„Transplantation in Multiple Myeloma“

YES or NO

Roman Hájek on behalf of CMG

September 21, 2009

Krakow

Current status of autologous transplantation (AT)

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

Current status of AT
EFS plus: 3/5; OS 2/5

Conventional chemotherapy versus ASCT

Author	n	Age	CR (%)	EFS	OS
IFM 90 (N Engl J Med 1996)	200	≤65	5 vs 22*	7-year EFS 8% vs 16%*	7-year OS 27% vs 43%*
MRC7 (N Engl J Med 2003)	401	≤65	8 vs 44*	19m vs 31m*	42m vs 54m*
Pethema (Blood 2003)	400	50–70	11 vs 30*	333m vs 43m*	56m vs 62m
US Intergroup (JCO 2006)	**813**	**25–70**	**15 vs 17**	**7-year estimate 14% vs 17%**	**7-year estimate 38% vs 38%**

*Significant difference

Single vs. Tandem AT
EFS plus: 4/5; OS 1/5

Author	n	Age	CR (%) 1 vs 2	EFS months	OS months
IFM 94	399	≤65	42 vs. 50	25 vs 30*	48 vs 58*
MAG95	227	≤65	39 vs 37	31 vs 33	49 vs 73
Bologna 96	220	<70	31 vs 43	21 vs 31*	56 vs 60
GMMG	261	<70	-	23 vs. NR*	-
Hovon 22	303		13 vs 28	20 vs 22*	55 vs 55

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

*Significant difference

Transplantation in MM - general conclusion

GOLD STANDARD
for all available patients

Safe: Transplant Related Mortality 1-2 %

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

LIMITS !

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

1. Long term results

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

AT: long - term results

- No Cure !
- Tandem AT can improve survival in patients who does not achieve CR or VGPR after the first transplantation
  - IFM 94 (7-year survival 42% vs 21%)

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

Attal *et al. N Engl J Med* 2003;3349:2495–502

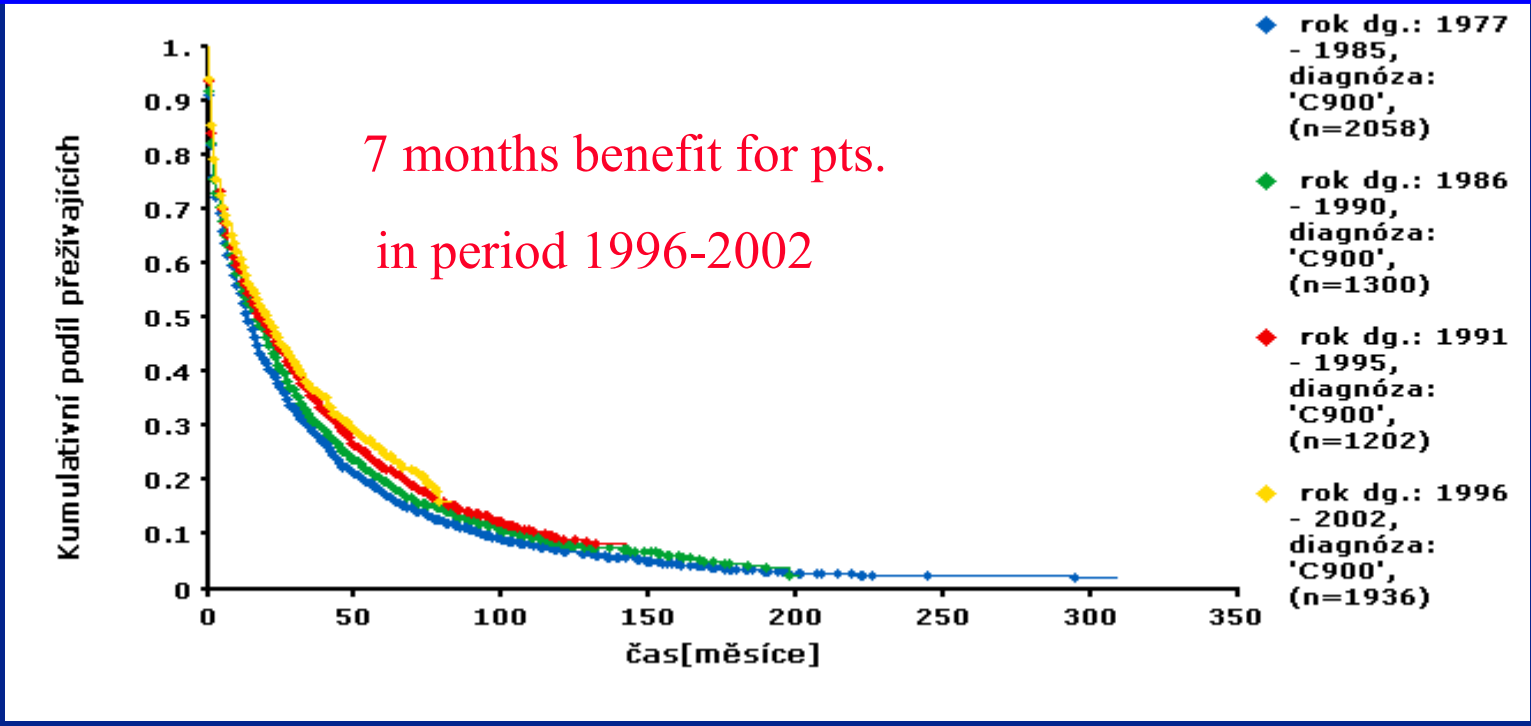
How the results of AT change overall long-term treatment results in multiple myeloma.

Lesson from Czech National Oncological Register (NOR)

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

Multiple Myeloma – NOR- Kaplan-Meier analysis of overall survival (OS)

Periods: 1977-1985, 1986-1990, 1991-1995 a 1996-2002



Period	Median OS months
1977 - 1985	13
1986 - 1990	16
1991 - 1995	18
1996 - 2002	20

Period	5-years OS	Period	8-years OS	Period	10-years OS
1977-1985	17.1%	1977-1985	9.3%	1977-1985	6.6%
1986-1990	18.4%	1986-1990	11.0%	1986-1990	8.0%
1991-1995	18.9%	1991-1994	11.1%	1991-1992	8.1%
1996-1997	21.8%				

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

ÚZIS ČR, NOR

Why can we see only minimal benefit (7 months) of AT, if the whole population suffered from MM is analysed ?

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

LIMITS !

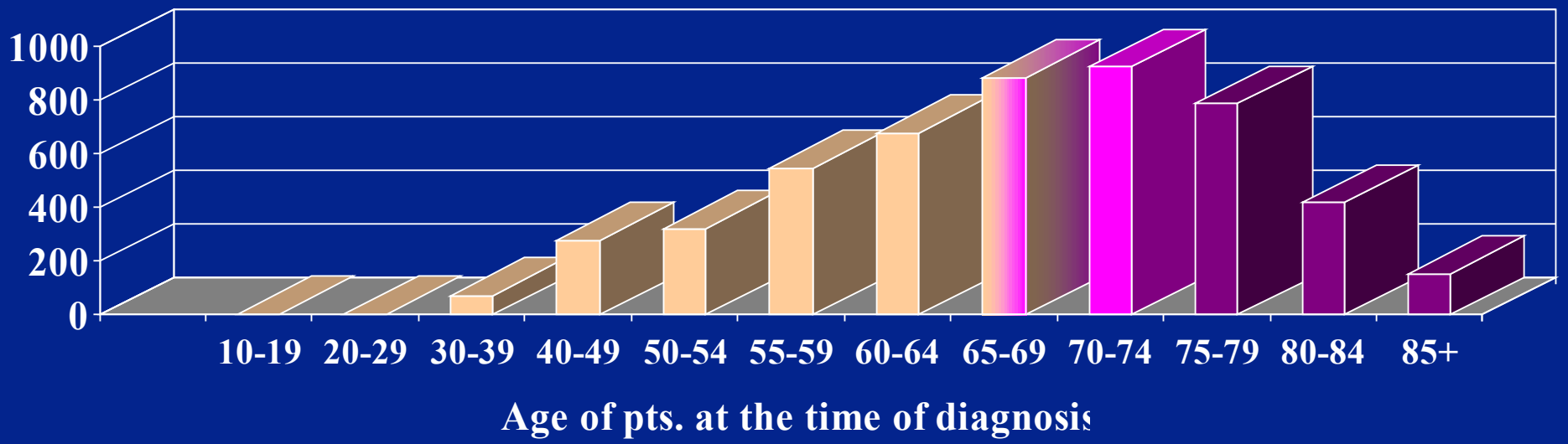
CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

1. Long term results
2. Availibility and indication for pts.

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

THE AGE DISTRIBUTION OF MM PTS. AT THE TIME OF DIAGNOSIS

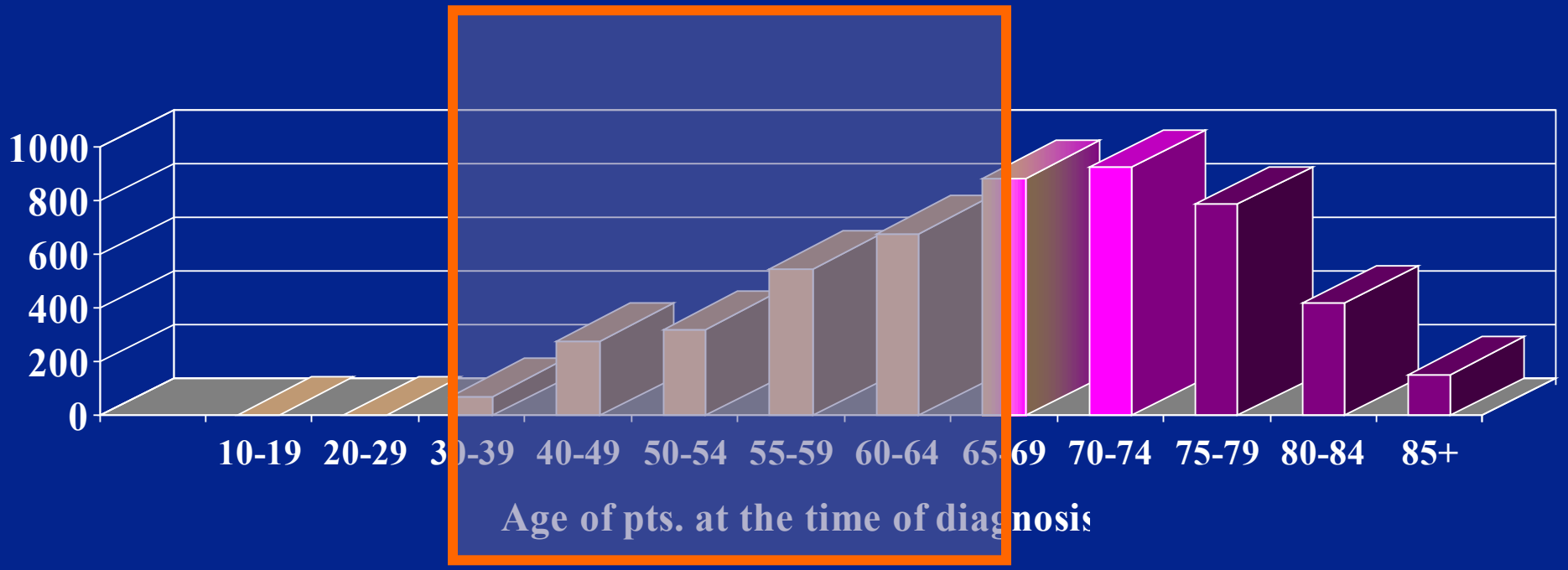
Age ranges	0 - 67 y	68 - 74 y	75+ y
• part from total No.	48 %	28%	27%



CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

THE AGE DISTRIBUTION OF MM PTS. AT THE TIME OF DIAGNOSIS

Age ranges	0 - 67 y	68 - 74 y	75+ y
• part from total No.	48 %	28%	27%



CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

THE AGE DISTRIBUTION OF MM PTS. AT THE TIME OF DIAGNOSIS

Age ranges	0 - 67 y	68 - 74 y	75+ y
• part from total No.	48 %	28%	27%

LESS THAN 50%

OF NEWLY DIAGNOSED PTS. ARE ELIGIBLE

FOR TRANSPLANTATION MAINLY DUE TO AGE LIMITATION AND/OR STANDARD CONTRAINDICATIONS

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

LIMITS !

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

1. Long term results
2. Availibity and indication for patients
3. Benefit from AT is limited by age

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

AT: long - term results

- Age as one of the main prognostic factor of long-term benefit of AT
  - IFM 90 long-term results confirmed benefit of transplantation only in patients under age 60

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

Attal *et al. N Engl J Med* 2003;3349:2495–502

MULTICENTRIC RANDOMISED CLINICAL TRIAL „4W“ Xth Annual Report Summary

Principal Investigator: **J. Vorlíček**

Co-principal Investigators: **R. Hájek, Z. Adam, M. Krejčí, J. Mayer, V. Ščudla, E. Thótová, V. Koza, K. Indrák**

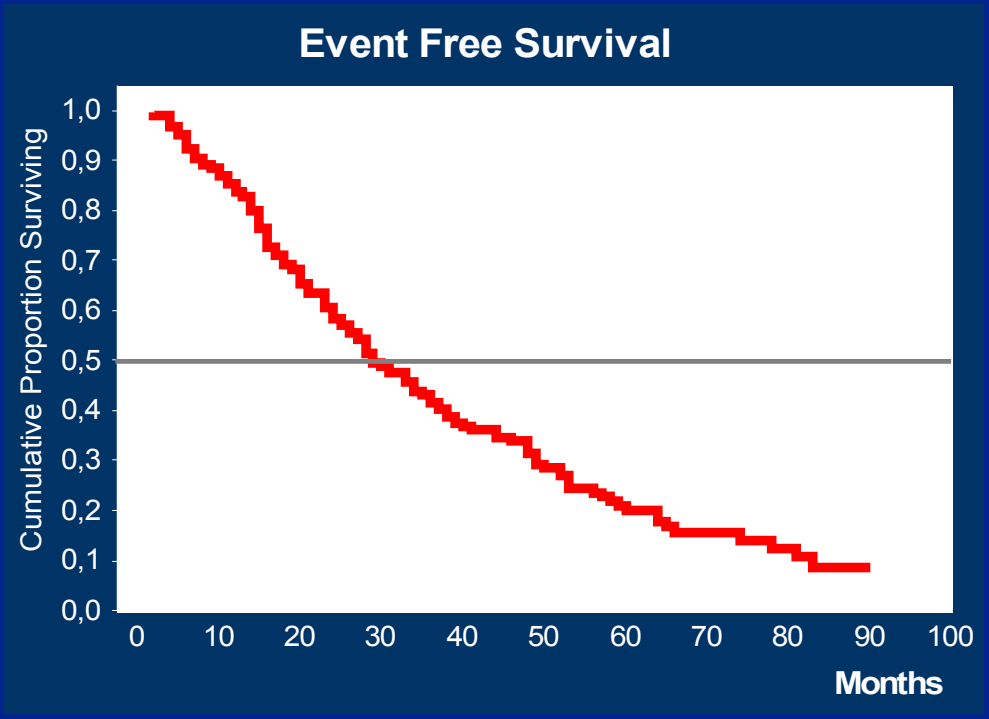
Data Analysis: **A. Svobodník, L. Dušek**

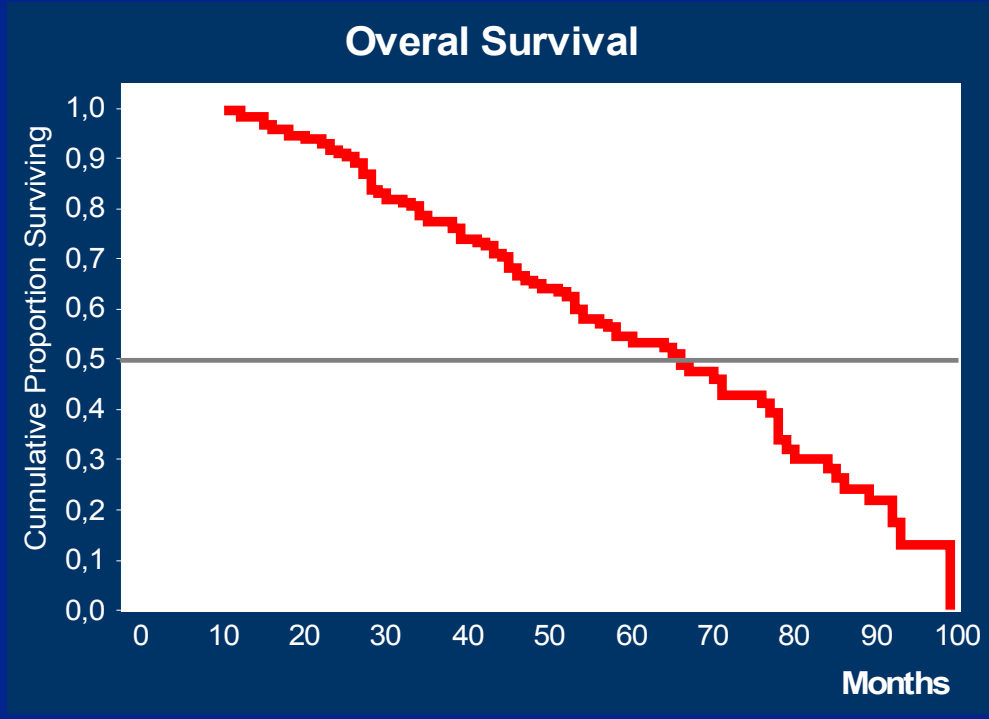
Data Center: **CBA LF MU**

PRIMARY ENDPOINT ANALYSIS

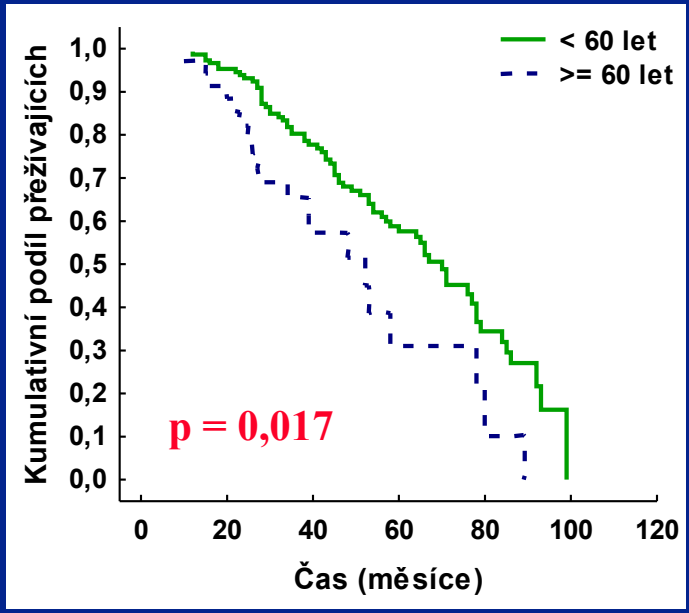
Event Free Survival, Overall Survival

Basic statistical summary (percentiles of survival times)				
		I	ID	All patients
EFS	25%	16.0	16.0	16.0
	50%	30.4	28.0	29.0
OS	25%	41.5	33.7	39.0
	50%	58.9	67.2	66.0

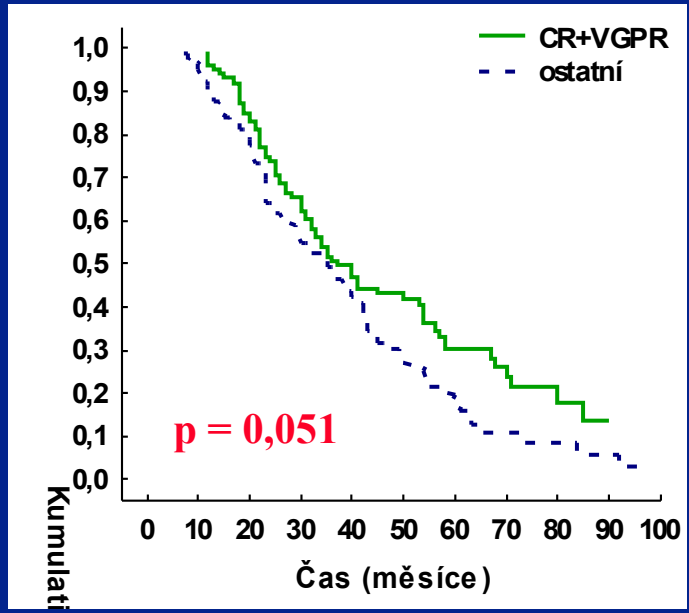




Age under 60 and CR + VGPR after AT



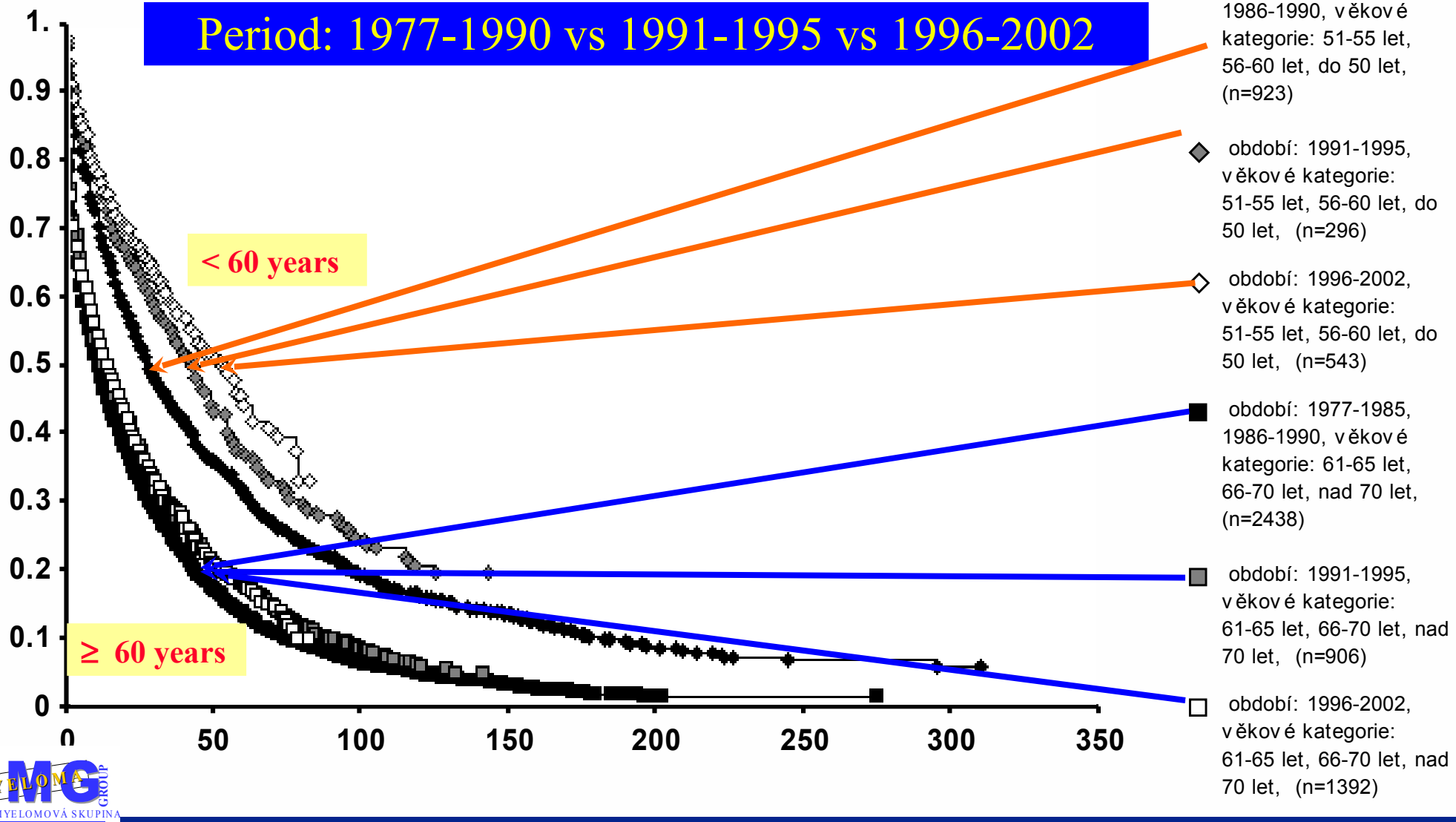
Age	N	Medián přežití (měsíce)
< 60 years	150	68,0
>≥ 60 years	35	48,9



Response	N	Median OS (months)
CR+VGPR	101	36,5
other	80	35,0

Multiple Myeloma – NOR- Kaplan-Meier analysis of overall survival (OS)

Comparison of age groups : ≥ 60 years vs. < 60 years



CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

LIMITS !

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

1. Long term results
2. Availibity and indication for patients
3. Benefit from AT is limited by age
4. Too toxic induction before AT
   (drop out during VAD 10-20%)

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

ADITIONAL LIMITATIONS:

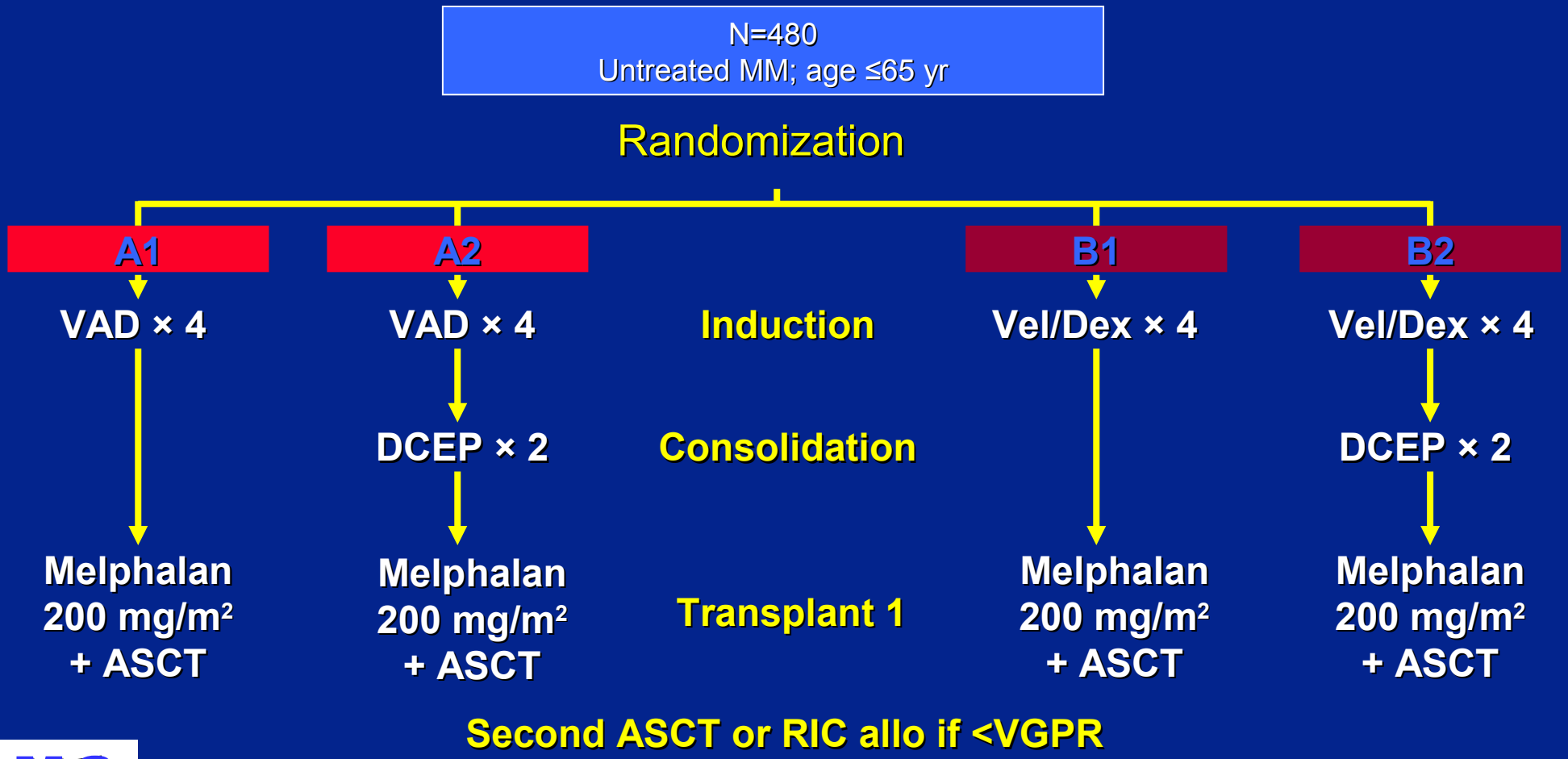
- **Clasical induction regimen VAD is too toxic and dropt out of patients indicated for AT strategy was, and still is too high (10-20%).**

- **Thus, substantional part of patients is lost during induction treatment and these patients cannot benefit from AT.**

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

IFM 2005-01: Vel/Dex vs VAD as Induction Treatment in MM

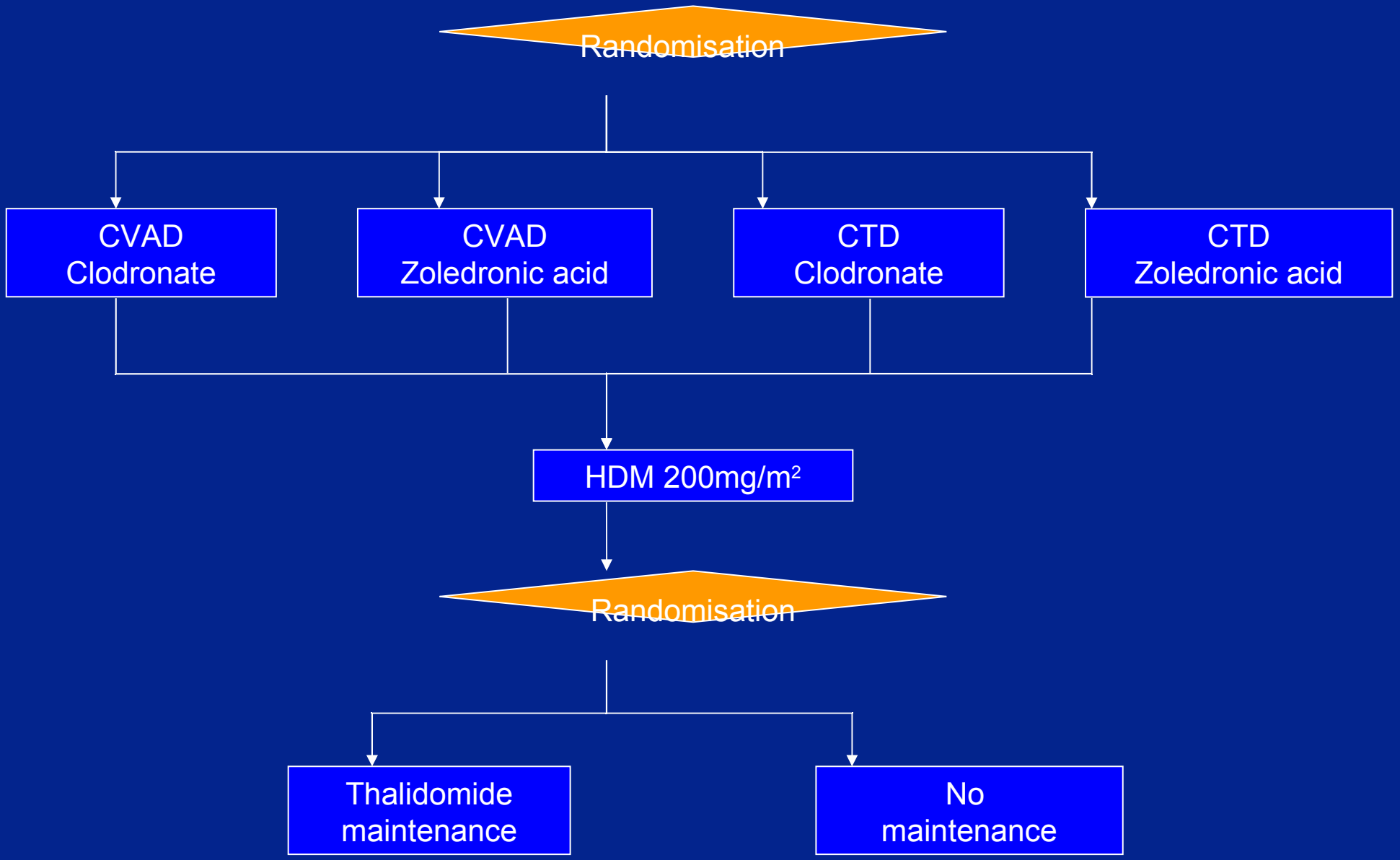
Primary analysis: post-induction response in VAD (A1+A2) vs Vel/Dex (B1+B2)



Second ASCT or RIC allo if <VGPR

Harousseau J-L et al. Presented at: ASH Annual Meeting; December 9–12, 2006; Orlando, FL

MRC IX TRIAL - Intensive pathway - schema



1. Long term results
2. Availibity and indication for patients
3. Benefit from AT is limited by age
4. Too toxic induction before AT
   (drop out during VAD 10-20%)
5. AT did not overcome cytogenetic negative

prognostic factors

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

Frequency and prognostic power of chromosomal abnormalities

Abnormalities	MGUS (%)	MM (%)	Up-regulated oncogens	Prognosis impact
Del 17p13	<5	11	*TP53*	Negative ---
Del 13q14	20	48	*RB1* and others	Neutral + --
t(4;14) (p16 .3;q32)	2-10	15	*FGFR3* and *MMSET*	Negative ---
t(11 ;14)(q13;q32)	15-30	16-20	Cyclin D1 gene and *Myeov*	Positive or neutral +
t(14;16) (q32;q23)	2-5	5	*C-maf* and *WWOX*	Negative ---
Amplification 1q21	10-15	42	*CKS1B* and others	Negative ---

Adopted from: Fonseca et al., 2004; Avet-Loiseau et al., 2007; Hanamura et al., 2006

Project

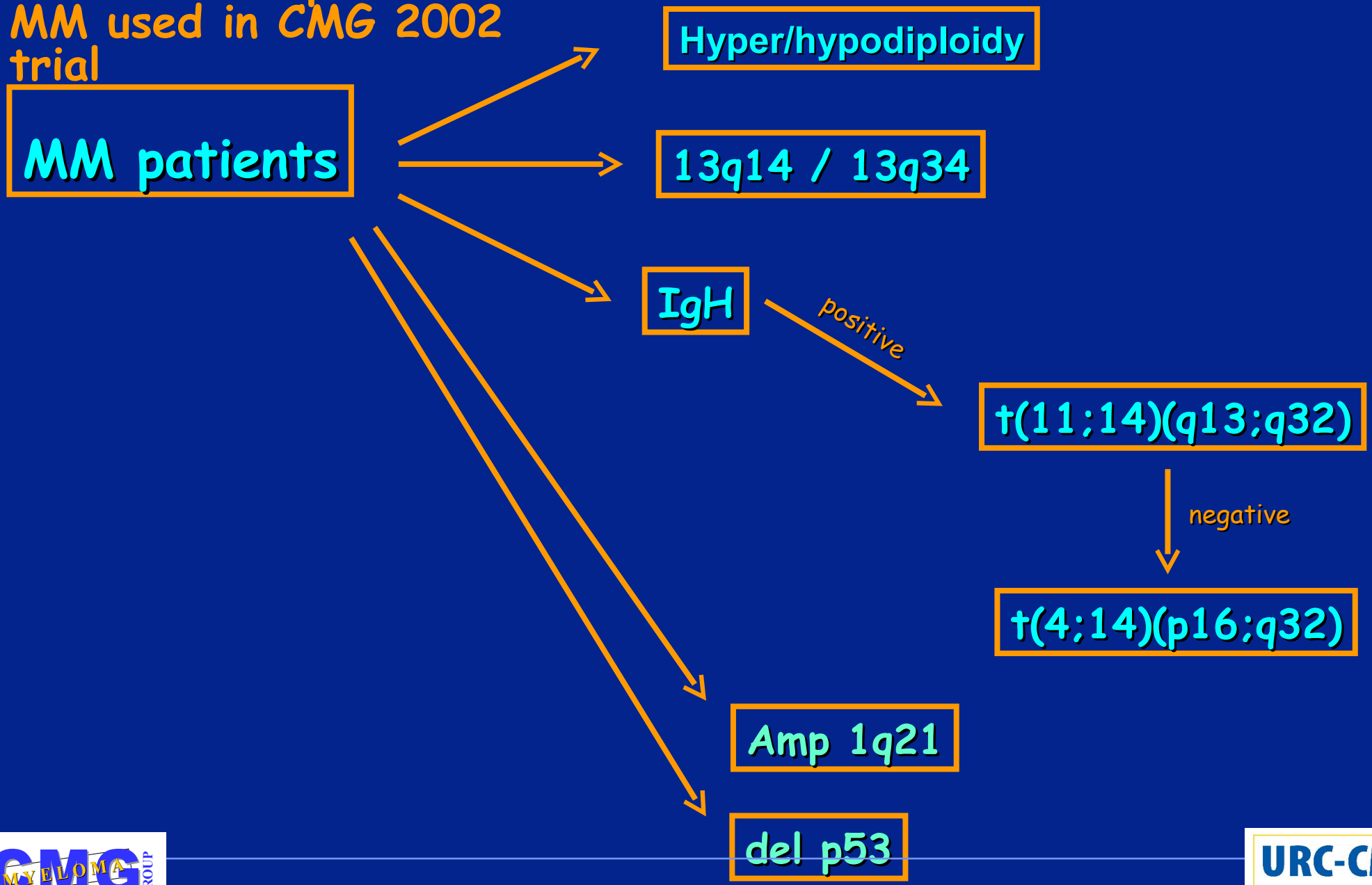
Autologous transplantation vs. chromosomal abnormalities

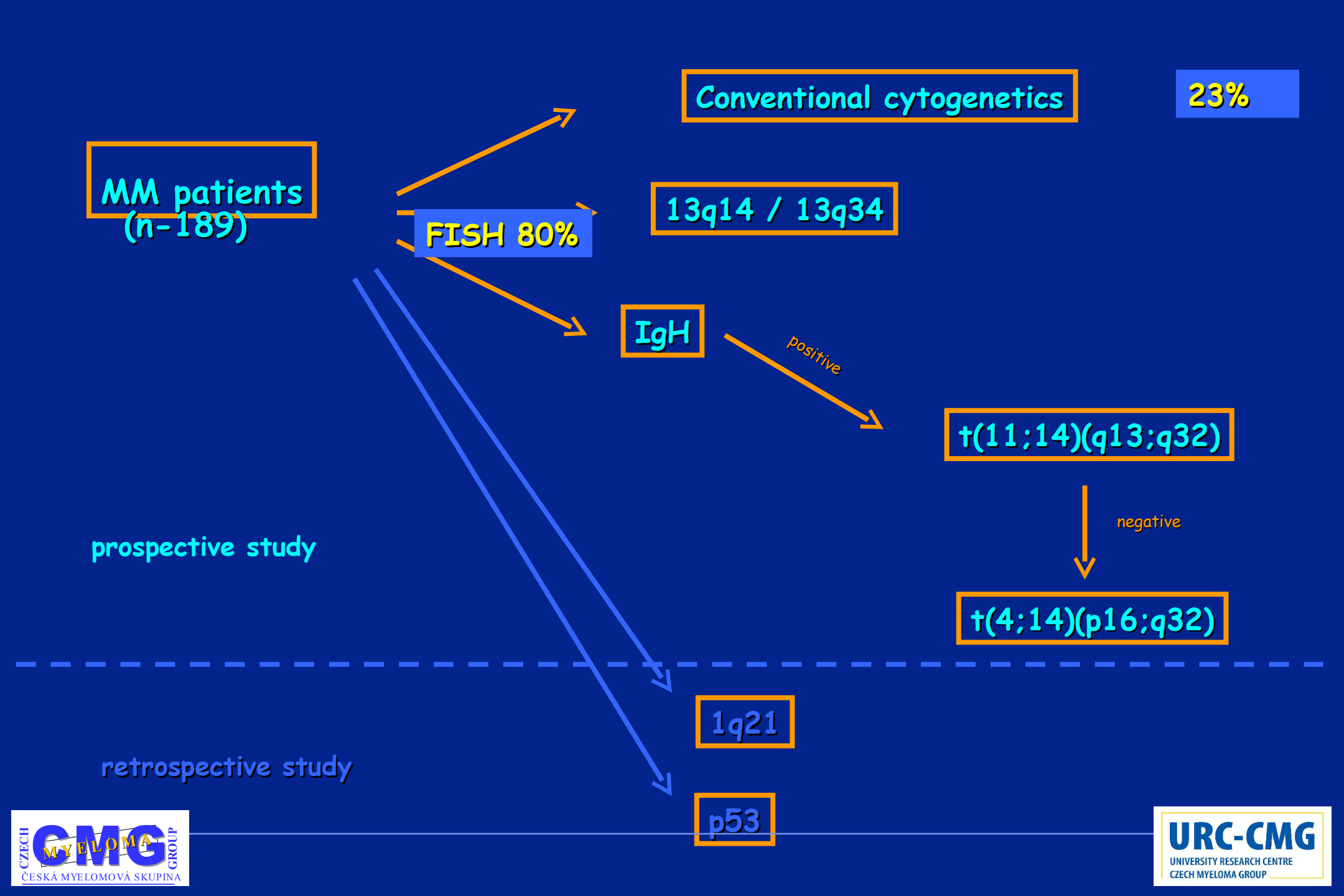
University Research Centre – The Czech Myeloma Group, Masaryk University, Brno, Czech Republic

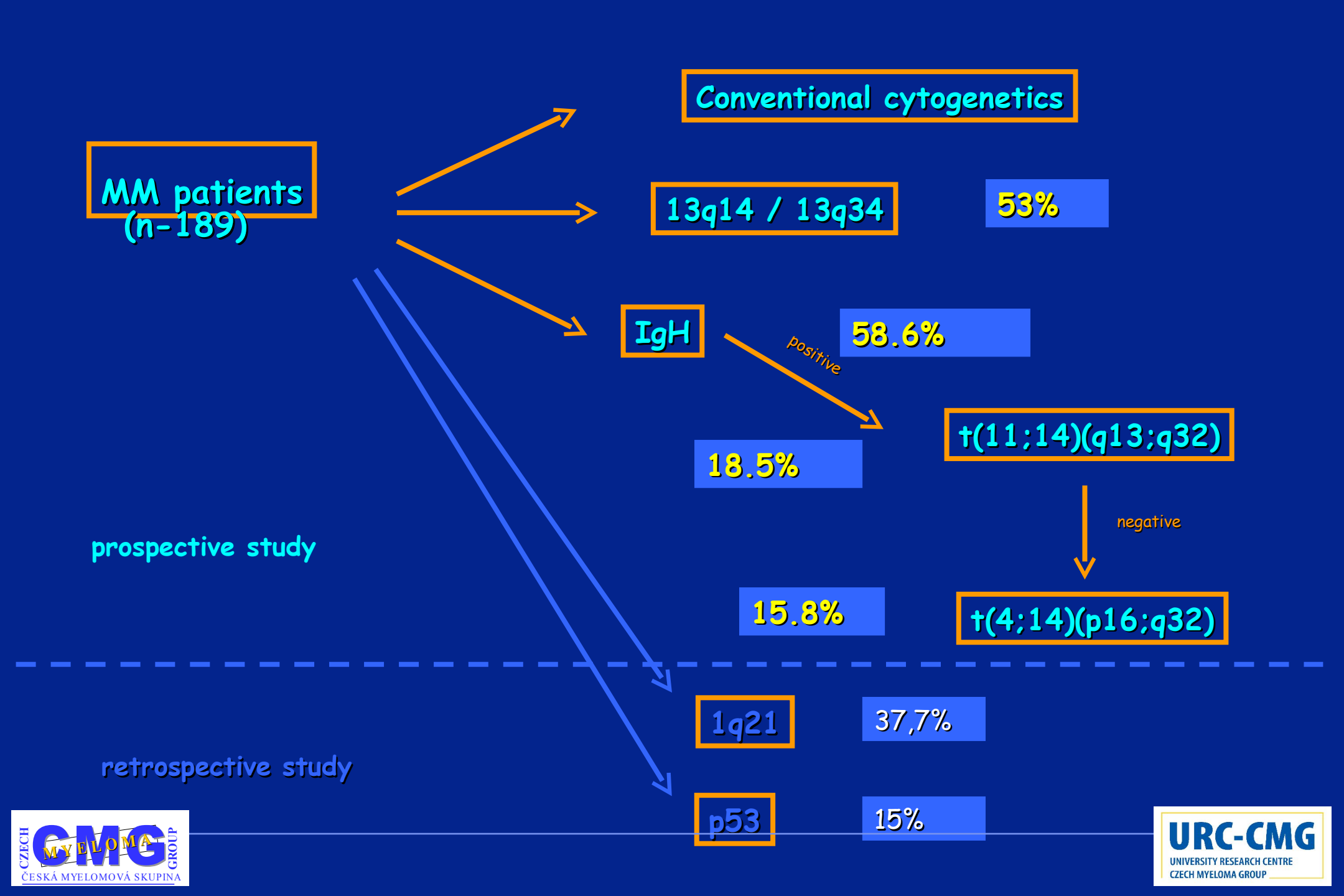
CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

URC-CMG
UNIVERSITY RESEARCH CENTRE
CZECH MYELOMA GROUP

FISH Probes portfolio for MM used in CMG 2002 trial



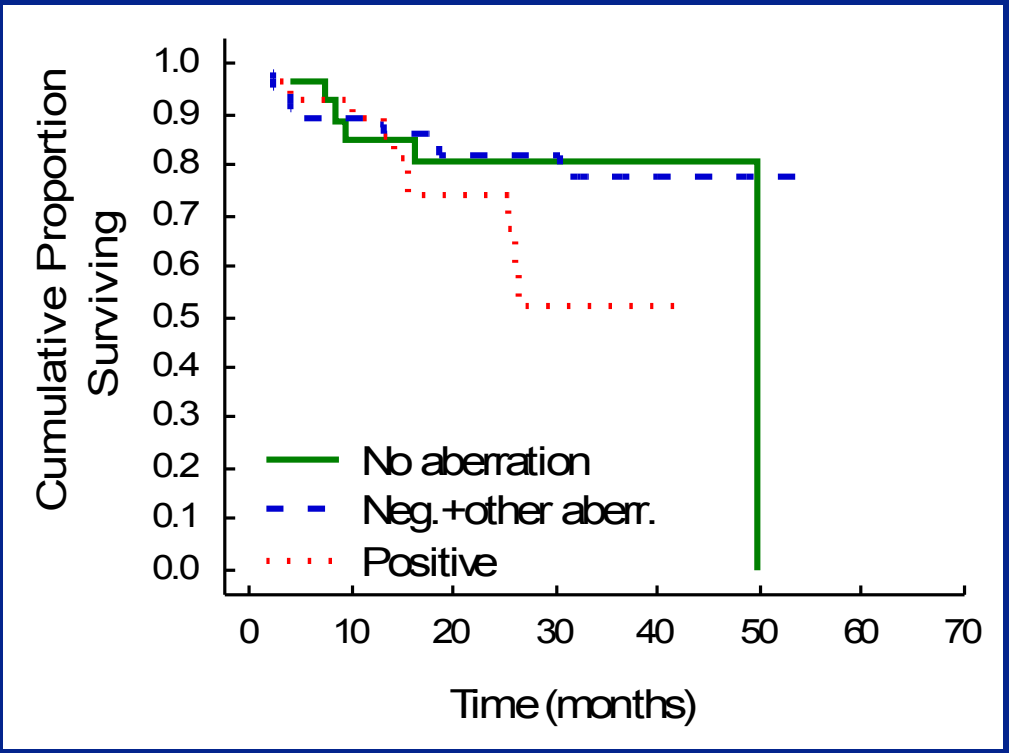

MM patients
(n-189)
Conventional cytogenetics
23%
FISH 80%
13q14 / 13q34
IgH
positive
t(11;14)(q13;q32)
negative
t(4;14)(p16;q32)
prospective study
1q21
retrospective study
p53


MM patients
(n-189)
Conventional cytogenetics
13q14 / 13q34
53%
IgH
positive
58.6%
t(11;14)(q13;q32)
18.5%
negative
t(4;14)(p16;q32)
15.8%
prospective study
1q21
37,7%
retrospective study
p53
15%

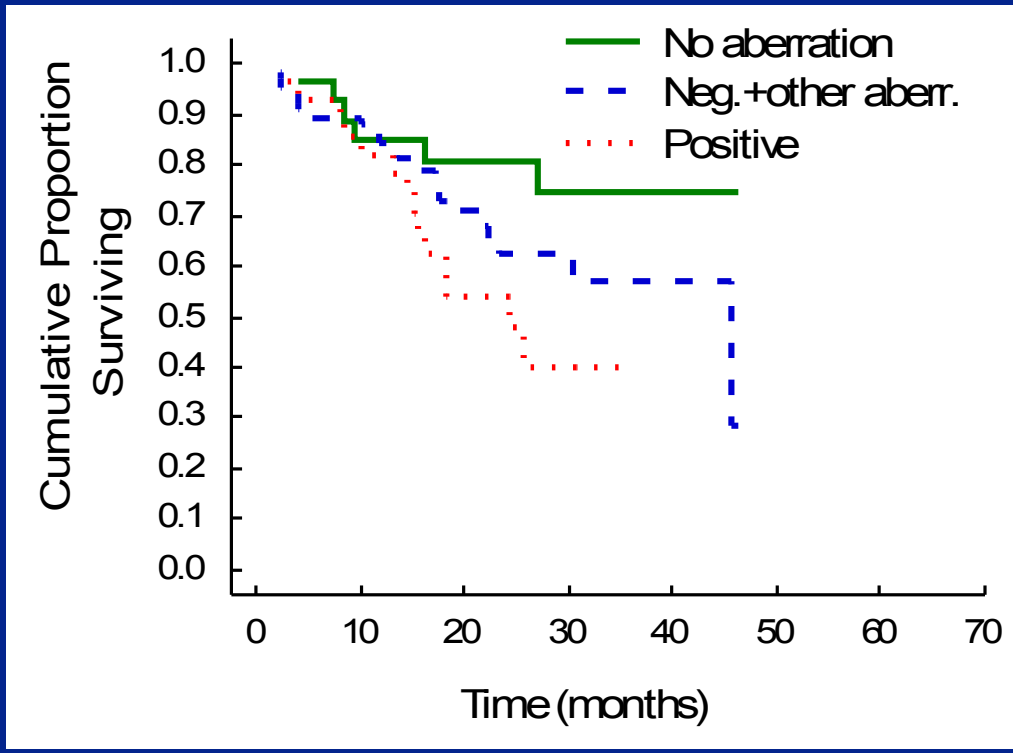
t(4;14)(p16;q32)

Translocation proved in 15.8% of patients (cIg-FISH)

Overall survival



Progression-free survival

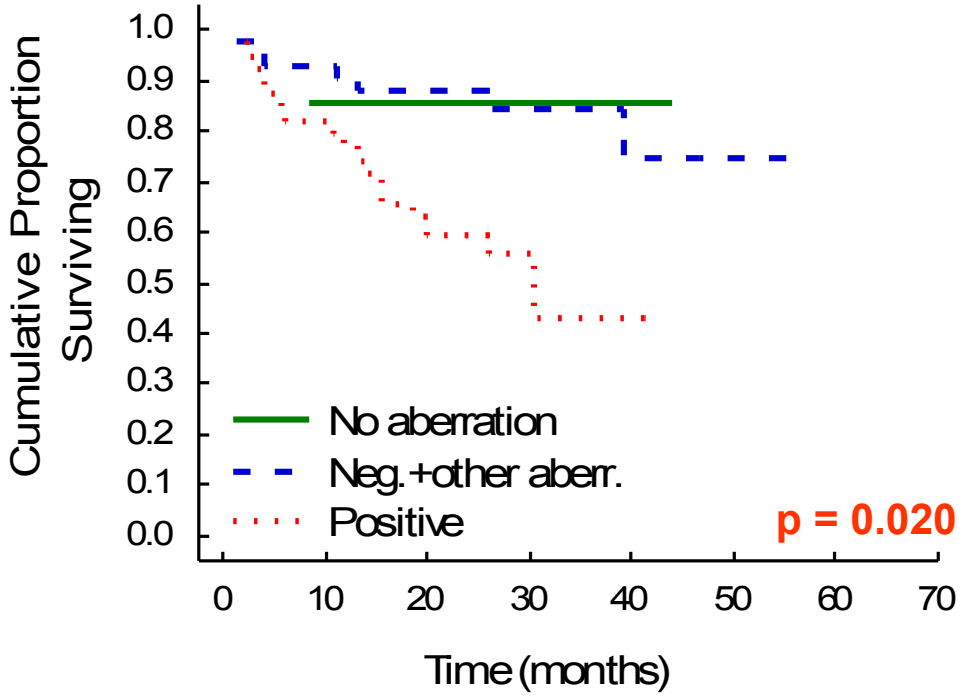


Trend towards shorter OS a PFS

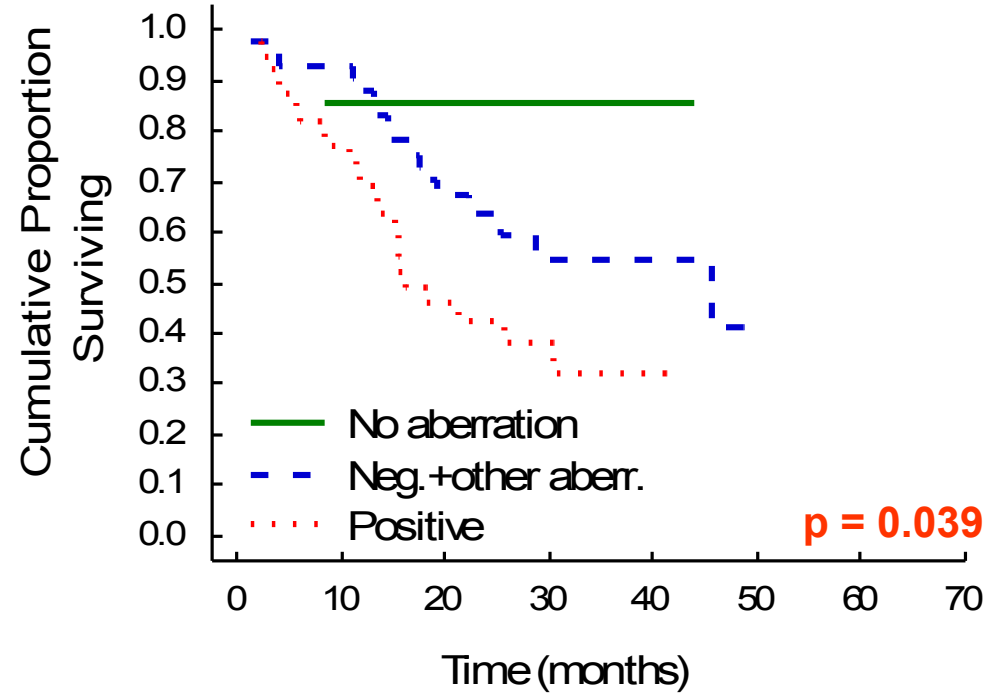
Gain of 1q21

Gain of 1q21 proved in 37.7% of patients (cIg-FISH)

Overall survival



Progression-free survival



Statistic analysis proved significantly shorter PFS and OS in patients with gain of 1q21

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

URC-CMG
UNIVERSITY RESEARCH CENTRE
CZECH MYELOMA GROUP

ARE THE NEW DRUGS OVERCOME NEGATIVE PROGNOSTIC FEATURE OF KNOWN CHROMOSOMAL ABNORMALITIES ?

Bortezomib
&
chromosomal abnormalities

VISTA trial - bortezomib is effective in patients with standard-risk as well as high risk disease

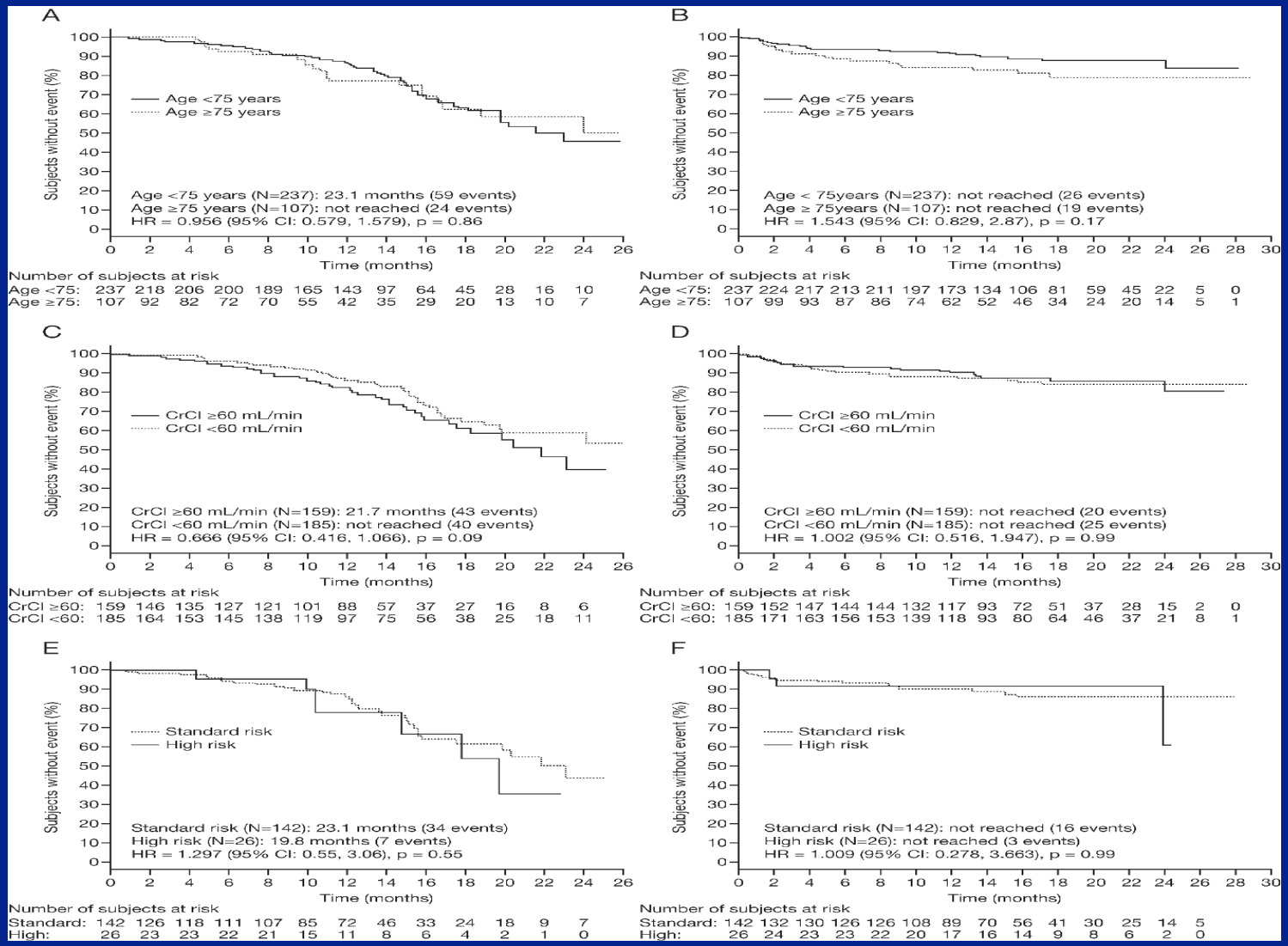
Time to progression

Overall survival

Age ≥75 vs. <75 years

CrCl <60 vs ≥60 mL/min

High-risk
t(4;14); t(14;16); del(17p)
vs.
Standard-risk
cytogenetics by FISH



LIMITS
&
CONCLUSION

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

There are several key limits of transplantation methods

1. Long term results
2. Availibity and indication for patients
3. Benefit from AT is limited by age
4. Too toxic induction before AT
   (drop out during VAD 10-20%)
5. AT did not overcome cytogenetic negative

   prognostic factors

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

In real life only 1/4 of all patients with MM benefits from AT

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

FUTURE
&
TRANSPLANTATION

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

Minimal space for further improvement of this treatment method

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

NEW DRUGS

NEW STRATEGIES

HOW TO OVERCOME TRANSPLANT LIMITATIONS

HOW TO INTRODUCE THE BENEFIT OF AT TO ALL SUITABLE PATIENTS

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

NEW DRUGS

MP + novel agents: study results

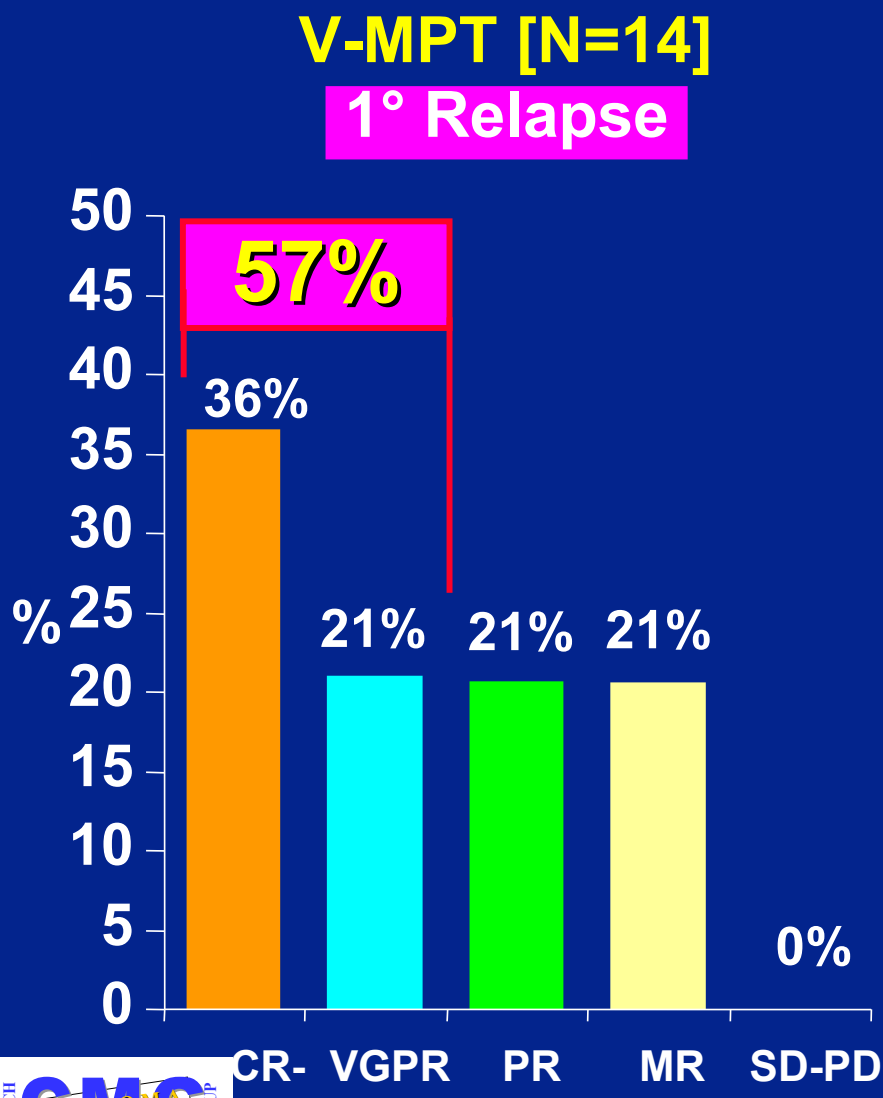
	MPT (n=124) Facon *et al.*	MPT (n=129) Palumbo *et al.*	MPV (n=60) *Mateos et al.*	R-MP (n=50) Palumbo *et al.*
Age (>75years)	0	25%	47%	6%
Efficacy				
CR + PR	81%	76%	88%	85%
CR	15%	16%	32%	17%
EFS	29m	54% at 24m	82% at 16m	87% at 16m

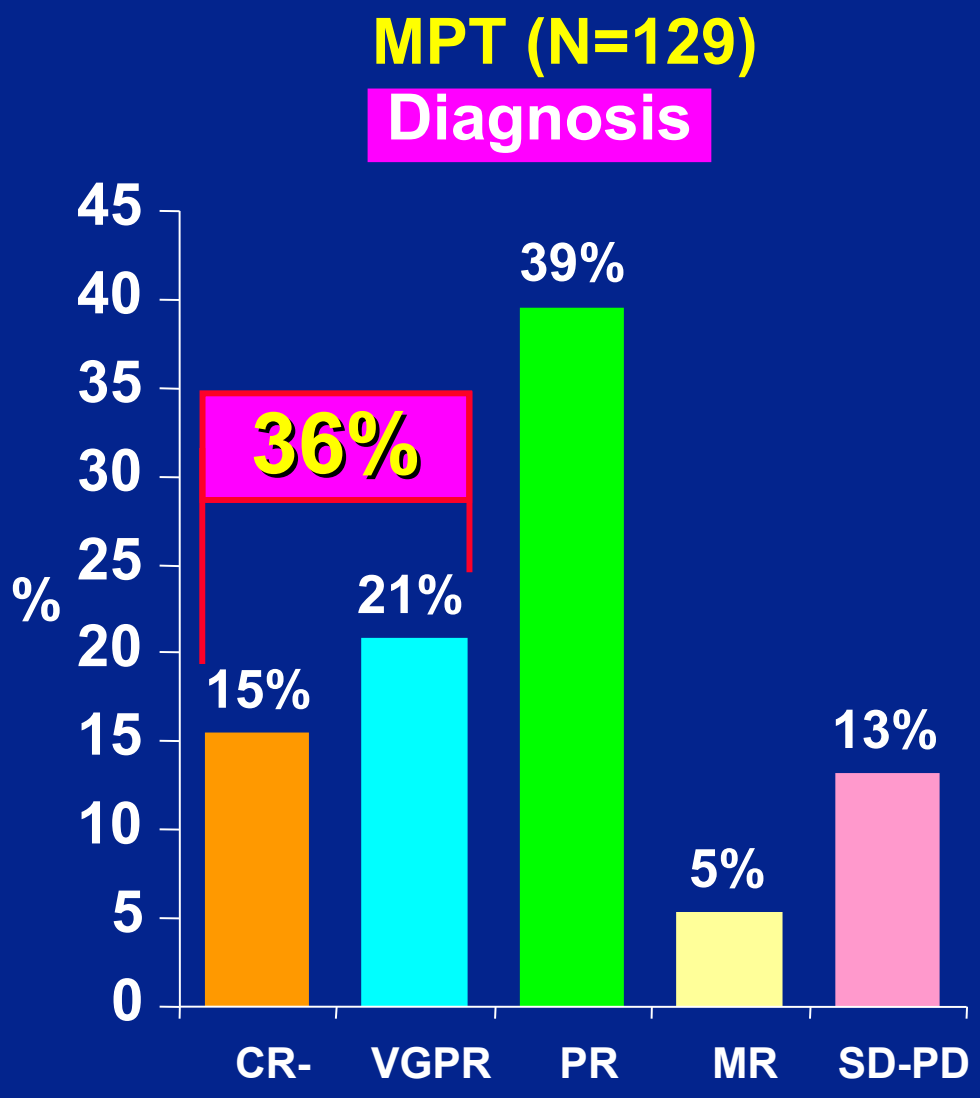
Palumbo *et al.* *Lancet* 2006; 367:825–31
Facon *et al.* ASCO 2006 (abstract 1)
Palumbo *et al.* ASH 2006 (abstract 800)
Mateos *et al.* *Blood* 2006;108:2165–72

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

URC-CMG
UNIVERSITY RESEARCH CENTRE
CZECH MYELOMA GROUP

V-MPT at 1° Relapse vs. MPT at Diagnosis





CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

Lancet 2006;367:825

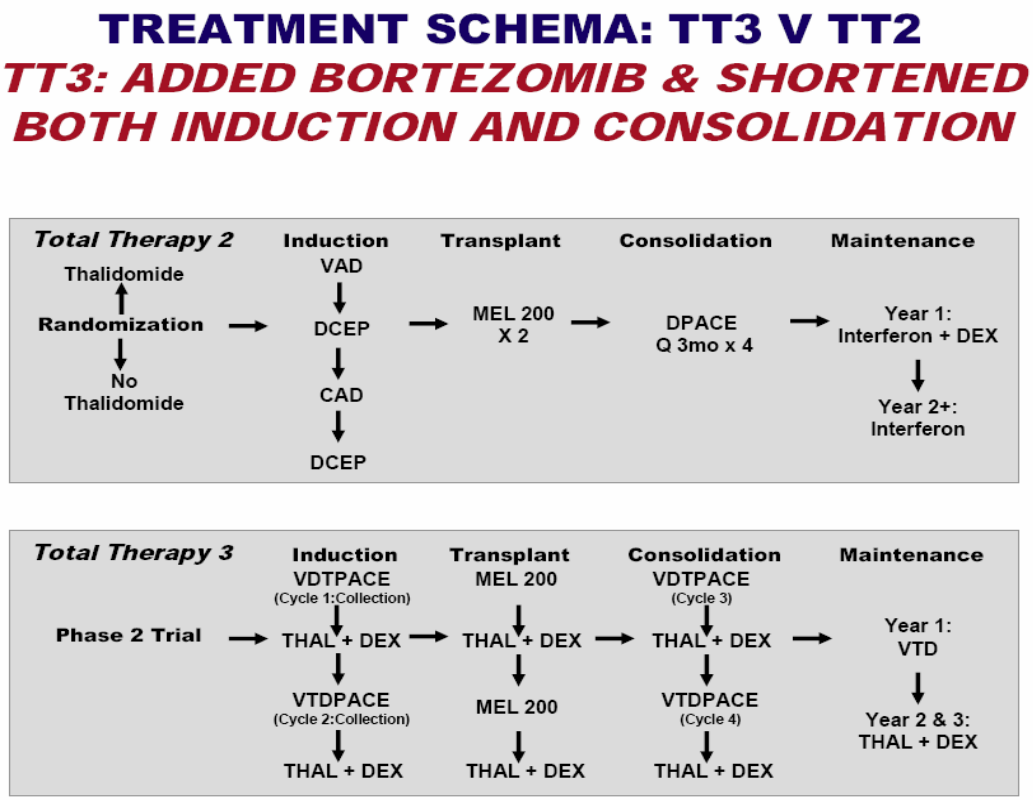
NEW DRUGS

NEW STRATEGIES

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

The most intensive treatment with new drugs and transplantation

Figure 1:



Progression through treatment phases was faster and completion of intended therapies greater in TT3 than TT2 (Figure 2).

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

TRIAL CMG 2008

Induction: RD 4 cycles

(á 4 wks; lenalidomide 25 mg den 1-21, dexamethasone 40 mg dny 1, 8, 15, 22)

PBSC collection(CFA 3g/m²+ G-CSF)

Randomization 1:

Arm A: CRD 6 cyklů

Arm B: ASCT (MEL 200)

CRD: Cyklofosfamid 300 mg/m² day 1, 8, 15; lenalidomide 25 mg day 1-21; dexamethasone 40 mg den 1, 8, 15, 22

NEW DRUGS

NEW STRATEGIES

HOW TO OVERCOME TRANSPLANT LIMITATIONS

1. Limited possibility to improve results achieved with myeloablative regimen

MEL 200 mg/m^2

2. The space for better results is still large in the methods of ALLO transplantation

NEW DRUGS

NEW STRATEGIES

HOW TO OVERCOME TRANSPLANT LIMITATIONS

HOW TO INTRODUCE THE BENEFIT OF AT TO ALL SUITABLE PATIENTS

The role of guidelines, patients organizations?

HOW TO INTRODUCE THE BENEFIT OF AT TO ALL SUITABLE PATIENTS

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

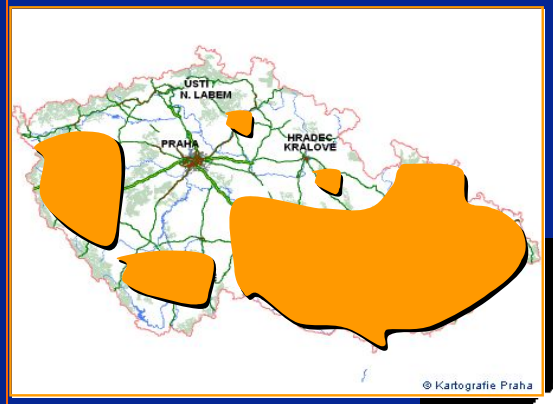
How the AT was introduced to patients with MM in Czech Republic in period 1995-2005

Lesson from Czech Myeloma Group

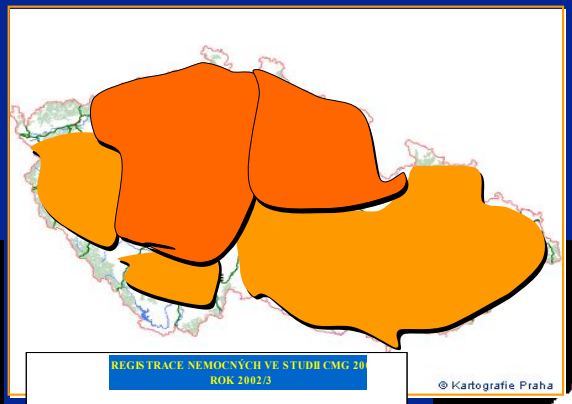
CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

Clinical trials (4W, CMG2002) of CMG with AT in period 1995-2005

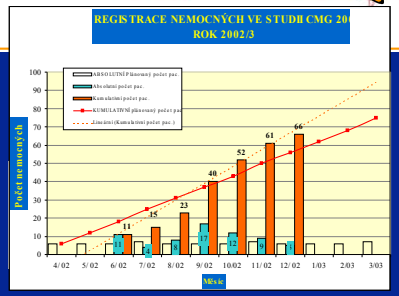
- Year 1995
- Year 2000
- Year 2005

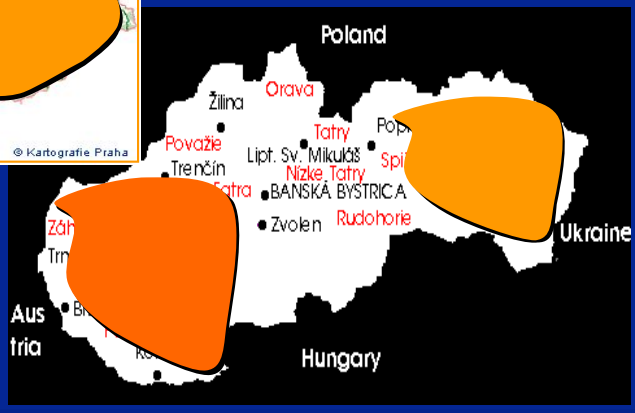


4W



CMG 2002





CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

INDICATION OF AT IN CZECH REPUBLIC

(% of indicated pts. from all potentionally suitable pts. for AT program)

- YEAR 1995

0 %

- YEAR 2000

60 %

- YEAR 2005

80 %

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

ACCURATE AND MAXIMAL ENROLMENT TO TRANSPLANTATION PROGRAM

KEY FOR EVERYDAY ROUTINE:

EFFECTIVE AND SHORT TRANSMISSION OF CLINICAL TRIALS RESULTS INTO EVERYDAY USE WITH POSITIVE BENEFIT FOR THE PATIENTS.

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

OBJECTIVES INTEGRITY:

STRENGTHENING OF SPECIALIZED NETWORK

PHYSICIAN KNOW-HOW AND EDUCATION

PATIENT KNOW-HOW AND EDUCATION

FUNCTIONAL AND EFFECTIVE CONNECTION OF REGIONS WITH SPECIALIZED CENTERS

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

CONCLUSIONS

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

AT has the crucial benefit for the patient with MM at age under 60

CZECH MYELOMA GROUP
CMG
ČESKÁ MYELOMOVÁ SKUPINA

Benefit of AT is limited in real life

1. There are several limitations of AT

2. Consequently, only ¼ of all patients with MM can profit from AT in real life

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

Benefit of AT is limited in real life

- **Limited possibility to improve results achieved with myeloablative regimen MEL 200 mg/m2**
- **Still space for improvement of allogeneic methods**
- **Trends to combine AT with new drugs seems to be good logic step forward**

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

How can myeloma organizations help?

It is very important, if any of tested therapies is considered as new perspective treatment.

The more important is, if the most patients can benefit from this treatment in short time period.

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

Thanks to

Dep. Hematooncology MU Brno

- Jiri Vorlicek
- Jiri Mayer
- Zdenek Adam
- Ludek Pour
- Marta Krejci
- Andrea Krivanova

Research Myeloma Nurses

- Silvie Vostrejsova
- Kamila Havlíkova
- Iveta Mareschova
- Eva Vetešníková

CIA UOC Group

- Ladislav Dusek
- Ludvik Dolezal
- P. Pavlis
- A. Svobodnik

Main Centers of CMG

- V. Scudla, E.Gregora,
- V. Koza, M. Schützova
- K. Indrak, I. Spicka
- M. Mistrik, E. Tothova
- all cooperating doctors

CZECH MYELOMA GROUP
ČESKÁ MYELOMOVÁ SKUPINA

Thank you for you attention

CZECH MYELOMA GROUP CMG