VOLUME 23 2004

ANNUAL MEETING PROCEEDINGS

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

40th Annual Meeting

June 5–8, 2004
Ernest N. Morial Convention Center
New Orleans, LA

ASCO®

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The *American Society of Clinical Oncology Annual Meeting Proceedings* (ISBN 1-932312-10-2) is published by the American Society of Clinical Oncology.

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Abstract management and indexing provided by Database Publishing Group, Inc., Cambridge, MA. Composition services and print production provided by Cadmus Professional Services, Linthicum, MD.

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Annual Meeting of the American Society of Clinical Oncology

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Annual Meeting Proceedings

American Society of Clinical Oncology
40th Annual Meeting

2004 Abstracts

Abstract Session Descriptions for Scheduled Presentations

Oral Abstract Presentation Sessions

Oral Abstract Presentation Sessions include didactic presentations of the abstracts determined by the Scientific Program Committee to be of the highest scientific merit. Experts in the field serve as Discussants to place the findings into perspective. The Plenary Session includes the abstracts selected by the Scientific Program Committee as having practice-changing findings.

Integrated Education Sessions

Integrated Education Sessions provide a forum for translational science in oncology, combining the presentation of selected abstracts on a specific topic with didactic lectures. Experts in the field place the studies in the appropriate context based on the strength of the evidence and critically discuss the conclusions in terms of their applicability to clinical practice.

Poster Discussion Sessions

Poster Discussion Sessions highlight selected abstracts of clinical research in poster format. The poster are grouped by topic or by the questions posed as a result of the research findings. The posters are on display for a specific time, followed by a discussion session in which experts provide commentary on the research findings.

General Poster Sessions

General Poster Sessions include selected abstracts of clinical research in poster format. The posters are grouped by topic and are on display for a specified time.

This publication contains abstracts selected by the ASCO Scientific Program Committee for presentation at the 2004 Annual Meeting and for publication. The type of session, the day, and the session start/end times are located to the right of the abstract number for scheduled presentations. To determine the location of the abstract session, refer to the Pocket Program or ASCO.org.

Dates and times are subject to change.

All modifications will be posted on *ASCO.org* (www.asco.org).

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ABSTRACTS

The American Society of Clinical Oncology
40th Annual Meeting
New Orleans, Louisiana

1 **Plenary Presentation, Mon, 1:00 PM - 4:00 PM**

HMG CoA reductase inhibitors and the risk of colorectal cancer. *J. N. Poynter, G. Rennert, J. D. Bonner, H. S. Rennert, J. K. Greenson, S. B. Gruber; University of Michigan, Ann Arbor, MI; CHS National Cancer Control Center, Haifa, Israel*

Background: 3-hydroxy-2-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors are effective lipid-lowering agents that also inhibit the growth of colon cancer cell lines and were noted to be associated with a reduced risk of colorectal cancer (CRC) in a randomized clinical trial of patients with myocardial infarction. We investigated the association between HMG CoA reductase inhibitors and CRC in a population-based case-control study of incident CRC. **Methods**: The Molecular Epidemiology of Colorectal Cancer Study (MECC) is a study of 1608 CRC cases diagnosed in northern Israel between 1998 and 2002, and 1734 population-based controls matched for age, gender, and ethnicity. Subjects participated in an interview which assessed personal and family history of cancer, screening practices, other medical conditions, medication use, physical activity, and nutritional data including a food frequency questionnaire. Diagnosis of colorectal cancer was confirmed by standardized pathology review. Use of HMG CoA reductase inhibitors was measured by self report as a dichotomous variable with a minimum duration of five years of use. **Results**: Use of HMG CoA reductase inhibitors was reported by 267/3342 subjects in the MECC study (7.99%). The unadjusted odds ratio for use of any HMG CoA reductase inhibitor had a significantly protective effect with an odds ratio of 0.46 (95% CI 0.35–0.60). This association remained unchanged (OR 0.49, 95% CI 0.36–0.68) after adjustment for age, hypercholesterolemia, ethnicity, aspirin or NSAID use, and the low penetrance susceptibility allele, *APC* I1307K. To assess whether the association was the result of a non-specific cholesterol lowering effect, we also looked at other cholesterol-lowering drugs and found no significant association between bezafibrate and CRC (OR 1.08, 95% CI 0.56–2.08). **Conclusions**: HMG CoA reductase inhibitors are associated with a 51% reduction in the risk of colorectal cancer, and the protective effect is specific to this class of lipid-lowering agents. The significant protective effect of HMG CoA reductase inhibitors in CRC indicates that these drugs deserve further investigation in chemoprevention and therapeutic clinical trials.

2 **Plenary Presentation, Mon, 1:00 PM - 4:00 PM**

Concomitant and adjuvant temozolomide (TMZ) and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM). Conclusive results of a randomized phase III trial by the EORTC Brain & RT Groups and NCIC Clinical Trials Group. *R. Stupp, W. P. Mason, M. J. Van Den Bent, M. Weller, B. Fisher, M. Taphoorn, A. A. Brandes, G. Cairncross, D. Lacombe, R. O. Mirimanoff; University Hospital (CHUV), Lausanne, Switzerland; Princess Margaret Hospital, Toronto, ON, Canada; University Hospital/Rotterdam Cancer Center, Rotterdam, Netherlands; University of Tübingen Medical School, Tübingen, Germany; University of Western Ontario, London, ON, Canada; University Medical Center, Utrecht, Netherlands; Azienda Ospedale-Università, Ospedale Busonera, Padova, Italy; University of Calgary, Calgary, AB, Canada; EORTC Data Center, Brussels, Belgium*

Background: Standard therapy of GBM after biopsy or resection is RT. TMZ, a novel methylating agent demonstrated some activity against recurrent glioma. In a phase II trial we observed a potential survival advantage by adding TMZ concomitantly and adjuvant to RT (Stupp et al. JCO 2002). In this randomized trial we tested this novel regimen against RT. **Methods:** Patients (pts) age 18–70 years with histologically proven newly diagnosed GBM (WHO grade IV) were eligible. Pts were randomized between standard RT (60 Gy in 30 daily fractions of 2 Gy) versus the same RT and concomitant (TMZ 75 mg/m2/d, daily up to 42 days) followed by up to 6 cycles of adjuvant TMZ (150–200 mg/m2, daily x 5d, q28 d). Survival (intent to treat) was the primary endpoint aiming at a 30% improvement (log-rank). Pathology was centrally reviewed. **Results:** Five hundred and seventy-three pts from 85 centers were randomized. Median follow-up is 2 years, 436 patients have died. Median time between histological diagnosis and treatment start was 5 weeks. RT was delivered as prescribed in 93% of pts. Concomitant TMZ was administered without interruption in 76%, temporarily interrupted in 11% and prematurely discontinued in 12%. Adjuvant TMZ was given to 76% of pts, 36% completed all 6 cycles for a total of 924 cycles. The increase in median survival is 3 months. The log-rank test is significant with a p-value of < .0001. The hazard ratio is 0.62 (95% c.i. 0.51–0.75). Grade 3/4 hematotoxicity was observed in 7% of pts during concomitant TMZ/RT treatment, and in 16% (5.2% of cycles) of the adjuvant TMZ. Patients continue to be followed to evaluate long term effects of treatment. **Conclusions:** Concomitant and adjuvant TMZ chemotherapy significantly improves PFS and overall survival in GBM pts. This treatment is safe and well tolerated.

	RT (n=286)	RT/TMZ (n=287)	p-value
Age, median (range) [years]	56.6 (23.1-70.8)	55.7 (19-70.5)	NS
Tumor resection	70%	68%	NS
WHO PS : 0 / 1 / 2	39% / 49% / 12%	39% / 48% / 13%	NS
Steroids at baseline	75%	67%	p=0.041
Progr.-free surv. (95% c.i.)	5.0 mo (4.2-5.5)	7.2 mo (5.8-8.3)	p< .0001
Median survival (95% c.i.)	12 mo (11.2-13.2)	15 mo (13.6-16.8)	p< .0001
2-year survival (95% c.i.)	8% (4-12%)	26% (20-32%)	p< .0001

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Clinical outcome of germ cell cancer patients (pts) treated with high-dose chemotherapy with stem cell support (HDC) – a single center experience. *E. G. Dos Santos, F. Leal-Da-costa, N. Miranda, A. Machado, A. Guimaraes, I. Ferreira, M. Abecasis, J. L. Passos-Coelho; Bone Marrow Transplantation Unit, IPOFG, CROL, SA, Lisbon, Portugal*

Background: Pts with International Germ Cell Cancer Collaborative Group (IGCCCG) "poor prognosis" disease achieve only a 41% 5-year progression-free survival (PFS) with standard chemotherapy. Pts who do not achieve a complete remission with BEP chemotherapy or who relapse after such treatment have a still worse prognosis. The clinical impact of HDC in such pts is still unclear. **Methods:** Pts with germ cell cancer with IGCCCCG "poor prognosis" disease at diagnosis (or, earlier, with Indiana group C) or with recurrent or refractory (i.e., less than marker negative partial remission) disease after initial BEP chemotherapy were eligible for HDC. **Results:** Between June 1996 and April 2003, 18 pts underwent one (13 pts) or two (5 pts) cycles of HDC with ICE (ifosfamide 10g/m2, carboplatin 1,500mg/m2 and etoposide 2,400mg/m2); 17 pts), or etoposide (1500mg/m2) plus thiotepa (900 mg/m2); 1 pt), in 6 pts as consolidation after BEP and in 12 pts for recurrent disease (7 pts) or refractoriness to BEP (5 pts). In the consolidation group (6 pts), with a median follow-up of 42 months (range 10–72 months), there are no events. Thus the PFS and overall survival (OS) at 3.5 years is 100%. In contrast, with a median follow-up of 18 months, the median PFS and OS for pts with recurrent or refractory disease subgroup are 4 months (0–40+) and 18 months (4–40+), respectively. In this subgroup, 10 pts relapsed by 8 months post-HDC and only 2 are progression-free at 20 and 40 months. **Conclusions:** Despite the small number of pts and short follow-up, these results compare at least as favorably to the outcome obtained with standard chemotherapy in pts with "poor prognosis" at diagnosis. In contrast the outcome of pts with recurrent or refractory disease after initial BEP chemotherapy are not better than those obtained with standard salvage chemotherapy.

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Effect of atrasentan (ABT-627, ATN) on the pharmacokinetics (PK) of midazolam (MDZ). *J. Z. Peng, T. Doan, D. Burt, D. Baran, T. Yanke, P. Wang, N. McCracken, G. Roske, R. A. Carr, A. Allen; Abbott Laboratories, Abbott Park, IL*

Background: ATN is an oral selective endothelin A receptor antagonist, currently in phase 3 clinical development for the treatment of hormone-refractory prostate cancer. In humans, extensive ATN metabolizm is equally distributed between oxidation (CYP3A) and glucuronidation. *In vitro*, ATN inhibits CYP3A with an IC_{50} of ~3 μM (15-fold the mean plasma C_{max} for 10 mg/d ATN). The sedative MDZ is extensively metabolized by CYP3A in both gut and liver. MDZ plasma concentrations are sensitive to CYP3A inhibition; MDZ is an FDA-recommended probe CYP3A4 substrate. **Methods:** To assess the effect of ATN on MDZ PK, a phase 1 double-blind, randomized, two-period crossover study was conducted in 16 healthy subjects (13 M and 3 F; mean±SD 41±11 yrs, 78±13 kg). Subjects received ATN 10 mg or placebo PO QD from Day 1 through 7; in both regimens MDZ was given on Day 4 (1 mg IV) and Day 6 (5 mg PO). Blood samples for MDZ assay were collected predose and over 48 h after each MDZ dose. Plasma concentrations of MDZ were determined using a validated LC/MS/MS method. **Results:** MDZ PK are summarized (mean±SD; N=15) in the following table. MDZ C_{max} and AUC were bioequivalent (+/-ATN). One subject withdrew from the study after the first period (MDZ alone), and was excluded from the PK analyses. Both regimens were well tolerated. Sleepiness and headache were the most common AEs, and all AEs were mild. **Conclusions:** ATN had no effect on MDZ PK, indicating 10 mg QD ATN does not alter CYP3A4 activity in gut or liver. Therefore, PK interactions would not be expected between ATN and drugs metabolized by CYP3A4.

MDZ Regimen	Parameter	MDZ Alone	MDZ + ATN
1 mg IV	AUC_∞ (ng•h/mL)	38±9	37±9
"	$T_{1/2}$ (h)	2.7±0.9	2.7±1.2
5 mg PO	C_{max} (ng/mL)	21±7	23±6
"	T_{max} (h)	0.7±0.4	0.6±0.1*
"	AUC_∞ (ng•h/mL)	57±24	64±28
"	$T_{1/2}$ (h)	3.1±1.4	2.9±1.3

* Different from MDZ Alone (ANOVA, p<0.05).

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Phase I trial of intramuscular estradiol valerate (I/M-E) in hormone refractory prostate cancer. *M. Kohli, M. A. Alikhan, H. J. Spencer, G. Carter; Central Arkansas Veterans Healthcare System and University of Arkansas for Medical Sciences, Little Rock, AR; University of Arkansas for Medical Sciences, Little Rock, AR; Central Arkansas Veterans Healthcare System, Little Rock, AR*

Introduction. We evaluated the safety of I/M-E depots administered every two weeks, in hormone refractory prostate cancer patients receiving chemotherapy. Due to high incidence of thrombo-embolic (TE) events associated with oral estrogens, sensitive markers of coagulation activation were monitored during I/M-E treatments to guide initiation of anticoagulant prophylaxis. The primary goal was to establish maximal tolerated dose (MTD) using 3 I/M-E doses (10mg, 20mg and 40 mg). **Methods:** Patients with no history of TE events were enrolled after consenting and screening for thrombosis. Treatment was delivered in cohorts of three, at the 3 dose levels. Three doses of I/M-E depots were given every two weeks. Prior to each dose, markers of coagulation activation were measured. These included thrombin anti-thrombin complex (TAT; reference range:1.0–4.1μ/l) and quantitative DDimers (QDD; range:0–250ng/ml). Patients with levels above reference ranges were also given daily prophylaxis with 60mg of LMWH. Dose limiting toxicity was defined as two consecutive dosing periods during which TAT/QDD levels remained elevated despite LMWH prophylaxis. **Results:** 9 patients have completed study on three dose levels (3 each). Study treatment durations varied between 6 and 8 weeks for each patient. All patients received variable duration of prophylaxis with LMWH due to increase in baseline TAT/QDD levels after receiving study drug. No study related TE/hemorrhagic event is seen. Grade 2 toxicities include gynacomastia (1/9), fluid retention (4/9) and local bruises at LMWH injection site (4/9). Anti-Xa activity in patients receiving prophylactic LMWH varied between 0.0–0.4U/ml. **Conclusions:** MTD is reached at 40mg of I/M-E with prophylactic LMWH in this patient population and is found safe and well tolerated. Where-as oral estramustine and estrogens share a high incidence of TE events, IM-E/LMWH combination appears a safe alternative in advanced prostate cancer. Efficacy trials will be conducted of this combination in prostate cancer patients on chemotherapy. Potential anti cancer effects of LMWH in advanced prostate cancer will also be explored in these future trials.

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Effect of ketoconazole (KET) on the pharmacokinetics (PK) of atrasentan (ABT-627, ATN). *T. Zhu, A. Andre, I. Facey, W. Chiu, P. Wang, N. McCracken, D. A. Katz, R. A. Carr, T. Doan, A. Allen; Abbott Laboratories, Abbott Park, IL*

Background: ATN is an oral selective endothelin A receptor antagonist, currently in phase 3 clinical development for the treatment of hormone-refractory prostate cancer. In humans, extensive ATN metabolism is equally distributed between oxidation and glucuronidation. *In vitro*, CYP3A was the predominant isozyme involved in oxidative metabolism. The antifungal KET is a potent and selective CYP3A inhibitor, and is a probe of choice to determine the maximal inhibitory effect against a CYP3A-metabolized drug. **Methods:** To assess the effect of KET on ATN PK, a phase 1 open label study was conducted in 12 healthy subjects (11 M and 1 F; mean±SD 35±9 yrs, 80±8 kg). Subjects received ATN 10 mg PO on Days 1 and 8, and KET 200 mg PO BID from Day 4 through 10. Blood samples for ATN assay were collected predose and over 72 h after each ATN dose. Plasma concentrations of ATN were determined using a validated LC/MS/MS method. **Results:** ATN PK data are summarized (mean±SD; N=12) in the following table. ATN $t_{1/2}$ increased most in the 2 subjects heterozygous for a low activity variant of *UGT2B4*; changes in ATN $t_{1/2}$ and AUC did not significantly vary by *UGT1A1, UGT2B15, CYP3A5, ABCB1, SLC21A6* or *SLC22A2* genotype. ATN with KET was generally well tolerated. The most common AE possibly related to study drug was headache. All AEs were mild. **Conclusions:** KET inhibited the systemic clearance of ATN but had little effect on ATN bioavailability. Predicted steady-state ATN concentrations in the presence of KET are within the range previously shown to be well-tolerated in cancer patients. These results suggest ATN can be safely co-administered with KET, a potent inhibitor of CYP3A and Pgp.

	ATN Alone	ATN + KET
C_{max} (ng/mL)	84±25	78±27
T_{max} (h)	0.5±0.1	0.6±0.2
AUC_∞ (ng•h/mL)	417±83	812±238*
$T_{1/2}$ (h)	18±4	31±7*

* Different from ATN Alone (ANOVA, p<0.05)