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Oncology Highlights ASCO 2009
Myeloma

Scottsdale, Arizona
Rochester, Minnesota
Jacksonville, Florida
Disclosures

Consulting AMGEN, BMS, Halozyme, Otsuka, Celgene, Medtronic

Past research support Pfizer
CyBORD

- CyBORD in previously untreated patients with MM
- Endpoints: 1°: ≥VGPR; 2°: included PFS, OS and safety
- Patients: 33 enrolled; mean age: 60 (38-75) yrs.; ISS stage II/III 36%/30%

Cycles 1 - 4 (4 week cycle)
Bortezomib 1.3 mg/m² IV: days 1,4,8,11
Cyclophosphamide 300 mg/m² days 1, 8, 15, 22
Dex 40 mg: days 1 - 4, 9 - 12, 17 - 20

- Response Assessment
- Stem Cell Collection
- Off Study to Transplant
- Continue Meds for further 8 Cycles
- Stem Cell Collection
- Off Study to Transplant

Prophylaxis with acyclovir and quinolone: growth factors allowed after cycle 1.

Reeder et al, Leukemia (2009) 23, 1337
Transplant Outcomes

- 33 patients enrolled
  - 23 transplanted
  - 5 too early to evaluate
- 18 transplanted evaluable
  - CR/nCR 72%
- 10 not transplanted
  - one MR and one PD
  - one in CR refused transplant
  - one death (fat embolus fx)
  - 3 off study - toxicity
  - 3 high risk genetics.

Reeder et al, Leukemia (2009) 23, 1337
Bortezomib, IV cyclophosphamide, and dexamethasone (VelCD) as induction therapy in newly diagnosed multiple myeloma: Results of an interim analysis of the German DSMM Xia trial

Abstract 8516

S. Knop, P. Liebisch, H. Wandt, M. Kropff, W. Jung, N. Kroeger, O. Sezer, C. Straka, G. Fingerle-Rowson, H. Einsele; University Hospital, Wuerzburg, Germany; University Hospital, Ulm, Germany; Klinikum Nord, Nuremberg, Germany; University of Muenster, Muenster, Germany; University Hospital, Goettingen, Germany; University Hospital Eppendorf, Hamburg, Germany; University Hospital Charite, Berlin, Germany; Clinic Dr. Argirov, Berg, Germany; Janssen-Cilag, Neuss, Germany
Bortezomib, IV cyclophosphamide, and dexamethasone (VelCD) as induction therapy in newly diagnosed multiple myeloma: Results of an interim analysis of the German DSMM Xia trial

- Open, prospective, multicenter, uncontrolled phase II/III study (up to age 60)
- Planned recruitment of 400 pts
- The first 30 pts were included in the dose finding study to determine the optimum dose of IV C in conjunction with Vel and D
  - Bz 1.3 mg/m2 IV d1, 4, 8, 11
  - D 40 mg/d d1, 2, 4, 5, 8, 9, 11, 12
  - Cytoxan 900mg/m2 IV d1

Knop et al J Clin Oncol 27:15s, 2009 Abstract 8516
Bortezomib, IV cyclophosphamide, and dexamethasone (VelCD) as induction therapy in newly diagnosed multiple myeloma: Results of an interim analysis of the German DSMM Xia trial

- Response to study therapy
- Response to VelCD n (%)
  - ORR 84.0
  - CR 12.5
  - PR 71.5
  - MR 5.5
  - SD 8.5
  - PD 2.0

- ITT population, n = 200

Knop et al J Clin Oncol 27:15s, 2009 Abstract 8516
Lenalidomide, bortezomib, pegylated liposomal doxorubicin hydrochloride, and dexamethasone in newly diagnosed multiple myeloma: Initial results of phase I/II MMRC trial

Abstract 8517

A. J. Jakubowiak, C. C. Hofmeister, E. L. Campagnaro, T. M. Zimmerman, R. L. Schlossman, S. Lonial, D. E. Reece, M. S. Kaminski, K. C. Anderson, P. G. Richardson; University of Michigan, Ann Arbor, MI; The Ohio State University, Columbus, OH; University of Chicago, Chicago, IL; Dana-Farber Cancer Institute, Boston, MA; Emory University School of Medicine, Atlanta, GA; Princess Margaret Hospital, Toronto, ON, Canada

Jakubowiak et al J Clin Oncol 27:15s, 2009 Abstract 8517
Lenalidomide, bortezomib, pegylated liposomal doxorubicin hydrochloride, and dexamethasone in newly diagnosed multiple myeloma: Initial results of phase I/II MMRC trial

- Objective is to add Peg Dox to RVD (RVDD)
- Phase I/II study MTD of RVDD
  - Rev 15-25 mg (days 1-14)
  - Vel 1.3 mg/m^2 (days 1, 4, 8, 11)
  - Dex 20/10 mg (cycles 1-4/5-8; days of and after Vel)
  - Dox 20 and 30 mg/m^2 (day 4)
- Eight 21-day cycles are planned with 38 pts to be treated at the MTD in phase II

Jakubowiak et al J Clin Oncol 27:15s, 2009 Abstract 8517
Lenalidomide, bortezomib, pegylated liposomal doxorubicin hydrochloride, and dexamethasone in newly diagnosed multiple myeloma: Initial results of phase I/II MMRC trial

- Pts who achieve > PR can proceed to autologous stem cell transplant (ASCT) after > 4 cycles
- Others receive 21-day maintenance cycles with Rev (days 1-14), Vel (day 1 and 8), and Dex (days of and after Vel)
- The study has enrolled 23 pts to date
- Preliminary response rates
  - 95% > PR,
  - 47% > VGPR
  - 26% CR/nCR

Jakubowiak et al J Clin Oncol 27:15s, 2009 Abstract 8517
Phase II study of pegylated liposomal doxorubicin (PLD), low-dose dexamethasone (DEX), and lenalidomide (LEN) in patients with newly diagnosed (ND) multiple myeloma (MM)

Abstract 8518

R. Baz, M. A. Hussein, D. Sullivan, J. Raychaudhuri, L. Ochoa, K. Kosakowski, L. Nardelli, W. S. Dalton, M. Alsina; H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL; Celgene Corporation, Summit, NJ
Phase II study of pegylated liposomal doxorubicin (PLD), low-dose dexamethasone (DEX), and lenalidomide (LEN) in patients with newly diagnosed (ND) multiple myeloma (MM)

- Phase 1 MTD of LEN in combo was 10 mg (for 21 of 28 days)
  - Overall response rate was 75%
  - 29% of patients achieving nCR or better
    - Ann Oncol 2006

- New testing in ND MM

- ND MM would tolerate this combination better
  - PLD (40 mg/m2 on day 1)
  - DEX (40 mg on days 1-4)
  - LEN (25 mg Days 1-21) every 28 days
  - (for 2 cycles beyond best response: 4-8 cycles)

- Pts not going to SCT go onto Len Dex maintenance.

Baz et al J Clin Oncol 27:15s, 2009 Abstract 8518
Phase II study of pegylated liposomal doxorubicin (PLD), low-dose dexamethasone (DEX), and lenalidomide (LEN) in patients with newly diagnosed (ND) multiple myeloma (MM)

- 31 of a planned 60 patients were enrolled
- Mean age 64 (41-82)
  - 58% were males
- After a median of 4 cycles
  - ORR 80%
  - 40% VGPR and better
- The combination of PLD, LEN and DEX is an active regimen in patients with ND MM
A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients

Abstract 8515

A. P. Palumbo, S. Bringhen, D. Rossi, S. Berretta, V. Montefusco, J. Peccatori, M. Galli, A. Carella, P. Omedè, M. Boccadoro, Italian Multiple Myeloma Network (GIMEMA); Azienda Ospedaliera San Giovanni Battista, Torino, Italy; Università del Piemonte Orientale Amedeo Avogadro, Novara, Italy; Ospedale Ferrarotto, Università di Catania, Catania, Italy; Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Istituto Scientifico San Raffaele, Milano, Italy; Ospedali Riuniti, Bergamo, Italy; A.O.U. San Martino, Genova, Italy
A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients

- 500 newly diagnosed MM patients ≥ 65 years
  - VMPT (N=247) or
  - VMP (N=253)
  - Patients were treated with nine 5-week cycles
- VMPT (Bz 1.3 mg/m² d 1, 8, 15, 22; mel 9 mg/m² d 1-4; pred 60 mg/m² d 1-4 and thalidomide 50 mg d 1-35)
- VMP same doses
- Primary end-point PFS
- Results 354 patients (median age 71 years), who received at least 1 cycle were evaluated
  - 177 VMPT
  - 177 VMP
- Data were analyzed in intention-to-treat

Palumbo et al J Clin Oncol 27:15s, 2009 Abstract 8515
A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients

- VGPR 55% VMPT and 45% for VMP (p<0.001)
- 3-year PFS was 74% vs 70% (p=0.28). (median FU 14.5 mos)
- 3-year OS was 88% vs 87% (p=0.75)
- No prognostic effect of ISS or HR cytogenetics
- Grade 3-4 adverse events (AEs) was similar in both groups
  - Neutropenia (36% vs 31%)
  - Thrombocytopenia (20% vs 19%)
  - PN(18% vs 12%)
  - Infections (14% vs 10%), respectively
- VMPT is superior to VMP in terms of response rates.
- Effects on high risk and ISS unknown.

Palumbo et al J Clin Oncol 27:15s, 2009 Abstract 8515
Tanespimycin plus bortezomib in patients with relapsed and refractory multiple myeloma: Final results of a phase I/II study

Abstract 8503

P. G. Richardson, A. Chanan-Khan, S. Lonial, A. Krishnan, M. Carroll, M. Alsina, M. Albitar, D. Berman, S. Kaplita, K. Anderson; Dana-Farber Cancer Institute, Boston, MA; Roswell Park Cancer Institute, Buffalo, NY; Emory University School of Medicine, Atlanta, GA; City of Hope Comprehensive Cancer Center, Duarte, CA; Sutter Regional Cancer Institute, Sacramento, CA; Moffitt Cancer Center, Tampa, FL; Quest Diagnostics Nichols Institute, San Juan Capistrano, CA; Bristol-Myers Squibb, Princeton, NJ; Bristol-Myers Squibb, Wallingford, CT

Richardson et al J Clin Oncol 27:15s, 2009 Abstract 8503
Tanespimycin plus bortezomib in patients with relapsed and refractory multiple myeloma: Final results of a phase I/II study

- Tanespimycin HSP90 inhibitor; anti-tumor synergy with Bz
- 72 pts with relapsed/refractory MM received
- 0.7 - 1.3 mg/m² Bz as IVB
- Tan 1-hr infusion of 100 - 340 mg/m² Tan d 1, 4, 8, 11 q 21d,
- 42 pts receiving the highest dose (phase II expansion).
- Median age 60 yo, time since MM diagnosis was 50 mos
- Median of 5 (1-15) prior regimens
  - stem cell transplant (69%)
  - thalidomide (74%)
  - Bz (69%)
  - lenalidomide (28%)

Richardson et al J Clin Oncol 27:15s, 2009 Abstract 8503
Tanespimycin plus bortezomib in patients with relapsed and refractory multiple myeloma: Final results of a phase I/II study

- Response rates (≥ MR) were
  - 41% Bz naïve
  - 20% Bz exposed
  - 14% in the Bz refractory
- DOR for responders (n=14) 10.7 mos
  - 3 Bz-refractory pts had durable PR 12, 22 and 28 mo
- AEs were diarrhea (60%), nausea (49%), fatigue (49%), thrombocytopenia (40%) and AST elevation (28%)
- G3-4 AEs included thrombocytopenia (25%), diarrhea, anemia and fatigue (7% each)
- Only 21% of pts had G1-2 PN; no G3-4 PN was seen
- A phase III study of Tan + Bz vs Bz is ongoing.

Richardson et al J Clin Oncol 27:15s, 2009 Abstract 8503
Final results of PX-171-003-A0, part 1 of an open-label, single-arm, phase II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM)

Abstract 8504

S. Jagannath, R. Vij, K. Stewart, G. Somlo, A. Jakubowiak, S. Trudel, R. Schwartz, D. Siegel, L. Kunkel, The Multiple Myeloma Research Consortium (MMRC); St. Vincent's Comprehensive Cancer Center, New York, NY; Washington University School of Medicine, St. Louis, MO; Mayo Clinic, Scottsdale, AZ; City of Hope, Duarte, CA; University of Michigan, Ann Arbor, MI; Princess Margaret Hospital, Toronto, ON, Canada; Proteolix, Inc., South San Francisco, CA; Hackensack University Medical Center, Hackensack, NJ

Jagannath et al J Clin Oncol 27:15s, 2009 Abstract 8504
Final results of PX-171-003-A0, part 1 of an open-label, single-arm, phase II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM)

- CFZ is a novel proteasome inhibitor
- PX-171-003-A0 was an open-label, multicenter study
- MM pts who relapsed from >2 prior therapies,
  - Failed BTZ and
  - At least 1 immunomodulatory agent
- Refractory to last treatment [progressing on or within 60 d of last therapy or <25% response to last therapy].
- Pts received CFZ 20 mg/m² IV d 1, 2, 8, 9, 15 and 16 q28 d for up to 12 cycles (C)
- Clinical benefit response (CBR) was defined as MR or better.

Jagannath et al J Clin Oncol 27:15s, 2009 Abstract 8504
Final results of PX-171-003-A0, part 1 of an open-label, single-arm, phase II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM)

• 46 pts were enrolled
  • 78% with progression on or within 60 d of last therapy
  • 22% with no response to last therapy

• 39 pts evaluable completed at least 1 C of CFZ
  • Median prior therapies was 5 (range 2-15)
  • 100% BTZ, 91% THAL, 89% LEN, and 83%SCT

• Pts received a median of 3 C (range 1-12)
  • 13 pts completed ≥6 C

• CBR was 26% (10/39 eval pts)
  • 5 pts achieving PR
  • 5 pts achieving MR
  • 5 BTZ-refractory pts achieved MR or PR

Jagannath et al J Clin Oncol 27:15s, 2009 Abstract 8504
Final results of PX-171-003-A0, part 1 of an open-label, single-arm, phase II study of carfilzomib (CFZ) in patients (pts) with relapsed and refractory multiple myeloma (MM)

- AE fatigue, anemia, thrombocytopenia, nausea, upper respiratory infection, increased creatinine and diarrhea. Peripheral neuropathy occurred in < 10% of pts with 1 Gr 3 in a pt with pre-existing Gr 2.
- The study has been expanded to enroll an additional 250 pts in this unmet medical need population at an escalated dose, and treatment has been extended beyond a year.

Jagannath et al J Clin Oncol 27:15s, 2009 Abstract 8504
Change from baseline

Waterfall Plot

At least 25% Increase

At least 25% Decrease

66% with MR or better

Lacy et al., ASH 08, abstract 866
Long-lasting responses after four doses of rituximab in Waldenström's macroglobulinemia: Clinical value of minor responses: A follow-up of the Eastern Cooperative Oncology Group E3A98 trial

Abstract 8513

M. A. Gertz, R. Abonour, L. T. Heffner, P. R. Greipp, H. Uno, S. V. Rajkumar; Mayo Clinic, Rochester, MN; Indiana University, Indianapolis, IN; The Emory Clinic, Atlanta, GA; Dana-Farber Cancer Institute, Boston, MA

Gertz et al J Clin Oncol 27:15s, 2009 Abstract 8513
Long-lasting responses after four doses of rituximab in Waldenström macroglobulinemia: Clinical value of minor responses: A follow-up of the Eastern Cooperative Oncology Group E3A98 trial

- Waldenström macroglobulinemia
- Minor response as a 25% reduction in IgM level
- 69 patients
- 34 previously untreated
- 35 previously treated (rituximab naive) were included
- Single four-week course of rituximab 375 mg/m²
Long-lasting responses after four doses of rituximab in Waldenström macroglobulinemia: Clinical value of minor responses: A follow-up of the Eastern Cooperative Oncology Group E3A98 trial

- Responses (52.2%)
  - 19 objective
  - 17 minor responses
- ORR and PFS (26.6 mo) were similar Rx vs. naive
- Previously treated rituximab-naïve and previously untreated patients had, five-year survivals of 48% and 85%, respectively.
- No difference in OS or PFS OR vs. minor (no baseline difference)
- IgM level did not predict OS, PFS, TTP or ORR progression-free survival, time to progression, or response
- Pts with MR derive significant clinical benefits.

Gertz et al J Clin Oncol 27:15s, 2009 Abstract 8513
Phase II trial of combination of bortezomib and rituximab in relapsed and/or refractory Waldenström macroglobulinemia

Abstract 8535

I. M. Ghobrial, J. Matous, S. Padmanabhan, A. Badros, S. Chuma, R. Leduc, M. Rourke, J. Kunsman, B. Harris, D. Warren, P. Richardson; Dana-Farber Cancer Institute, Boston, MA; Rocky Mountain Cancer Center, Denver, CO; UT Health Science Center, San Antonio, TX; University of Maryland, Washington, DC
Phase II trial of combination of bortezomib and rituximab in relapsed and/or refractory Waldenström macroglobulinemia

- Patients with relapsed/refractory WM
- Bz IV weekly at 1.6mg/m2 on days 1, 8, 15, q 28 days x 6 cycles
- Rituximab 375 mg/m2 at days 1, 8, 15, 22, on cycles 1 and 4
- 37 pts (median age 62 years, range 42 - 73) have been treated to date
- Median 3 prior therapies
  - All prior rituximab
- Median IgM at baseline was 3540 mg/dL (range 700-10,800)
- The median follow up is 12 months (range 5 - 26 months

Ghobrial et al J Clin Oncol 27:15s, 2009 Abstract 8535
Phase II trial of combination of bortezomib and rituximab in relapsed and/or refractory Waldenström macroglobulinemia

- Thirty-five pts are evaluable for response (83%)
  - CR/nCR in 2 (6%)
  - PR in 17 (48%)
  - MR in 10 (29%)
- Most patients achieved response rapidly within 3 months of therapy (2-7 months)
- Flare only on 20%
- TTP and DOR not reached yet (24 mo FU)
- Gr3 PN in only 2 pts
- Gr1 and 2 neuropathy occurred in 10 pts (26%)

Ghobrial et al J Clin Oncol 27:15s, 2009 Abstract 8535