KRAS. No predictive value of OS benefit following ACT according to KRAS mutation status was observed. The question was raised whether the analyzed population was truly representative of the trials' population but the results were agreed to be conclusive. (Tsao, abstract 1560).

Practice point and future research opportunities

KRAS mutation is not a significant prognostic marker and cannot be used to select patients who will benefit from cisplatin-based adjuvant chemotherapy.

The association of three biomarkers with outcome in patients with NSCLC treated with epidermal growth factor (EGF) tyrosine kinase inhibitors (TKIs) was evaluated by Ludovini et al. This study included 166 patients with advanced NSCLC who had been treated with EGFR-TKIs and had available tissue specimens.

PIK3CA, EGFR and KRAS mutations were found in 6 (4.8%), 42 (25.3%), and 11 (6.8%) patients, respectively. An association between PIK3CA mutation and shorter median time to progression (TTP) (P=0.01) was seen in treated patients and PIK3CA mutation was a significant indicator of poor OS (P=0.001), but did not correlate with response rate. EGFR mutation significantly correlated with favorable response (P< 0.0001) and TTP was 3 versus 6 months in mutant and wild type (WT), respectively. Correlation was seen between KRAS mutation and shorter TTP (P=0.03), but did not correlate with overall survival (OS). Patients with mutations in these three genes did not show an OS benefit from TKI treatment (Ludovini, abstract 1570).

Practice point and future research opportunities

This study contributes to the growing evidence that the panel of markers used to predict response to EGFR-TKIs in NSCLC should be expanded to include KRAS and PIK3CA.

Breast cancer

Metastatic disease

Two studies which enrolled patients with very different treatment histories demonstrated that targeted therapy using trastuzumab (T) to selectively deliver the microtubule inhibiting agent DM1 (T-DM1) to HER1-positive tumor cells yielded encouraging results in the treatment of advanced breast cancer.

Perez reported promising preliminary results from the first trial of T-DM1 in 137 patients with HER2+ metastatic breast cancer (MBC) who were chemotherapy naive. This randomized phase II study determined the efficacy and safety of targeted therapy with T-DM1 compared with T plus docetaxel (T+D). The median follow-up was 6.1 and 5.9 months, with objective response rates of 48% and 41% in the T-DM1 and the T+D arms, respectively. Clinical benefit was seen in 37 (55.2%) patients receiving T-DM1 and 40 (57.1%) with T+D treatment. Stable disease was observed in 22 (33%) of T-DM1 and 29 (41%) T+D patients. T-DM1 had a favorable safety profile compared to T+D; the rates of adverse events (AEs) were similar in both arms but the incidence of grade 3-4 AEs was much lower in the T-DM1 (37%) than in the T+D treated arm (75%). Neutropenia was reported in 5 (8%) and 39 (57%) patients in the T-DM1 and T+D groups, respectively; no grade 3 neutropenia was reported, in the T-DM1 arm, nor was T-DM1 associated with an increased risk of cardiotoxicity. Patients treated with T-DM1 experienced less alopecia of any grade, 1 (1.5%) compared to 45 (66.2%) patients in the T+D arm. However, a total of 27 (40.3%) versus 9 (13.2%) patients experienced transient hepatic dysfunction; grade 1-2 occurred in 18 (26.9%) versus 8 (11.8%) and grade 3

in 9 (13.4%) versus 1 (1.5%) patients in the T-DM1 and T+D arms, respectively. The final primary endpoint analysis of progression-free survival (PFS) is expected in early 2011 (Perez, abstract LBA3).

Practice point and future research opportunities

Trastuzumab-DM1 appears to be better tolerated than combination of trastuzumab and docetaxel first-line therapy with similar efficacy due to targeted delivery.

A study by Krop et al. demonstrated improved outcomes with T-DM1 in a population of heavily pretreated women with HER2 positive MBC. This multicenter, open label, phase II trial enrolled 110 patients who had previously received a median of 7 prior agents for MBC (range 3-17) including anthracycline, taxane, capecitabine, trastuzumab, and lapatinib. The median follow-up was 12.1 months (range 10.9-12.9); the objective response rate (ORR) was 35% and clinical benefit rate (CBR) was 48%. The median duration of response (DOR) was not reached; PFS was 6.9 months. Patients with centrally confirmed HER2-positive disease showed better outcomes; ORR was 41%, CBR was 55% and the median PFS was 8.0 months. Treatment was discontinued in 92 patients (83.6%), mainly due to progressive disease (69%) but discontinuation due to adverse events was seen in just 7 (6%) patients. The acceptable safety profile demonstrated in this trial is remarkable given the substantial pre-treatment received by these patients (Krop, abstract 2770).

Practice point and future research opportunities

Trastuzumab-DM1 shows promising efficacy and an acceptable safety profile as second line treatment in patients heavily pretreated for metastatic breast cancer.

Triple negative breast cancer (TNBC)

An attempt to address the therapeutic gap in 'targetless' triple negative breast cancer (TNBC) was made by adding the PARP inhibitor iniparib to gemcitabine and carboplatin (G/C). O'Shaughnessy et al. reported results from a phase II study of 123 patients; iniparib improved the outcome without important associated toxicity. An improved observed response rate of 52.5% was seen with iniparib versus 32.3% with placebo (P=0.023) and a combined benefit rate of 55.7% versus 33.9%, (P=0.015) was demonstrated with iniparib and placebo, respectively. Median progression–free survival was 5.9 and 3.6 months (P=0.012) and median overall survival was 12.3 and 7.7 months (P=0.014) in the iniparib and placebo arms, respectively.

Further study is planned to confirm the results, determine the late effects, explore whether iniparib is active against other types of breast cancer and to define the target(s) (O'Shaughnessy, abstract LBA11).

Practice point and future research opportunities

The underlying mechanism of TNBC includes PARP mediated defects in DNA repair; patients with TNBC responded well when a PARP inhibitor (iniparib) was added to standard chemotherapy. The improved outcome includes an increase in median survival, a rare finding in advanced disease. While results from this relatively small phase II study add to currently available data on this new therapeutic option, any enthusiasm must be balanced with some degree of caution until data are confirmed by large randomized phase III studies.

Early disease

Musolino et al. examined the frequency of markers of poor prognosis associated with the risk of breast cancer diagnosis in-between screening examinations. The database was from the Cancer Registry of the Parma Province from all women aged 50 to 69 diagnosed with breast cancer from 2004 to 2007, which included 370 screen-detected and 271 symptomatic breast cancers (63 women with interval cancers and 208 who had not attended screening). Interval-detected cancers occurred in younger women and were more advanced; these tumors had a higher histologic grade, a high proliferation rate, and were more often HER2 positive than screen-detected tumors (Musolino, abstract 2150).

Practice point and future research opportunities

The distribution of molecular subtypes in screen-detected breast cancer differs from that of interval cancers and women with screen-detected cancer displayed a survival advantage.

The Ki-67 labelling index (LI) is a potential biomarker for therapeutic activity following lapatinib treatment, according to Decensi, et al. who conducted a placebo controlled trial in 60 women with HER-2 positive breast cancer who had received lapatinib prior to surgery. Ki-67LI showed a mean percent (SD) change of -9.3 %(±34.2) and +15.1% (±30.9) in the lapatinib and placebo arms, respectively, (P= 0.008). The Ki-67 decrease following lapatinib was greater in estrogen receptor (ER) negative than ER positive tumors, (-34.8% and -12.3%, respectively) and in PTEN over-expressing tumors (P=0.057).

The Ki-67 profile was examined in post lapatinib-treatment surgical specimens; the median Ki-67 was 15% and 20% with lapatinib and placebo in ductal intraepithelial neoplasia (P=0.06), and 1% versus 3% (P=0.006) in ductal hyperplasia. The median surgical tumor diameter was 18 mm in the lapatinib arm and 24 mm in the placebo arm (P=0.009) (Decensi, abstract 220PD).

Practice point and future research opportunities

Ki-67 levels are associated with response to pre-surgical lapatinib treatment. Lapatinib reduced cell proliferation and tumor size in women with HER-2 positive breast cancer: a greater effect was seen in ER negative and PTEN expressing tumors.

A Swiss group headed by Moor further validated PRO_10, a prognostic score based on a qRT-PCR array of 10 proliferation-associated genes obtained from formalin fixed breast cancer samples. This study reviewed patient data and matched 48 cases (patients with a first relapse of breast cancer within 5 years from diagnosis) 1 to 1 with controls (relapse occurring after 5 or more years) examining a panel of factors that included histological grade, percent ER+ cells, HER-2 expression, age, and prior therapy. PRO_10 score was strongly associated with relapse free (RFS) and OS rates; 5-year RFS was 29% and 67% in patients with high and low scores, respectively (P=0.002) and the median RFS was also associated with high and low scores (4.0 years and not reached, respectively). PRO_10 was prognostic for 5-year OS (71% vs. 91%), and median OS (8.1 years versus not reached), for high and low scores, respectively (P=0.0057). The authors suggest optimizing a prognostic model by using an array of 47 genes (Moor, abstract 221PD).

Practice point and future research opportunities

The prognostic value of PRO_10 was validated in postmenopausal patients with ER positive breast cancer and could serve as an independent prognostic marker.

Chest Tumors

Non small cell lung cancer (NSCLC)

Miller et al. reported a phase IIb/III double-blind randomized trial with 585 patients with stage IIIB/IV adenocarcinoma treated with afatinib, an irreversible inhibitor of EGFR/HER1 and HER2 in patients with NSCLC who had failed chemotherapy and treatment with reversible EGFR tyrosine kinase inhibitors (TKIs).

The primary endpoint of OS improvement was not met; median OS was 10.78 and 11.96 months with afatinib compared with placebo, respectively. . However, a significant advantage was seen with afatinib over placebo for the secondary endpoints; median PFS increased 3-fold from 1.1 to 3.3 months, (P<0.0001) and the disease control rate (DCR) at 8 weeks was 58% versus 19%, (P<0.0001), in the afatinib and placebo arms respectively. The objective response rate (ORR) was 11% vs. 0.5% by investigator and 7.4% and 0.5% by independent analyses (P<0.01). Fewer patients received post-progression chemotherapy (61% vs. 70%) and EGFR TKIs (11% vs. 23%) following treatment with afatinib than placebo. The side effects of afatinib were effectively managed by supportive care and/or dose reduction. Further data analyses for molecular associations to quality of life and OS are ongoing (Miller, abstract LBA1).

Practice point and future research opportunities

Although the LUX-lung 1 study did not meet its primary endpoint of extending overall survival. The fact that this new irreversible inhibitor of EGFR/HER1 and HER2 induced objective regressions in heavily pre-treated NSCLC patients and led to a better progression-free survival with improvements in some of cancer-related symptoms, witnesses the possibility that afatinib could be a new active compound in the lung cancer field.

The addition of MetMAb (a monovalent antibody that binds the Met receptor) to erlotinib in patients with immunohistochemically Met+ NSCLC improved both PFS and OS, while Met- NSCLC patients experienced shortened PFS and OS. Spigel et al. reported results from a global randomized, double-blind phase II study comparing MetMAb plus erlotinib (ME) to placebo plus erlotinib (PE) in 112 patients treated by 2ndand 3rd line therapy for NSCLC. Benefit in PFS (P=0.05,) and OS (P=0.11) was observed in Met+ patients treated with ME, but in the Met- population, PFS (P=0.04) and OS (HR 3.26; P=0.01) worsened in the ME cohort. Hazard ratios for PFS and OS in the intention-to-treat (ITT) population were 1.09 (P=0.70) and 1.13 (P=0.68). Patients in the PE arm were allowed to crossover to ME following disease progression. The benefit was not observed in other subgroups, including: non-squamous, EGFR or KRAS mutants. Adverse events (AEs) were similar in both arms; incidence of grade ≥3 AEs was similar in ME (54%) compared with PE (53%) (Spigel, abstract LBA15).

Practice point and future research opportunities

Although the LUX-lung 1 study did not meet its primary endpoint of extending overall survival. The fact that this new irreversible inhibitor of EGFR/HER1 and HER2 induced objective regressions in heavily pre-treated NSCLC patients and led to a better progression-free survival with improvements in some of cancer-related symptoms, witnesses the possibility that afatinib could be a new active compound in the lung cancer field.

EGFR activating mutation-positive (Act Mut+) NSCLC is a biologically distinct form of NSCLC that has demonstrated benefit from treatment with EGFR tyrosine kinase inhibitors (TKIs). The efficacy of first-line erlotinib compared to gemcitabine plus carboplatin (gem/carb) was evaluated in OPTIMAL, a prospective phase III study by Zhou et al. Chemonaive patients with Act Mut + advanced NSCLC (154) showed significant benefit in PFS from erlotinib over gem/carb ($P<0.0001$) and an updated analysis showed median PFS of 13.1 versus 4.6 months, respectively. The erlotinib treatment showed an improved objective response rate over gem/carb: 83 vs. 36%, respectively; ($P=0.0000$), and disease control rate (CR + PR + SD; 96 vs. 82%; $P=0.002$). Overall survival data are not yet mature. Erlotinib showed a more favorable safety profile with lower AE and serious AEs incidence than gem/carb. To further characterize the molecular impact on erlotinib response, Wu et al. performed an exploratory analysis on OPTIMAL patient data to determine whether other genes or submutations of EGFR played a role in outcome. KRAS, EGFR T790M, HER2, BRAF, PIK3CA, and PTEN mutations were sequenced from pre-treatment tumor samples and c-MET amplification status was analyzed using real-time PCR. Progression-free survival was not found to differ significantly between EGFR activating mutation type and no other mutations were identified in either treatment arm. Baseline c-MET amplification status was not predictive for the efficacy of erlotinib or gem/carb (Zhou, abstract LBA13; Wu, abstract LBA14).

Practice point and future research opportunities

OPTIMAL is the first prospective phase III study demonstrating that erlotinib is superior to standard platinum-based first-line chemotherapy in EGFR activating mutation-positive NSCLC patients. EGFR exon 19 mutation is the best predictor of efficacy and no additional biomarkers were identified to predict greater benefit of erlotinib in this patient population.

Preliminary data from a Phase II trial reported by Mok et al. demonstrated safety and encouraging efficacy of first-line PF299804, a pan-HER (HER1, 2, and 4) inhibitor with activity against EGFR activating and resistance mutations (EGFR mu) in 74 patients with advanced NSCLC who were molecularly selected for EGFR mu. Preliminary PFS data showed 73%, 67%, and 57% of patients who were progression-free at 4, 6 and 9 months. One patient achieved complete response, 41 partial response, 44 stable disease and 8 patients experienced progressive disease. All evaluable patients with EGFR mu NSCLC (n=27) demonstrated tumor shrinkage. Treatment was well tolerated with no grade 4/5 treatment related AEs reported; however three patients discontinued due to AEs. From these preliminary data, patients receiving <70% of the planned dose appeared to experience equivalent PFS benefit to higher dosed patients (Mok, abstract LBA18).

Practice point and future research opportunities

Preliminary results show encouraging efficacy, demonstrated by progression-free survival rates and tumor shrinkage, for PF299804 as first-line treatment of EGFR mu selected patients with NSCLC.

Gefitinib did not show increased OS over carboplatin/paclitaxel (C/P) in 1217 clinically selected patients with advanced NSCLC, according to Yang et al. who reported final overall survival results from the phase III IPASS study. Overall survival was similar with gefitinib and C/P treatment with no statistical difference between arms (P=0.109) and equivalent treatment effect was seen in all mutational subgroups. No statistically significant difference in OS was seen between gefitinib and C/P in EGFR M+ (P=0.990) or EGFR M- subgroups (P=0.309). However, progression free survival (PFS) data from this study reported by Mok et al. at the 2008 ESMO Congress showed a statistically significant difference in favor of gefitinib in a subgroup of patients positive for the EGFR mutation. The PFS for these 132 patients on first-line gefitinib was 9.5 months, compared with 6.3 months for 81 EGFR patients first treated with chemotherapy (P<0.001). The OS results may have been affected by crossover; upon treatment failure patients were free to switch to other active regimens - including gefitinib. The safety profile for gefitinib was consistent with that previously established (Yang, abstract LBA2).

Practice point and future research opportunities

Treatment crossover in randomized trials remains a significant problem for proper interpretation of survival results in oncology. The high percentage of patients receiving the alternative study treatment or other subsequent therapies in landmark IPASS study may account for comparable overall survival

for gefitinib and standard chemotherapy in overall and in EGFR biomarker positive or negative NSCLC populations.

CNS tumors

A phase III randomized study on 325 recurrent glioblastoma patients by Batchelor et al. showed that cediranib alone or in combination with lomustine gave no significant advantage over lomustine alone. The primary objective, determination of whether either cediranib alone or in combination with lomustine prolonged PFS was not met; median PFS was 92, 125 and 82 days with cediranib, combination and lomustine treatment, respectively. Cediranib showed signs of clinical activity in some secondary endpoints; a statistically significant difference was observed in mean change in steroid use between cediranib monotherapy (–26.2%) versus lomustine (+5.3%, P=0.006), and in cediranib in combination with lomustine (–23.4%) versus lomustine (+5.3; P=0.012) and in time to deterioration in neurological status between cediranib plus lomustine (170 days) and lomustine (111 days; P=0.009). No significant advantage for either cediranib arm over lomustine was seen for PFS, overall survival, or response rate. Adverse events were consistent with the safety profile of each drug (Batchelor, abstract LBA7)

Practice point and future research opportunities

Cediranib failed to improve progression-free survival in patients with recurrent glioblastoma.

Developmental Therapeutics

Results were presented for novel agents that target the phosphoinositide 3-kinase, key element in the PI3K-AKT-mTOR pathway, a key signal transduction system linking oncogenes and multiple classes of receptors to essential cellular functions, including cell survival, proliferation, differentiation, motility, glucose use and angiogenesis deregulated in many cancer types. This pathway is constitutively active in several cancer types.

The protein kinase MEK1/2 acts downstream of EGFR and other growth factor receptors in the p42/43 MAPK pathway to amplify signals and increase vascular permeability and also figures in the Ras-Raf-MEK-ERK pathway. As such, it is a rational target for cancer therapeutics such as GSK1120212 a potent and selective inhibitor of MEK1/2.

Falchook et al. conducted a study in 162 patients with advanced solid tumors and lymphoma and found that the long, effective half-life and small peak: trough ratio of GSK1120212 allows constant target inhibition within a narrow range of exposure. Compelling responses were recorded in BRAF mutant melanoma, and evidence of antitumor activity in BRAF wild type melanoma, pancreatic cancer, and KRAS mutant NSCLC were observed. GSK1120212 was well tolerated (Falchook, abstract 4950).

Practice point and future research opportunities

The ongoing phase II study in patients with pancreatic cancer and the planned phase III study in BRAF mutant melanoma are warranted due to the encouraging anti-tumor activity observed with GSK1120212.

GDC-0980 is a potent and selective oral dual inhibitor of both class I PI3K and mTOR kinase, which figure prominently in the PI3K-AKT-mTOR pathway; dual target is preferred to single target inhibition since single mTORC1 inhibitors, such as rapamycin analogues, may induce a feedback activation of PI3K in some cancers which could be mitigated by dual PI3K inhibition. GDC-0980 demonstrated broad activity in a range of cancer types, according to Bendell who reported results from a first-in-human phase I study in 26 patients with advanced solid tumors or non-Hodgkin's lymphoma. GDC-0980 was generally well tolerated with no grade 4 or higher drug-related adverse events reported to date. Early signs of anti-tumor activity were observed; a 26% decrease in tumor size in a patient with epithelioid mesothelioma, a peritoneal mesothelioma patient experiencing 20% tumor decrease by RECIST and 80% decrease in measurable tumor marker and one patient with GIST experiencing a 49% decrease in tumor mean SUVmax assessed by FDG-PET. One adrenal cell carcinoma patient has remained on study for 8 months (Bendell, abstract 4960).

Practice point and future research opportunities

A dual inhibitor of class I PI3K and mTOR kinase, GDC-0980, demonstrated potential anti-tumor activity in specific cancer types.

Wagner et al. conducted a first-in-human phase I study to evaluate GDC-0941, a potent and selective oral pan-inhibitor of the class 1 PI3K and isoforms of p110, key elements in the PI3K-PTEN-AKT signalling pathway. GDC-0941 was tested and generally well tolerated in 80 patients.

Potential signs of anti-tumour activity were seen; one patient with triple negative breast cancer achieved partial response, an ovarian cancer patient who remained on study for over one year had a 23% decrease in target lesion by RECIST and 2.8-fold decrease in CA-125, a patient with dermatofibrosarcoma protuberans had an approximately 58% decrease in tumor FDG activity-7 by PET, and 4 other ovarian cancer patients achieved either stable disease by RECIST for at least 6 months, decreases in CA-125 or 30% or more decreases in tumor mean SUVmax by FDG-PET (Wagner, abstract 4970).

Practice point and future research opportunities

GDC-0941 was generally well tolerated and displayed signs of anti-tumor activity in several difficult to treat cancers.

At this ESMO Congress, there were five presentations on Hedgehog inhibition. Two phase II placebo-controlled randomized studies were designed to assess efficacy and safety of GDC-0449 in first-line treatment of metastatic colorectal cancer, and as maintenance therapy in patients with ovarian cancer in second or third complete remission. In both settings, results do not demonstrate a clinical benefit and early drug discontinuation due to adverse events may suggest a lower tolerance in the maintenance setting. Another potent, selective Hedgehog inhibitor, LDE225, has been assessed in the "first-in-human study" with observed good tolerance, a favorable pharmacokinetic profile and target modulation. An anti-tumor response was noted in patients with recurrent medulloblastoma, and disease stabilization in patients with basal cell carcinoma, spindle cell and osteosarcoma. A report of the first clinical experience of IPI-926 shows preliminary evidence of clinical activity in patients with basal cell carcinoma, medulloblastoma and chondrosarcoma. In addition, a small preclinical study shows heterogeneous expression patterns of the Hedgehog pathway in biliary tract cancer cell lines.

Practice point and future research opportunities

Hedgehog inhibition failed to show efficacy in colorectal and ovarian cancers. Even though markers predicting the efficiency of Hedgehog pathway inhibition are yet to be identified, such an approach may prove valid for novel treatment strategies in some difficult to treat cancer with limited therapeutic options in metastatic phase (e.g. basal-cell carcinoma).

Innovation in the therapeutic armamentarium against cancer can also be achieved by new formulations of 'old' drugs.

Wynne et al. reported results of a phase Ib dose escalation test of a subcutaneous delivery system developed to simplify trastuzumab treatment and increase patient comfort using recombinant human hyaluronidase (rHuPH20) that has been developed and approved to improve dispersion and absorption of co-administered drugs and allows for delivery of volumes ≥3 mL. Subcutaneous trastuzumab (8 mg/kg dose) gave a serum exposure in the range of the approved 6 mg/kg IV dose in both male subjects and HER2-positive patients. The formulation was well tolerated, with no apparent increase in incidence of AEs with increasing dose and patient experience was favourable (Wynne, abstract 218PD).

Practice point and future research opportunities

Subcutaneous trastuzumab delivery system gave serum exposure comparable to the approved IV formulation in male volunteers and HER2-positive breast cancer patients and was comfortable and well tolerated by patients, warranting further investigation.

Gastrointestinal malignancies

Colorectal cancer

The Nordic Colorectal Cancer Biomodulation Group evaluated whether there was clinical benefit of adding cetuximab to continuous or intermittent Nordic FLOX treatment delivered until progression in patients with metastatic colorectal cancer (mCRC). The Nordic VII study by Tveit et al. evaluated cetuximab addition to continuous Nordic FLOX (CFLOX) regimen (5-fluorouracil/folinate/oxaliplatin) in 566 patients with mCRC and found no significant difference between the three treatment arms; PFS was 7.9, 8.3 and 7.3 months (P=0.31) with continuous FLOX, CFLOX and intermittent FLOX plus continuous cetuximab. Cetuximab combined with Nordic FLOX did not significantly improve RR, PFS or OS compared to FLOX alone; OS was similar for patients treated with FLOX intermittently and continuously. KRAS mutation was not predictive for cetuximab effect but BRAF mutation was a strong negative prognostic factor; PFS was 8.3 and 5.1months (P=<0.001) and median OS was 20.4 versus 9.5 months in wild type and mutated BRAF, respectively (P<0.001) (Tveit, abstract LBA20).

Practice point and future research opportunities

Nordic FLOX was confirmed as an effective first line treatment of patients with mCRC and the concept of intermittent delivery was reinforced; however results of the FLOX regimen were not improved by adjuvant cetuximab. BRAF was a strong negative biomarker for response to cetuximab.

Upper gastrointestinal malignancies

The final results of PRODIGE 4 – ACCORD 11/0402, a randomized phase III trial that compared folfirinox (5FU/leucovorin, irinotecan and oxaliplatin) to gemcitabine as first-line treatment of 342 patients with metastatic pancreatic adenocarcinoma were reported by Desseigne et al. Folfirinox improved OS but resulted in a higher frequency of grade 3/4 febrile neutropenia (5.4%) and required diligent patient selection and monitoring. At a median follow-up of 26.6 months the median OS in the folfirinox arm was 11.1 months versus placebo of 6.8 months ($P<0.0001$). Median progression-free survival was 6.4 versus 3.3 months, for folfirinox and placebo, respectively ($p<0.0001$). The risk of disease progression was reduced by 53% with folfirinox treatment. The one year and 18 month survival rates were 48.4%, 18.6% and 20.6% and 6% in the folfirinox and gemcitabine arms, respectively. Grade 3/4 toxicities were diarrhea 12.8% vs. 1.2%, nausea 12.0% vs. 5.3%, vomiting 14.5% vs. 4.5%, fatigue 23.2% vs. 14.2%, neuropathy 9% vs. 0%, neutropenia 45.7% vs. 18.7% and febrile neutropenia 5.4% vs. 0.6% in the folfirinox and placebo arms, respectively (Desseigne, abstract 730).

Practice point and future research opportunities

Folfirinox increased overall and progression-free survival and should be considered as first line treatment for patients with metastatic pancreatic adenocarcinoma with the caveat that it is more toxic than gemcitabine and requires diligent patient selection and treatment monitoring.

The addition of preoperative chemoradiotherapy (CRT, 5-fluorouracil and cisplatin) to resection in patients with localized (stages I or II) esophageal tumors to ameliorate the problems of local recurrence and distant metastases following surgery was tested in 195 patients by Mariette et al. in a randomized controlled phase III trial. Neo-adjuvant CRT did not significantly improve outcomes; postoperative morbidity rates were 49.5% vs. 43.9% ($P=0.17$), and 30 day-mortality rates were 1.1% versus 7.3% ($P=0.054$), in the surgery and CRT groups, respectively.

The R0 resection rates were 85.7% with surgery versus 88.1% with CRT. Overall and progression-free survival endpoints were not met; at median follow-up of 5.7 years, the 3-year overall survival was longer with surgery than CRT, 55.2% versus 48.6%, respectively (P=0.68), as was the 3-year progression-free survival. (Mariette, abstract 8000).

Practice point and future research opportunities

Neoadjuvant chemoradiotherapy did not significantly improve outcome in patients with stage I or II oesophageal cancers over surgery alone.

The final results of the Intergroup FFCD-GERCOR-FNCLCC 03-07 phase III study by Guimbaud et al. comparing epirubicine, cisplatin plus capecitabine (ECX) 1st line therapy until progression, followed by FOLFIRI in 2nd line (Arm A) or the reverse sequence (Arm B) in 416 patients with gastric or cardiac adenocarcinoma, locally advanced or metastatic were reported. The primary endpoint was met; the median time to treatment failure for 1st line increased over 20 weeks in arm B (18.5 vs. 22.1 weeks in arms A and B, respectively; P=0.008). However, there was no observed difference in PFS (5.30 and 5.75 months in arms A and B, respectively) or OS, which was 9.5 and 9.7 months in arms A and B, respectively. There was more grade 3/4 toxicity during 1st line with ECX than FOLFIRI (85% vs. 70%) which resulted in a higher rate of 1st line discontinuation in arm A (16.7%) than in arm B (3.5%); 2nd line toxicity did not differ between arms (Guimbaud, abstract 8010).

Practice point and future research opportunities

Better tolerance and extended time to treatment failure, similar overall survival and progression-free survival are seen with FOLFIRI in 1st line followed by ECX which should be preferred to ECX 1st line.

Genitourinary tumors

A phase III study conducted by de Bono, et al demonstrated that abiraterone acetate, which targets persistent androgen synthesis (PAS) and androgen receptor (AR) signaling, improved OS in patients with metastatic castration-resistant prostate cancer (mCRPC). Men whose disease progressed following chemotherapy with docetaxel experienced a median 3.9 months increased survival with arbiraterone plus prednisone (AA+P) treatment compared to placebo. An interim analysis of 552 events showed a median

OS of 14.8 versus 10.9 months with AA+P or placebo+P, respectively (P=0.0001). All secondary endpoints were statistically significant; time to progression (TTP) was 10.2 vs. 6.6 (P=0.0001) and PFS 5.6 vs. 3.6 (P=0.0001) months in the AA+P vs. placebo+P arms, respectively. The drug also significantly improved time to prostate-specific antigen (PSA) progression, radiographic PFS, and PSA response rate. A fall in circulating cells matches with the overall survival data and side effects show almost no difference in comparison to placebo. (de Bono, abstract LBA5).

Practice point and future research opportunities

This is the first clinical trial that prospectively studied hormonal therapy after docetaxel treatment and the first clinical trial in prostate cancer with prospective collection of circulating tumor cells. In addition, it is the first trial that prospectively used the Prostate Cancer Clinical Trials Working Group Criteria in the context of a randomized phase III trial. Abiraterone offers a new option in the treatment of patients with CRPC. Further follow-up on survival data is awaited as well as report on long-term side effects.

Final OS and a safety update for a phase III study of pazopanib (paz), an oral multikinase angiogenesis inhibitor that targets VEGFR, PDGFR, and cKit were reported by Sternberg et al. This study in 335 patients with metastatic renal cell carcinoma (mRCC) met the primary endpoint, increased PFS; median PFS was 9.2 and 4.2 months in the paz and placebo arms, respectively (P <0.0001). Statistically significantly superior outcomes were seen in subpopulation analysis: PFS in the treatment naive arm was 11.1 and 2.8 months (P <0.001) and 7.4 and 4.2 months (P <0.001) in the cytokine pretreated arm, for paz and placebo, respectively. The final OS analysis was done after reaching 290 deaths; OS was 22.9 months with paz and 20.5 months in the placebo arms (P = 0.224). Final OS results showed a trend towards benefit with paz that is confounded by the 54% crossover rate of placebo patients, occurring as early as week 6, who received paz. Two analyses were done to adjust for crossover; The Inverse Probability of Censoring Weighted demonstrated a 50% reduction in the risk of death with paz versus placebo (P = 0.002) and the Rank Preserving Structural Failure Time showed a 57% reduction in the risk of death with paz versus placebo (P = 0.172). Fewer patients in the paz arm (30%) than in the placebo arm (66%) received subsequent treatment (66% vs. 30%, respectively). Following crossover, there was a 30% increase in cumulative exposure in the pazopanib arm with no important changes of the type, frequency or severity of adverse events; 23 (8%), 43(15%) and 93 (32%) patients received paz for more than 36, 24 and 12 months, respectively. Analysis of the crossover OS data suggest that delaying treatment is not detrimental (Sternberg, abstract LBA22).

Practice point and future research opportunities

Pazopanib treatment in patients with mRCC significantly increased progression-free survival compared to placebo and analyses adjusted for crossover showed a trend toward increased overall survival.

Pazopanib may also be effective in patients with relapsed/refractory urothelial cancer, an aggressive disease that is only mildly sensitive to chemotherapy. Necchi et al. reported interim results of a phase II trial of pazopanib in 18 patients with histologically documented, unresponsive or relapsing urothelial cancers who are being treated with pazopanib until disease progression or unacceptable toxicity. Four (22%) patients had confirmed RECIST-defined partial response (PR), 11 (61%) had stable disease, yielding an overall 83% clinical benefit. Progression-free survival at two months was 64%. Computed tomography densitometry results indicated tumor necrosis by a HU decrease of 15% or more in the tumors of 12 (67%) patients. There were no grade 3/4 AEs; grade 1-2 hypertension and hand-foot syndrome occurred in 3 and diarrhea in 4 patients, and a grade 2 increase of liver transaminases was recorded in 2 patients (Necchi, abstract LBA23).

Practice point and future research opportunities

Pazopanib demonstrated antitumor activity in patients with pre-treated and unresponsive urothelial cancers; in the majority of patients a necrotic evolution was observed inside metastases.

Patients with advanced renal cell carcinoma (RCC) benefited from treatment with tivozanib, an inhibitor of VEGFR-1, -2, and -3 kinases, compared to placebo according to Nosov et al. They conducted a phase II trial to determine PFS and (ORR) following 16 weeks of tivozanib therapy. Patients (n=272) received 16 weeks of tivozanib during an open label phase, stratified thereafter according to tumor response, and randomized to 12 weeks of double-blind tivozanib (n=58) or placebo (n=53,) and 78 patients continued tivozanib; at the time of progressive disease (PD) patients on placebo were allowed to resume tivozanib. The median PFS by independent radiology review was 11.8 months and 14.8 months in the overall population and patients who had undergone nephrectomy, respectively. Median progression-free survival was 17.7 months in patients who continued tivozanib, not reached in patients randomized to tivozanib and 6.3 months in patients receiving placebo. In the placebo arm, PD was seen in 29 patients. Among 26 patients who crossed over to tivozanib, 24 (82%) patients demonstrated clinical benefit. The objective response rate was 29%. The most frequent adverse events reported were hypertension and dysphonia which occurred in 50% and 22% of patients, respectively (Nosov, abstract 8680).

Practice point and future research opportunities

Tivozanib doubled the median PFS in patients with RCC and displayed a safety profile consistent with that of a selective VEGFR inhibitor.

Geriatric oncology

Elderly patients are underrepresented in prospective trials, perhaps due to patients' unwillingness, but more commonly due to age inclusion criteria of less than 65-70 years; this is paradoxical to cancer incidence rates which increase with age and is particularly counterproductive in trials specifically designed for elderly. This issue was addressed in a companion study of a multicenter phase II trial of adjuvant chemotherapy for hormonal receptors-negative (HR-) early breast cancer in 70+ women, the GERICO-06 study, which had as primary objective to assess the impact of non- pegylated liposomal doxorubicin (Myocet®) plus cyclophosphamide in women ≥70 with HR- invasive breast cancer on activities of daily living. Screening for eligible cases targeting age 70 plus women and HR- status, was recommended to improve enrolment. The substudy determined the inclusion and failure rates in 48 women 70 years and older. Following screening, 40 women (83% screening success rate) were invited to the trial; only 2 declined (4% failure rate). Age was rarely a determinant for not participating in a clinical trial and proper screening may improve recruitment (Brain, abstract 572PD).

Practice point and future research opportunities

Age rarely impacted the enrolment of elderly in clinical trial when inclusion criteria match the standard elderly population addressed by the scientific question.

Gynecologic tumors

Preliminary results from the ICON7 phase III trial comparing concurrent bevacizumab and chemotherapy followed by maintenance bevacizumab, with chemotherapy alone in women with newly diagnosed epithelial ovarian, primary peritoneal or fallopian tube cancer was presented by Perren. The study enrolled 1528 patients with high-risk early or advanced cancers; the primary endpoint of increasing PFS from 18 to 23 months by RECIST was met.

At the median follow-up of 19.4 months, median PFS was 19,0 in the bevacizumab arm compared to 17.3 months in control (P=0.0041); there was a 15% PFS improvement at 12 months, and 1.7 month improvement in median PFS, and a 1.5 month overall improvement in PFS. Upon preliminary analysis of OS, the one year OS was 95% vs. 93% in the bevacizumab and control arms, respectively (P=0.098). Progressions/deaths occurred in 759 (50%) patients, (P=0.0041) favoring the bevacizumab arm. Bevacizumab treatment was well tolerated, consistent with previous bevacizumab studies and no new safety concerns were noted. (Perren, abstract LBA4).

Practice point and future research opportunities

This is the second large positive randomized trial in ovarian cancer patients that met the primary endpoint of prolonging progression-free survival in the bevacizumab arm. The major benefit is obtained in sub-optimally de-bulked and advanced-stage patients.

Some new therapy candidates did not show encouraging clinical benefit for the treatment of gynecological cancers in two well conducted trials.

Patupilone (P), a microtubule-targeting agent, was studied in the largest phase III trial ever conducted in resistant/refractory ovarian cancer patients. This study by Colombo et al. compared P with pegylated liposomal doxorubicin (PLD) in patients with histologically confirmed epithelial ovarian, primary fallopian tube or primary peritoneal cancer who were refractory or resistant to first-line taxane- and platinum-based chemotherapy and who had fewer than 3 prior regimens and who had progressed while receiving or within 6 months after completion of the most recent platinum-containing regimen. The primary endpoint, OS was not met; there was no statistically significant difference in OS between the two arms with median OS 13.2 and 12.7 months, in P and PLD arms, respectively. Median progression-free survival was 3.7 months for both arms. There was a trend toward higher overall response rate (all partial responses) in the P (15.5%) arm compared to the PLD arm (7.9%); however, disease control rates were similar (59.5% vs. 56.3%). Patupilone was well tolerated and had an acceptable safety profile. (Colombo, abstract LBA24).

Practice point and future research opportunities

Patupilone demonstrated higher, although not significant, overall response rates compared with the active control, pegylated liposomal doxorubicin but this did not translate into improved OS or PFS.

Saracatinib is a potent inhibitor of Src which is associated with a poorer prognosis in patients with epithelial ovarian cancer. When saracatinib was added to carboplatin-paclitaxel chemotherapy, Poole at al. did not show improved activity in a phase II study.

Practice point and future research opportunities

Addition of saracatinib to standard chemotherapy did not improve efficacy in patients with epithelial ovarian cancer.

Head & Neck Cancer

Vermorken et al conducted the phase III SPECTRUM trial to determine the safety and efficacy of adding panitumumab (pmab) to cisplatin, in 657 patients with recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN). The primary endpoint of OS was not met; median OS was 11.1 and 9.0 months in pmab+cis and cis treated patients, respectively ($P = 0.14$). However, PFS and ORR were numerically improved; median PFS was 5.8 and 4.6 months in pmab+cis and cis, respectively ($P = 0.004$). The ORR was 36% and 25% with pmab+cis and cis, respectively. Adverse events were similar between groups but SAEs were higher with pmab and occurred in 48% and 43% of pmab and cis treated patients, respectively. The overall survival may have been confounded by additional treatment received by an equivalent percent of patients in both groups and also could have been affected by ethnic and geographic differences, which may reflect differences in treatment practice. (Vermorken, abstract LBA26)

Practice point and future research opportunities

Overall survival was not significantly improved by the addition of panitumumab to cisplatin in patients with R/M SCCHN but PFS and ORR were numerically improved. Panitumumab showed activity consistent with other EGFR antibodies.

Pemetrexed competitively inhibits three key enzymes, two of which are the targets of standard therapies, and therefore was tested as a therapy for head and neck cancer by Urba, et al. This phase III study compared pemetrexed in combination with cisplatin (PEM/CIS) and placebo plus cisplatin (CIS) in patients with recurrent or metastatic squamous cell head and neck cancer.

No significant difference in median OS, the study's primary endpoint, was observed. Median OS was 7.3 and 6.3 months in the PEM/CIS and CIS arms, respectively [P=0.082]. A similar trend was seen in PFS; 3.6 versus 2.8 months, (P=0.166) and the response rate of 12% versus 8%, P=0.061 with PEM/CIS and CIS treatment, respectively. Subgroup analyses showed longer OS and PFS in patients with ECOG PS 0 or 1 (n=690) who had OS and PFS of 8.4 versus 6.7 months (P=0.026) and 4.0 versus 3.0 months (P=0.044), with PEM/CIS and CIS respectively. Patients with oropharyngeal cancers treated with PEM/CIS had OS of 9.9 versus 6.1 months, (P=0.002) and PFS of 4.0 versus 3.4 months (P=0.047) compared with the CIS arm. The death rate following study discontinuation was similar between arms but the PEM/CIS arm showed higher drug-related serious adverse events. Quality of life (FACT-HandN) did not significantly differ from baseline in either arm. (Urba, abstract 10030).

Practice point and future research opportunities

The addition of pemetrexed to cisplatin did not result in significant survival benefit in the total patient population with recurrent or metastatic squamous cell head and neck cancer but did show significantly longer OS and PFS in patients with PS 0 or 1 and patients with oropharyngeal cancers and may be a treatment option for these subgroups.

The importance of Human papillomavirus (HPV) as a biomarker for response in oropharyngeal cancer (OPC) was investigated in by Posner et al in a subanalysis of data from the TAX 324 clinical trial. HPV is seen increasingly in OPC (HPVOPC) and has a distinct biology from environmental OPC (EROPC). This phase III study compared the response to treatment in patients with locally advanced head and neck cancer who received sequential therapy (ST). HPV16 was identified in untreated patients tissue samples and the patient response was evaluated according to HPVOPC (n=56) and EROPC (n=55) status. Median follow-up for the HPVOPC and EROPC groups was 83 and 82 months, respectively. Although the study's primary endpoint was not met, significant and durable response differences emerged; the one-year OS was significantly higher and durable in HPVOPC than EROPC patients, 79% versus 31% (P<.0001), and progression-free survival was similar; at follow-up 73% of HPVOPC and 29% EROPC P<.0001) patients had not progressed. Seven (13%) local-regional failures and 3 (5%) distant metastases occurred among HPVOPC patients compared to 23 (42%) and 6 (11%) for the EROPC group (P< .006). Five (9%) and 12 (22%) deaths from non-primary OPC cancer related causes were reported in the HPVOPC and EROPC groups, respectively (P=0.07) (Posner, abstract 10040).

Practice point and future research opportunities

The HPV in oropharyngeal cancer is a biomarker that predicts better survival, largely due to 3 fold fewer failures in local regional control than in patients with environmental disease which may warrant more aggressive sequential therapy and/or chemoradiotherapy.

Hematologic malignancies

Long-term follow-up of rituximab (R) plus infusional cyclophosphamide, doxorubicin, and etoposide (R-CDE) in treating patients with HIV related non-Hodgkin lymphoma (HIV-NHL) was reported by Spina et al. This phase II study showed that 52 of 74 patients (70%) achieved a complete remission (CR), 4 (5%) had a partial remission and disease progressed in 18 patients, following R-CDE treatment. At median follow-up of 61 months, only 17% of CRs have relapsed and 41 of 74 patients were alive. Of the 34 patients who died the cause of death was NHL in 25 patients. The overall survival, disease free survival and time to treatment failure at 77 months were 54%, 81% and 52%, respectively. Five incidents of secondary tumours occurred. No case of late pulmonary or cardiac toxicity has been reported. Prognostic factors associated with poorer survival on multi- and univariate analysis were the presence of Burkitt's disease (P=0.02), men who have sex with men (P=0.02), and detectable viral load (P=0.08) (Spina abstract number 11350).

Practice point and future research opportunities

Rituximab and CDE in HIV-NHL patients treated concomitantly with Highly Active Anti-Retroviral Therapy (HAART) is very active and durable and a high proportion of these patients can be cured of NHL without significant negative impact on the HIV treatment.

Melanoma

GSK2118436, a selective inhibitor of V600 mutant (mut) BRAF kinase showed hints of activity in patients with melanoma brain metastases (mets) in a phase 1/2 trial reported by Long et al.

Clinical benefit in patients with previously untreated asymptomatic brain mets were noted in a subset of patients in part 1 of the study, prompting further investigation (part 2) in an additional cohort of 10 patients with previously untreated asymptomatic brain mets ≥3mm; the first interim analysis showed 7 of these patients achieved reduction in brain mets, including 3 who showed complete radiographic resolution of brain lesions (bCR). An 80% response was seen in tumors larger than 3mm that correlated with reduced extra-cranial disease. Of the patients in part 1 with previously untreated brain mets at baseline, two demonstrated tumor reduction and 1 patient achieved bCR, three patients achieved PR and 2 patients progressed following response duration of 169 and 194 days, respectively. (Long, abstract LBA27).

Practice point and future research opportunities

A targeted agent for brain mets in V600 BRAF mut melanoma demonstrated response in brain mets that correlated with extra-cranial tumor response, supporting further study in patients with BRAF mut melanoma and brain mets.

A phase III trial of ipilimumab (MDX010-20) reported by O'Day et al. at ASCO 2010 demonstrated improved OS in patients with previously treated advanced melanoma. Lebbé reported at the ESMO Congress in Milan results of a subgroup analysis of this trial of OS in 676 previously treated patients with poor prognostic factors; 70% of patients had M1c disease and more than 36% had elevated LDH levels at baseline. Ipilimumab, alone or together with gp100 peptide vaccine, showed a statistically significant improvement in OS over gp100 (HR 0.68; HR 0.66, respectively) in the patient population with poor prognostic factors (Lebbé, abstract 13240).

Practice point and future research opportunities

Ipilimumab improved overall survival in previously treated, advanced melanoma patients with both good and poor prognostic factors.

Neuroendocrine tumors

Progression-free survival was increased by the addition of everolimus (E), an mTOR inhibitor, to octreotide LAR (O) in patients with advanced neuroendocrine tumors (NET). Pavel et al. reported results from a phase III trial of everolimus in 429 patients with advanced NET and a history of carcinoid symptoms.

Median PFS was 16.4 and 11.3 months, and median PFS by investigator review was 12.0 and 8.6 for E+O and P+O, respectively. Combination treatment was associated with a 23% reduction in risk of progression (P=0.026). Safety was consistent with that previously reported for everolimus (Pavel, abstract LBA8).

Practice point and future research opportunities

Treatment options for advanced neuroendocrine tumours are limited. Everolimus + octreotide LAR treatment showed a 5.1 month clinically meaningful increase in median PFS compared to placebo + octreotide LAR in patients with advanced neuroendocrine tumors.

Yao et al. reported results from RADIANT-3, a randomized, double-blind, placebo-controlled, multicenter phase III trial of everolimus in 410 patients with advanced pancreatic neuroendocrine tumors (PNET). The primary endpoint of PFS was met; everolimus plus best supportive care was associated with a greater than 6 month or 2.4 fold increase in median PFS (11.0 versus 4.6) months compared to placebo plus best supportive care (P<0.0001) and a 65% reduction in the risk of progression. Eighteen-month PFS estimates indicated prolonged benefit and were 34% for everolimus and 9% for placebo, consistent with median PFS by adjudicated central assessment for everolimus 11.4 and 5.4 for placebo (P<0.001]. At progression, patients were unblinded and those randomized to placebo were offered open-label everolimus. Drug-related adverse events were higher in the everolimus arm but the safety profile was acceptable and consistent with the known toxicity profile of everolimus in cancer patients (Yao, abstract LBA8).

Practice point and future research opportunities

Results of this study are clinically meaningful achievement in patients with neuroendocrine tumors. Everolimus significantly prolonged PFS and provides a new treatment option for patients with pNET.

Sarcoma

Juergens et al. reported results of a phase 1/ 2 study conducted to determine the safety and efficacy of figitumumab, a monoclonal antibody against the insulin-like growth factor-I receptor (IGF-IR) in patients with refractory Ewing sarcoma and other sarcomas. In a phase 1, dose escalation proceeded to the Maximum Feasible Dose of 30 mg/Kg q28d with no Dose Limiting Toxicity (DLT) identified in 31 patients.

Potential efficacy was demonstrated in phase 2 in 107 patients; median PFS and OS were 1.9 and 8.9 months, respectively and patients with pre-treatment circulating IGF-I>110 ng/ml experienced median OS of 10.5 months compared to patients with baseline IGF-I<110 who had a median OS of 4.5 months. Of 106 currently available phase 2 patients, 15 had a partial response and 25 had stable disease (RECIST). Figitumumab was well tolerated; one grade 4 event (decreased appetite) and 11 grade 3 events attributed to figitumumab were reported (Juergens, abstract 13440).

Practice point and future research opportunities

Figitumumab was potentially efficacious in patients with refractory Ewing's and other sarcomas and a potential correlation between high pre-treatment IGIF-I ligand levels and survival benefit was identified.

Supportive/Palliative Care

Intriguing results were reported by Bastian et al from the first trial assessing the efficacy and safety of balloon kyphoplasty (BKP) in 70 of 134 cancer patients with painful vertebral compression fractures (VCFs). BKP-treated patients experienced a reduction of back pain by 3.8 points as early as one week ($P<0.0001$) compared with non-surgical methods (NSM) patients who had no significant change (NSC). The primary endpoint evaluation at one month showed significant improvement by Roland-Morris Disability questionnaire for BKP-treated patients of –8.3 points compared to no NSC in the NSM group ($P<0.0001$) and cross-over to BKP was allowed for NSM patients. BKP patients reported fewer days of back pain-related limited activity (6.3 fewer days, treatment effect $P<0.0001$) and greater improvements in QOL measured by the SF-36 PCS score (treatment effect 8.4 points higher; $P<0.0001$). The 38 NSM patients who crossed over were included in the safety and efficacy analysis and showed similar benefits. Results in all BKP patients were durable through the 12 month follow-up. Adverse events were infrequent but similar between groups. One serious AE of aesthesia related myocardial infarction, one patient with cement leakage to the disc had an adjacent fracture 1 day post-surgery and one soft tissue hematoma were reported (Bastian, abstract 11810).

Practice point and future research opportunities

Balloon kyphoplasty tested in this first international, randomized trial, shows as a safe, minimally invasive procedure that significantly decreased back pain and improved quality of life in cancer patients with painful and debilitating vertebral compression fractures, demonstrating superiority to non-surgical pain management and warrants further investigation, especially within blind study design.

A trial conducted by Kurokawa et al. provided informative data on intraoperative antimicrobial prophylaxis (AMP) for the prevention of surgical-site infections. This randomized controlled trial involved 385 patients with gastric cancer which was resectable by distal gastrectomy who received either intraoperative AMP (cefazolin 1g, at <30min before incision, every 3 hours intraoperative supplements) or an extended AMP group (intraoperative AMP plus cefazolin 1g, once after closure and twice daily for 2 postoperative days) to determine the incidence of surgical site infection (SSI). The median operation time and the median blood loss in all patients were 204 minutes and 200 mL, respectively. Non-inferiority of intraoperative AMP compared to extended AMP was demonstrated with statistical significance (P <0.001); incidence of SSI was 4.5% and 8.9% in the intraoperative AMP and extended AMP groups, respectively. The risk ratios for SSI, remote site infection and fever (≥Gr. 1) in the extended AMP group were 1.97, 0.65 and 0.85, respectively (Kurokawa, abstract 1235O).

Practice point and future research opportunities

Extended antimicrobial prophylaxis showed no additional clinical benefit over intraoperative and therefore is not recommended for gastric cancer patients who receive distal gastrectomy.

Fentanyl pectin nasal spray (FPNS) provided superior pain relief from breakthrough cancer pain (BTCP) in 522 patients who participated in 3 separate trials compared with placebo or oral morphine. Torres, et al reported results from a phase 3 clinical trial for FPNS wherein a broad range of patient types was successfully titrated to the following dosages: 100 µg (17.7%), 200 µg (21.8%), 400 µg (32.0%) and 800 µg (28.5%); just 8.0%of patients were unable to titrate for FPNS-related reasons. Successful dose titration was not affected by patient age or weight but males displayed a slight trend to tolerate higher doses. Treatment-related AEs were consistent with the pharmacological effects of fentanyl and were not dose dependent (Torres, abstract 1239PD).

Practice point and future research opportunities

Controlled studies with fentanyl pectin nasal spray demonstrate a rapid onset of effect and greater clinically meaningful pain relief compared to placebo and oral morphine. Potential advantages of nasal route are rapid absorption, no first pass metabolism, avoiding problem in mouth and swallowing. A new technology allows low volume, fine mist, and consistent particle size delivery and therefore controlled dosing.

Resources from the ESMO 2010 Congress are now online at the ESMO website (www.esmo.org), including the Abstract Book complete with late breaking abstracts, the Congress Webcast Library, Congress Online Posters, daily Press Conferences with Press Releases and the Educational Book. The Congress Webcast Library contains audio and visual presentations of selected research and thought-provoking commentary by invited speakers.

Be sure to save the following dates in your calendar for the:
ECCO16–ESMO36-ESTRO30 European Multidisciplinary Cancer Congress in Stockholm, Sweden (23-27 September, 2011).
and the 37th ESMO Congress in Vienna, Austria (28 September-2 October 2012).

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