

Supplement to

Clinical
Cancer
Research

3-DEC 1999 B000
CLINICAL CANCER RESEARCH

LS23 75W
*ETOC



3286.264750

VOL 5 PART 11 SUPP 1

AC⁴⁰

JCP⁸⁶⁶

1/1

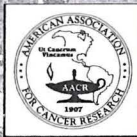
265EPO2
2001119

AACR-NCI-EORTC International Conference

Molecular Targets and Cancer Therapeutics

Discovery, Development, and Clinical Validation

November 16-19, 1999 • Washington Hilton and Towers • Washington, DC



American
Association
for Cancer
Research



November 1999 • Volume 5 • Supplement
PP. 3729s-3897s • ISSN 1078-0432

BRITISH LIBRARY
DOCUMENT SUPPLY CENTRE

-8 DEC 1999
CONFERENCE
INDEXED

**DOCKET
ALARM**

Find authenticated court documents without watermarks at docketalarm.com.

A

- Aapro, M., 215
 Abbensetts, K., 473
 Abbruzzese, J., 224, 290, 341, 414
 Abbruzzese, J. L., 225, 300, 336, 380, 412
 Abdalla, M., 163, 473
 Abdel-Meguid, S. S., 382
 Abel, K. L., 510
 Aboagye, E., 491, p. 3871s
 Abo deeb, A., 72, 163
 Aboody, K. S., 460
 Abradelo, C., 620
 Abrahamsen, N., 510
 Abrahamson, J., 209
 Abrams, R., p. 3876s
 Achilles, E. G., 196, 415
 Achterrath, W., 346, 649
 Acinapura, A. J., 72, 163, 473
 Adams, A., 619
 Adams, J., 6, 184, 204, 290, 414
 Adcock, I., 239
 Adelaide, J., 32
 Adema, G. J., 377
 Adjei, A. A., p. 3873s
 Advani, R., 580
 Afar, D. E. H., 154, 156
 Agarwal, V., 340
 Agha-Mohammadi, S., 503
 Agrawal, S., 584
 Agus, D. B., 41
 Aherne, G. W., 572, 659
 Ahmad, R., 692
 Ahmed, A., 694
 Ailey, B., p. 3869s
 Aingorn, E., 49
 Akinaga, S., 119, 291
 Akiyama, S., 526
 Akiyama, T., 119
 Aktas, H., 174, 175
 Akusjarvi, G., 366
 Al-Awar, R., 127
 Albaek, C., 510
 Albers, A., 150
 Albertioni, F., 431
 Alberts, D., 22
 Alberts, S., 340
 Albertson, H. M., 243
 Alexander, W. A., 94
 Alexandre, J., 7
 Alford, T.L., 664
 Algazy, K., 338, 345, 579
 Algenstaedt, P., 196
 Alghazi, Y., 694
 Ali, S., 239
 Ali-Osman, F., 555
 Alisaukas, R., 454
 Allen, D., 64
 Allen, M., 694
 Alli, E., 685
 Allis, D. C., 238
 Allred, E. N., 415
 Allsbrook, W. C., 19
 Almiroudis, D., 428
 Alnemri, E., 260
 Alonso, G., 165
 Alonso, S., 313
 Alrawi, S. J., 72, 163, 473
 Altomonte, V., 24
 Alvarez, E., 657
 Alvarez-Salas, L. M., 587
 Amado, R., 13
 An, G. W., 291
 Anasagasti, M. J., 65
 Anderson, M., 191
 Andion, C., 165
 Andreassi, J. L., 178
 Angers, E., 530
 Angevin, E., 7
 Anthoney, A., 307, 313
 Anthony, L., 212, 213
 Anthony, N. J., p. 3869s
 Antolin, S., 165
 Anton, L., 165
 Antonian, L., 410
 Aoki, K., 592
 Appia, F., 10
 Aracil, C., 474
 Arafat, W. O., 419
 Arakawa, F., 506
 Arany, I., 386
 Arasteh, K., 12
 Ardila-Osorio, H., 276
 Arencibia, I., 442
 Argnani, A., 678
 Ariel, I., 407
 Armand, J. P., 7
 Armand, J-P., 348
 Armould, S., 599
 Arrastia, C. D., 386
 Arris, C. E., 124
 Artemov, D., 397
 Asao, T., 262, 563
 Ashktorab, H., 694
 Asim, M., 692
 Asimakis, M., 115
 Atkas, H., 173
 Aubert, C., 578
 Augenlicht, L., 211
 Aulitzky, W. E., 378
 Avallone, A., 218, 226, 447
 Averbuch, S., 29, 99, 554
 Avila, J., 314
 Awada, A., 20, 513
 Ayers, D., 325
 Aylesworth, C., 332
 Ayres, M., 538
 Azimahlol Hawariah, L. P., 679
 Azuma, I., 158
 Azure, M. T., 199, 200
 Azzabi, A. S. T., 333
- ## B
- Baba, M., 494
 Baccini, C., 384
 Back, T. C., 379, 381
 Baddeley, H., 14
 Badae, I., 272
 Baggs, R., 199, 200
 Baguley, B. C., 396, 675
 Bai, R., 630, 643
 Baichwal, V., 635, 637, 651
 Bailey, H. H., 39
 Baker, C., 351
 Baker, S., 1, 332
 Baker, S. D., 319
 Bakke, S., 553
 Balana, C., 330
 Balcerzak, S. P., 223, 553
 Balestrazzi, E., 402
 Banerjee, D., 534
 Baohua, H., 464
 Baranov, E., 59
 Barazzuol, J., 122
 Barbarino, M., 118
 Bardelli, A., 36
 Barer, F., 357
 Barkhimer, D., 12
 Barlow, H. C., 564
 Barnadas, A., 214
 Barnard, D., 362
 Barret, J-M., 322, 674
 Bartsevich, V. V., 251
 Bar-Yehuda, S., 357
 Basanez, G., 429
 Basart, D., 539, 552
 Basas, J., 478
 Baselga, J., 29
 Bash-Babula, J., 685
 Basilico, C., 36
 Bassano, L., 312
 Basser, R., 10
 Bassetto, M. A., 222
 Bastow, K. F., 671
 Bates, S., 641
 Bates, S. E., 553
 Batey, M. A., 543
 Batist, G., 221, 530, 554
 Baumgart, J., 551
 Baumgarten, J., 666
 Bavetsias, V., 565, 566
 Baynes, R. D., 349
 Bealieu, B. B., 343
 Beauchamp, R. D., 21
 Bechtel, P. E., 687
 Beck, J., 378
 Beckebaum, S., 149
 Becker, K-F., 87
 Becker, M., 69
 Beckmann, H., 635, 637, 651
 Bedi, A., 397
 Beer, T., 531
 Beerheide, W., 294
 Begleiter, A., 259
 Begley, M., 114
 Beijnen, J. H., 307, 308
 Bekesi, J. G., 281, 627, 628
 Belanger, K., 1
 Belcourt, M. F., 458, 459
 Bell, P., 233
 Bellizzi, A., 356
 Bellomy, K., 544
 Bender, J., 553
 Bennett, R. J., 607
 Ben-Porath, I., 371
 Bentzen, C., 22
 Bentzen, C. L., 62, 186
 Benvenisty, N., 371
 Ben-Yosef, T., 371
 Benyumov, A., 270
 Benz, C. C., 26, 92
 Bera, T., p. 3869s
 Berg, W., 465
 Bergeron, R. J., 467
 Berlin, J., 614
 Bermudes, D., 459, 501
 Bernard, H-U., 294
 Bernardi, R. J., 37
 Bernareggi, A., 329, 333, 613
 Bernhard, E. J., 193
 Berry, S., 194
 Bertino, J. R., 305, 534, 654
 Bessette, P., 530
 Bevan, P., 512
 Bevers, S., 618
 Bewley, J. R., 657
 Bhalla, K., 76
 Bharaj, B., 481
 Bhaskaran, V., 480
 Bhat, A. S., 321, 632
 Bhujwalla, Z. M., 397
 Biachwal, V., 652
 Bianco, A. R., 28, 584
 Bianco, R., 28, 584
 Bibby, M. C., 470
 Biedrzycki, B., p. 3876s
 Bigg, D. C. H., 665
 Biglietto, M., 218
 Binderup, L., 267
 Bingcang, A. L., 560
 Bimbaum, D., 32
 Biroccio, A., 280
 Bishop, C., 39
 Bishop, W., 77
 Bittencourt, M., 50
 Black, M. H., 482, 484
 Black, P. M., 460
 Blackledge, G., 554
 Bladou, F., 45
 Blagosklonny, M., 134
 Blagosklonny, M. V., 359, 641
 Blair, I. A., 345
 Blake, R., 410, 411
 Blanke, C. D., 21
 Blasi, M. A., 402
 Blask, D. E., 146
 Bleiberg, H., 20, 513
 Blumenthal, R. D., 147, 390, 408, 432, 454, 456
 Boadu, E., 475
 Bodey, B., 74
 Bodey, B. Jr., 74
 Boeing, A., 21, 614
 Boerner, S., 615
 Boise, L., 647
 Bol, K., 513
 Bold, G., 256

#5 Phase I clinical and pharmacokinetic (PK) trial of E7070, a novel sulphonamide, administered daily × 5 every 3 weeks in patients with solid tumors. Fumoleau, P., Punt, C.J.A., Priou, F., de Mulder, P.H.M., Bourcier, C., Van de Walle, B., Wanders, J., Faber, M.N., Hanauske, A.R., Ravic, M., Finnegan, V., from *EORTC/ECSCG, NDDO Oncology and EISAI Ltd-London, UK.*

Introduction: E7070 is a new chloroindolyl sulfonamide inhibiting the activation of cdk2 and cyclin E in cancer cells at concentrations ranging from 1.4–131.4 µg/ml *in vitro* and inducing cell cycle arrest in G1 and apoptosis. E7070 showed an original cytotoxicity profile suggesting a unique mechanism of action using the NCI-COMPARE program. **Study design:** E7070 was given as a 1 h. i.v. infusion (IV) on 5 consecutive days (d), repeated every 3 weeks. The total E7070 dose was escalated from 50 to 1000 mg/m²/course through 7 dose levels using a standard Phase I design (3–6 pts cohort). PK study was performed during the 1st course (cr). Patient characteristics: to date, 25 patients with miscellaneous solid tumors: 17 females/8 males, median age (yrs): 53 (27–69), median PS: 1 (0–2). **Study results:** data is summarized for 25 pts and 69 crs (1–6).

Dose-Level	No. of pts	No. of crs	DLT's
10 mg/m ² × 5	6	17	1/6 -atrial fibrillation at 2nd course
13 mg/m ² × 5	3	6	0/3
26 mg/m ² × 5	3	6	0/3
52 mg/m ² × 5	3	14	0/3
104 mg/m ² × 5	3	7	0/3
200 mg/m ² × 5 (MTD)	3	9	2/3 -febrile neutropenia, -gd 4 neutropenia & thrombocytopenia
160 mg/m ² × 5 (currently explored)	4	10	1/4 -gd 4 neutropenia & thrombocytopenia & gd 4 mucositis

Preliminary PK results indicate that E7070 displays a long half-life T_{1/2} and a large volume of distribution. At dose-levels above 52 × 5 mg/m² C_{max} increases proportionally while AUC increases more than dose-proportional and the clearance & V_{d,ss} tend to decrease suggesting a non linearity in the PK's. So far, no response is reported.

#6 Phase I study of PS-341, a novel proteasome inhibitor, in patients with advanced malignancies. Papandreou Christos N, Pagliaro Lance, Millikan Randall, Daliani Danai, Herrmann John, Hong Yang, Smith Mathew, Adams Julian, Elliott Peter, Lightcap Eric, McCormack Teresa, Pien Chris, Newman Robert, Logothetis Christopher J. *Department of Genitourinary Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030 and Leukosite, Inc., Boston, MA 02139*

The ubiquitin-proteasome pathway plays an important role in neoplastic growth and metastasis through regulation of cell-cycle regulatory proteins (p53, p21^{waf1}, and p27^{Kip1}). In addition, it regulates the activation of the nuclear factor NF-κB, a key transcriptional regulator of cell adhesion molecules {E-Selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)}, which are involved in tumor metastasis and angiogenesis *in vivo*. We are currently conducting a Phase I trial with PS-341, a proteasome inhibitor, in patients with advanced malignancies. **Objectives:** 1) Define maximum tolerated dose and dose limiting toxicity of PS-341 as an intravenous (i.v.) push administration over a range of doses (0.13–0.75 mg/m²) in patients with advanced malignancies. 2) Correlate toxicity with proteasome inhibition in peripheral blood.

Methods: To date, 12 patients (9: androgen-independent prostate cancer, 2: metastatic renal cell carcinoma, 1: metastatic colon cancer) have been treated (4 at: 0.13 mg/m² and 2 each at: 0.25, 0.4, 0.6, 0.75 mg/m²) with i.v. PS-341 weekly for 4 weeks in a 6-week cycle. Dose escalation is defined by the continuous reassessment method. Proteasome activity in patients' peripheral blood is measured ex-vivo using fluorogenic peptide substrates.

Results: All patients completed at least one cycle of treatment. Four of 12 patients received 2 or more cycles of PS-341. No toxicity has been observed so far. One patient achieved partial response (major radiographic response of retroperitoneal lymph nodes (RPLN) without PSA change) and a second patient had radiographic stabilization of RPLN with unchanged PSA. A 55–60% proteasome inhibition in peripheral blood has been achieved at the current dose level (0.75 mg/m²). **Conclusion:** 1) Up to the current dose of PS-341, no toxicity was observed. 2) At 24 hrs after drug infusion, proteasome inhibition was achieved as predicted. 3) Responses were seen even at low levels of proteasome inhibition. Further dose escalation (with pharmacokinetics and proteasome inhibition studies) is in progress. This early evidence of clinical activity without toxicity justifies further development of this agent with a novel mechanism of action. This work was supported by awards from the Association for the Cure of Cancer of the Prostate (CaPCURE) to C.N.P. and C.J.L.

#7 CCI-779, A new Rapamycin analog, Has Antitumor Activity at Doses Inducing Only Mild Cutaneous Effects and Mucositis: Early Results of an Ongoing Phase I Study. J. Alexandre*, E. Raymond*, H. Depenbrock*, S. Mekhaldi*, E. Angevin*, C. Paillet*, A. Hanauske*, J. Frisch, A. Feussner, J.P. Armand*. *Department of Medicine, Institut Gustave-Roussy, 94805 Villejuif cedex, France, Onkologische Tagesklinik*, München, Germany, Genetics Institute, München, Germany.*

Like rapamycin, CCI-779 interacts with the protein kinase mTOR thus preventing the phosphorylation of eIF4E-BP1 and p70S6K thereby inhibiting the initiation of the translation of messenger RNAs. We report the early results of a phase I study of CCI-779 given as a weekly 30 min. i.v. infusion in patients (pts) with advanced solid tumors. So far, 12 patients (pts) have been treated at the doses of 7.5, 15.0, 22.5, 34.0, 45.0, and 60.0 mg/m²/w using a modify continuous reassessment method for dose escalation. CCI-779 does not appear so far to have any significant immunosuppressive effect. No opportunistic infection was observed. The immunophenotype of peripheral lymphocytes (CD3, CD4, CD8, CD45, CD14, and CD56) and the mitogen proliferation assays (phytohemagglutinin, concanavaline A, PWM) did not reveal any significant modifications. However, a reactivation of peri-oral herpes lesions was observed in 5 pts within the first month of treatment and rapidly resolved under oral acyclovir. Interestingly, significant tumor regressions were rapidly observed in 2 pts with lung metastasis of renal cell carcinomas both treated with 15 mg/m²/w and in one patient with a neuroendocrine tumor of the lung treated with 22.5 mg/m²/w. Responses occurred after 8 weekly doses. Additionally, 2 patients experienced tumor stabilization. Neither grade III–IV nor dose-limiting toxicity have been reported so far. Only mild grade I–II skin reactions and mucositis were observed at each dose level but did not increase in intensity while the dose-escalation was performed. Dryness of the skin with mild itching, fine scaling, and mild facial erythema occurred in 6 pts after the 1st infusion and lasted during the overall period of treatment. Mild hypersensitivity reactions were observed in all the pts including: (1) sub-acute urticaria in 1 pt immediately after the 1st infusion which did not reoccur during subsequent cycles, (2) <<Eczema-like>> lesions on the anterior side of arms in 2 pts, and (3) aseptic follicles were associated with self-limited erythematous papules with central vesiculations occurring in bold areas in 7 pts. In the latest 7 pts, concomitantly to the skin reactions, grades I or II mucositis were observed associated with genital mucous membrane erosion in 1 pt. Skin biopsies were performed in all the pts experiencing skin reactions and consistently showed an aspect of folliculitis with infiltrate of neutrophils associated with non-specific superficial peri-capillar dermatitis. With repeated dosing transient regressions were usual, accelerated in some patients by topical steroid therapy and antiseptics. No alopecia was reported. Nails changes consisting of thickness and dystrophia progressively increased in pts receiving more than 8 doses. The study is ongoing to determine the dose limiting toxicity and the dose to be recommended for phase II studies.

#8 Phase I clinical and pharmacokinetic (PK) study of the Cryptophycin analog LY 355703 administered on an every 3 weeks (wks) schedule. Pagani, O., Greim, G., Weigang, K., Westphal, K., Van den Bosch, S., DePas, T., Burgess, M., Weimer, I. and Sessa, C. *IOSI, Bellinzona, CH; Klinikum Nürnberg, Nürnberg, D; EIO, Milano, I; Lilly Research Centre, Windlesham, UK.*

Cryptophycins are antimetabolic antitumor agents from blue-green algae which inhibit microtubule dynamics with characteristics partially like vinblastine and partially like paclitaxel. The synthetic Cryptophycin LY355703 is highly potent (*in vitro* activity at picomolar concentrations) has antitumor activity in murine and human tumour xenografts, and high activity in tumours expressing the MDR phenotype, including models resistant to paclitaxel. In toxicology studies dose-limiting toxicities (DLT) were neutropenia in rats and diarrhea in dogs, the latter being the most sensitive species. The starting dose for this study on a single q 3wks schedule was 0.1 mg/m², corresponding to 1/10 of the Maximum Tolerated Dose in dogs; doses were escalated according to a modified Continual Reassessment Method. LY355703 was administered as 2 h i.v. infusion. Premedication with i.v. Dexamethasone, H₁ and H₂ antagonists 30 min before LY dose was given starting from the 0.88 mg/m² dose because of moderate hypersensitivity reactions to Cremophor EL observed at the previous dose (0.68 mg/m²). The plasma concentration of LY355703 was investigated by LC-MS-MS method with a detection limit of 0.25 ng/mL. Twenty-nine patients (pts) with a variety of solid tumours (soft tissue sarcoma 8, renal 5, colon 4) and 10 dose levels have been evaluated so far. At the highest dose level of 1.92 mg/m², 2 of 5 pts presented self-limiting DLTs (G3 neuropathic pain in 1 pt, G3 myalgia and constipation in the other) which appeared within 3 days of the infusion and required opioids. The dose of 1.7 mg/m² was then tested in 2 pts with occurrence of self-limiting G3 myalgia within 48 hours in both, in spite of prophylactic analgesia. Overall, peripheral neuropathy was mainly sensory and of moderate degree and not necessarily dose related nor cumulative; neutropenia was sporadic and only moderate; total alopecia was observed only in pts who presented DLTs. PK was linear from 0.1 mg/m² to 1.92 mg/m² with mean (±SD) t_{1/2} of 2.6 hr (±1.02), Cl_p of 90.4 L/hr (±50.3) and no apparent correlation to