National Essential Medicine List
Tertiary Level Medication Review Process
Component: Immunomodulatory agents: Thalidomide

MEDICINE MOTIVATION:

1. **Executive Summary**

Date: 30 July 2018
Medicine (INN): Thalidomide
Medicine (ATC): L04AX02
Indication (ICD10 code): *C90.0, C90.1, C90.2, C90.3*
Patient population:
1. Multiple Myeloma – Transplant eligible
2. Multiple Myeloma – Transplant ineligible

Incidence of condition: 6.2 per 100 000 persons at age 65 (Schonfeld SJ 2016)
310 new cases/ year (National Cancer Registry 2009-2014*)(public and private)*
Level of Care: Tertiary level, Specialist – Oncology/Haematology
Prescriber Level: Specialist – Oncology/Haematology
Current standard of Care: Melphalan/Prednisone. Vincristine/Doxorubicin/Dexamethasone +/- Cyclophosphamide.
Efficacy estimates: (preferably NNT):
1. Transplant eligible
TD vs D/VAD Response Rate NNT = 5 *(Cavo et.al. 2005)*
CTD vs CVAD Response Rate NNT = 9, Post autologous stem cell transplant complete response NNT = 8 *(Morgan et.al. 2012)*

2. Transplant ineligible
MPT vs MP Overall Response Rate NNT = 4, Complete response NNT = 5, 3y Overall Survival NNT = 7 *(Palumbo et.al. 2006)*
CTDa vs MP Overall Response Rate NNT = 3, Complete Response NNT = 10 *(Morgan et.al. 2011)*
Motivator/reviewer name(s): Tertiary Expert Review Committee, Ratified by NEMLC

2. **Name of author(s)/motivator(s)** Tertiary Expert Review Committee

3. **Author affiliation and conflict of interest details** *On member declared following:*

Conflicts of Interest

- Janssen (Supplier of Bortezomib): Nature of what received: conference sponsorship, honoraria for talks, and scientific advisory committee
- Key Oncologics (Supplier of Thalidomide and Lenalidomide): Nature of what received: conference sponsorship, honoraria for talks

Assessed to be potentially significant, thus the review was peer reviewed by the Tertiary Committee as a whole, and such individual not responsible for final recommendation.

4. Introduction/ Background

Multiple myeloma is a malignancy of mature plasma cells that primarily affects the bone marrow, but can also present with extramedullary plasmacytomas. Classical clinical features include anemia, renal failure, lytic bone lesions, and hypercalcaemia. Patients can present with spinal cord compression due to vertebral fractures or plasmacytomas. Other clinical features include recurrent infections, hyperviscocity, thrombosis and various other paraneoplastic phenomena.

In South Africa haematological malignancies comprise approximately 6% of all malignancies reported to the National Cancer Registry (NCR). Myeloma accounts for approximately 10% of haematological malignancies. The age standardized incidence rate for the population over the age of 15 is 0.83 per 100 000 persons for females and 1.00 for males. The mean age of diagnosis is 65 with an incidence rate of 6.2 per 100 000 persons. (Schonfeld SJ 2016) Based on NCR data an average of 310 (Range 288 to 347) new myeloma cases were diagnosed per year in South Africa from 2009 to 2014.

With currently available therapy myeloma is not curable, but outcomes and survival has improved significantly over the past 10 to 15 years. Median OS improved from 4.6 years in 2001-2005 to 5.2 years in 2006-2010. This is linked to the availability of new treatment options. Good risk patients can have prolonged survival extending past 10 to 15 years. (Kumar SK 2014)

The natural history of myeloma follows a relapse remitting course. Progressing disease is associated with morbidity and mortality associated with renal failure, bone marrow failure, and bone destruction. Multiple treatment episodes are followed by disease free periods of varying duration. With each relapse and subsequent treatment the duration of relapse free survival tends to decrease. This chronic relapse remitting nature of myeloma associated with multiple lines of different treatment regimens leads to a difficulty in showing OS differences in research clinical trials. Progression free survival difference is however relatively easy to demonstrate. In settings where multiple lines of therapy are available patients often receive novel treatment options on relapse.

It is important to note that depth of treatment response has been clearly linked to PFS and OS with deeper responses leading to better outcomes (Lonial S 2015). Response is defined by the International Myeloma Working Group (IMWG), and is assessed by looking at the change in serum/urine monoclonal protein (M-protein), serum free light chains (SFLC), and bone marrow plasma cell burden. Briefly, partial response (PR) is ≥ 50% decrease in serum M-protein or SFLC, while complete response (CR) is absence of serum/urine m-prot and normal SFLC. Very good partial response is a serum/urine M-protein that is detectable by immunofixation but not on electrophoresis.

Myeloma therapy is highly complex, and involves various modalities. Treatment plans incorporating high dose melphalan with stem cell rescue (autologous stem cell transplant, ASCT), although not curative, is associated with a significant improvement in overall survival (OS). One of the earlier landmark trials showed an improvement in median overall survival from 42.3 to 54.1 months. (Child JA 2003).
Therefore the initial treatment decision involves deciding if a patient is transplant eligible or not. This decision is based on the age and comorbidities of the patient. Eligibility criteria differ between treatment centers. In general patients<65 years are deemed eligible for autotransplant, but older patients with a good performance status and no significant co-morbidities can also be transplanted. If one ignores co-morbidities, and takes 60 years as a cut-off approximately 42% of myeloma patients will be transplant eligible. This increases to 59% if 65 years is taken as the cut-off.

Transplant eligible patients are induced with 4 to 6 cycles of any one of various induction regimens. It is important that a good partial response (>50% reduction in tumour burden) is attained before transplant, and failure generally precludes transplant. Once a good partial response is achieved autologous peripheral blood stem cells are collected, followed by either early or delayed ASCT. ASCT may be followed by observation, consolidation or maintenance therapy depending on patient criteria and options available. Patients not eligible for transplant are treated with chemotherapy alone.

Drugs used in the treatment of myeloma can broadly be divided into corticosteroids (prednisone, dexamethasone), conventional chemotherapy (melphalan, cyclophosphamide, doxorubicin, vincristine, bendamustine) and novel agents. Novel agents comprise proteasome inhibitors (bortezomib, *carfilzomib*, *ixazomib*), immunomodulators (thalidomide, lenalidomide, *pomalidomide*), and anti-CD38 monoclonal antibodies (*daratumumab*). Note that at the time of writing, the drugs in italics were not registered yet in South Africa. The current international standard of care is the combination of one or two novel agents with corticosteroids with or without conventional chemotherapy.

A major challenge in interpreting outcome data of different regimens in myeloma is the striking paucity of trials directly comparing different regimens, and often surrogate end-points are used to arrive at conclusions. Various trials have shown that depth of response is a valid surrogate for progression free and overall survival. Regimens incorporating novel agents leads to more and deeper responses. So-called triplet regimens (proteasome inhibitor, immunomodulatory agent, corticosteroid/chemotherapy) is associated with the best responses. (Lonial S 2015)

The only drugs routinely available in the public sector are corticosteroids, melphalan, cyclophosphamide, doxorubicin, and vincristine. ASCT is not uniformly available throughout the country although is available in a number of academic hospitals. Transplant eligible patients are usually treated with induction cyclophosphamide/dexamethasone (CD) or vincristine/doxorubicin/dexamethasone (VAD) ± cyclophosphamide (CVAD). Melphalan is avoided during induction for transplant eligible patients due to potential stem cell toxicity.

5. Purpose/Objective

-P *(patient/population):* Newly diagnosed transplant eligible and ineligible multiple myeloma
-I *(intervention):* Incorporation of thalidomide in treatment regimens
-C *(comparator):* Standard chemotherapy without novel agents
-O *(outcome):* Response rate, progression free survival, overall survival

6. Methods:

- **Data sources** *Pubmed, Reference list of articles*

7. Evidence synthesis

Author, date	*Type of study*	n	Population	Primary outcome	Effect sizes	Comments
Transplant Eligible						
Cavo 2005	Retrospective matched case-control analysis. TD vs VAD	TD = 100 VAD = 100	Induction before ASCT	Response rate 76% TD vs 52% VAD (P<0.001)	RR NNT 5	Thalidomide 200mg/day Dexamethasone 40mg day 1-4, 9-12, 17-20. No OS data reported.

Rajkumar 2006	Phase III RCT TD vs D	TD = 103 D = 104	Induction before ASCT	Response rate 65% TD vs 41% D (P=0.0017)	RR NNT 5	Thalidomide 200mg/day Dexamethsone 40mg day 1-4, 9-12, 17-20. Grade 3 or higher toxicity 45% TD vs 21% D. P<.001. Not powered for OS.
Morgan 2012	Phase III RCT (MRC IX trial) CTD vs CVAD	CTD = 555 CVAD = 556 Thalidomide start dose 100mg (max 200mg)	Induction before ASCT	Response rate 82.5% CTD vs 71.2 CVAD (P< 0.0001) CR 13.0% vs 8.1% (P=0.0083) Post ASCT CR 50% vs 37.2% (P=0.00052)	RR NNT 9. CR NNT 21. Post ASCT CR NNT 8.	CTD Non-inferior for PFS and OS. PFS in patients with CR 39m vs 32m P=0.0099. CTD is oral regimen compared to 5 day infusional CVAD
Morgan 2013	Phase III RCT (Long term follow-up of MRC IX. Median follow-up 5.9 years)		Induction before ASCT	Median OS 71m in CTD vs. 63m in CVAD (P=0.23) Median OS in favorable cytogenetics (n = 333) 98m vs 81m (P=0.068)		Trend towards OS benefit in CTD arm. Authors note that availability of salvage therapy with bortezomib or lenalidomide probably impacted OS data.
Transplant Ineligible						
Palumbo 2006	RCT: MPT vs MP 6 months therapy *(thalidomide at 100mg)*	MP = 126 MPT = 129	Transplant ineligible, age 60 to 85	ORR MPT 76% vs MP 47.6%. CR/nCR MPT 27.9% vs MP 7.2%. 2y EFS MPT 54% vs MP 27% (P=0.0006). 3y OS MPT 80% vs MP 64% (P=0.19)	ORR NNT 4. CR/nCR NNT 5. 2y EFS NNT 4. 3y OS NNT 7	Grade 3 or 4 adverse event 48% in MPT and 25% in MP (p=0.0002). Enoxaparin prophylaxis reduced thrombosis rate from 20% to 3%
Facon 2007	Phase III RCT MPT vs MP vs M 100 (mini ASCT). MP/MPT for 12 months.	MP = 196 MPT = 125 Mel100 = 126 Thal starting dose: 64 started at	Transplant ineligible, age 65 to 75	Median Follow-up 51.5m. Median OS MPT 51.6m vs. MP 33.2m vs. Mel100 38.3m. MPT vs MP (p=0.0006)		Authors note that persistent survival difference after 51m of follow-up is particularly significant as some patients in MP arm probably received thalidomide after

	Aim was for 400mg Thalidomide	≤200mg. 60 at ≥200mg. Only 11 increased dose later		MPT vs Mel100 (p=0.027) MP vs Mel100 (p=0.32)		patient accrual ended in line with IFM recommendations. More toxicity in MPT arm, but less early or toxic deaths.
Hulin 2009	Phase III placebo controlled RCT. MPT vs MP + Placebo 12 courses. 6 weekly administration Thalidomide 100mg	MP = 116 MPT = 113	Transplant ineligible, age over 75	Median follow up 47.5m. Median OS MPT 44m vs MP 29.1m (p=0.028) PFS MPT 24.1m vs 18.5m p=0.001.		Grade 2 to 4 peripheral neuropathy (20% vs 5%) and grade 3 to 4 neutropenia significantly increased in MPT arm
Fayers 2011	Meta-analysis 6 randomized trials of MPT vs MP (Including 3 above trials)	1685	Transplant ineligible, elderly	Median OS MPT 39.3m vs. 32.7m MP p=0.004 PFS MPT 20.3m vs. MP 14.9m (P<0.0001) VGPR or better at 12 months MPT 25% vs 9% PR or better MPT 59% vs MP 37% (P<0.0001)	NNT to be alive at 2 years = 20 (63.7% alive on MP vs 68.8% on MPT). Noted that absolute differences at 3 and 4 years is larger	Included trials vary with respect to treatment protocol (dose/number of cycles/duration of thalidomide). Two trials placebo controlled. Differences in baseline characteristics of patients (age/stage) Differences in outcome more pronounced with longer follow up
Morgan 2011	Phase III RCT (Part of MRC IX trial) CTDa vs. MP (Min 6 cycles, max 9 cycles)	CTDa = 426 MP = 423 CTDa = lower dose Thalidomide (start at 50mg, increase by 50mg every	Transplant ineligible. Median age 73 (57 to 89)	Overall response CTDa 63.8% vs MP 32.6% (P<0.0001) Complete response CTDa 13.1% vs MP 2.4%	NNT ORR = 3 NNR CR = 10	Significantly better responses to CTDa with marginal benefit in terms of OS and PFS. Survival curves suggest late benefit for CTDa. Overall survival better in those

		4 weeks as tolerated to max of 200mg) Reduced Dexamethasone dose from 40mg to 20mg		PFS CTDa 13m vs. MP 12.4m P=0.01 OS CTDa 33.2m vs MP 30.6m P=0.24		patients with better cytogenetic risk disease 37m vs 24m (P<0.001) Median OS significantly better (Not reached at 44m) in those achieving CR (66 patients, of which 56 in CTDa arm)
VAD: *vincristine-doxorubicin-dexamethasone;* TD: *Thalidomide-dexamethasone;* D*: Dexamethasone;* ASCT: *Autologous stem cell transplant*; RR: *response rate;* CTD: *cyclophosphamide-thalidomide-dexamethasone;* CVAD: *cyclophosphamide-vincristine-doxorubicin-dexamethasone;* PFS*: progression free survival;* OS: *Overall survival;* CR: *complete response;* MP: *melphalan-prednisone;* MPT: *melphalan-prednisone-thalidomide;* EFS: *event-free survival;* nCR*: near-complete response rate;* ORR: *overall response rate;* IFM*: intergroup Francophone du Myelome*						

- **Evidence quality:** Although there is relatively few trials with head-to-head comparisons between all the various available treatment regimens, the quality of data is generally moderate to good. Most of the data presented stems from randomized controlled trials (One placebo controlled trial, and one meta-analysis of available RCT's). One retrospective matched case control analysis also included.

8. **Alternative agents:** The only drugs routinely available in the public sector are corticosteroids, melphalan, cyclophosphamide, doxorubicin, and vincristine (used in various combinations). Thalidomide may be accessed on buy-out in some provinces and treatment centers.
   Other novel agents such as bortezomib and lenalinomide are not available is the public sector. Bendamustine is an alternative chemotherapeutic agent in the relapsed setting, but is also not available in the public sector.

9. **Side effect/Toxicity:** Thalidomide has important adverse effects, and these need to be monitored for and actively prevented/managed. The four most important adverse effects are:
   - Venous thromboembolism. Especially in combination with corticosteroids. Patients require active thromboprophylaxis. Options include low dose aspirin, heparin, LMWH and warfarin, and the decision of which to use is individualized based on thrombosis/bleeding risk.
   - Peripheral neuropathy. Reduction in dose and/or interruption for painful neuropathy associated with weakness is necessary.
   - Teratogenicity. A risk management system is used to prevent pregnancy exposure.
   - Sedation. Patients are advised to take therapy at night.

10. **Cost**
    The standard dose of thalidomide for multiple myeloma is 100mg daily for 6 months. The cost per course based on Single Exit Pricing is R44 496.81, and based on current buy-out price (October 2018) it is R30 670.56.

Budget impact

The National Cancer Registry reports 310 new multiple myeloma cases per year. This includes both private and public sector patients. It was estimated that two thirds of these patients would be in the public sector (~200 patients). Of these patients, some would be transplant eligible, and some transplant ineligible. Considering comorbidities, ⅔ would be transplant ineligible (~140), and the rest transplant eligible (~60). The annual budget impact based on SEP and buy out price is estimated as follows:

TRANSPLANT ELIGIBLE			
100mg/day (6 months)	**Thalidomide cost/patient/6 months**	**no. patients**	**Budget impact/yr**
Buy-out	R30,670.56	60	R1,840,233.60

TRANSPLANT INELIGIBLE			
100mg/day (6 months)	**Thalidomide cost/patient/6 months**	**no. patients**	**Budget impact/yr**
Buy-out	R30,670.56	140	R4,293,878.40

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	The addition of thalidomide to treatment regimens improves response rates and depth of response. Better responses will lead to more patients getting transplanted. In the transplant eligible setting there is evidence for late benefit in PFS and OS. PFS and OS benefit is shown in transplant ineligible setting.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	Thalidomide has important side effects, and these need to be monitored for and actively prevented/managed. The four most important side effects is: 1. Venous thromboembolism. 2. Peripheral neuropathy. 3. Teratogenicity. 4. Sedation.

<table>
<tr><td>VALES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [X] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td><td>Thalidomide allows for highly effective oral outpatient induction chemotherapy for myeloma patients. This reduces utilization of limited hospital beds.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?

More intensive [ ] Less intensive [ ] Uncertain [ ]</td><td>Cost of medicines/ month:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Thalidomide 6 month course</td><td>R30,670.56</td></tr></table>
Additional resources:</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?

Yes [ ] No [X] Uncertain [ ]</td><td>Thalidomide is accessed on buy-out in certain provinces and hospitals. Availability of thalidomide on the EML will ensure equal treatment of myeloma in all public sector hospitals.</td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☒	☐

Recommendation	Thalidomide should be available on the Essential Medicines list for the treatment of newly diagnosed transplant eligible and ineligible patients, to be prescribed by designated specialist.
NEMLC Recommendation	NEMLC accepted thalidomide for multiple myeloma, provided a fair price is attained.
Review Indicator	**Price** Reference Price: 80% reduction from Single Exit Price
Monitoring and evaluation considerations	Monitoring for and managing of adverse effects is critical, and should form part of routine myeloma care. Risk management to prevent pregnancy exposure.
Research priorities	

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Figures

Characteristic	GIMEMA	HOVON	IFM-I	IFM-II	NMSG	TMSG
Trial label	GIMEMA	HOVON49	IFM99–06	IFM01/01	NMSG12	TMSG
Country	Italy	The Netherlands/Belgium	France	France	Nordic	Turkey
No. of patients	331	333	321	229	357	114
Inclusion year	2002-05	2002-07	2000-05	2002-06	2002-07	2006-09
Age, y	> 65	> 65	65-75	> 75	> 65	> 55
SD stage	II, III	Ib, II, III	II, III, and I high-risk	II, III, and I high-risk	I-III symptomatic	I-III symptomatic
WHO status	0-4	0-3	0-4	0-4	0-4	0-2
Placebo	No	No	No	Yes	Yes	No
Melphalan	4 mg/m^2	0.25 mg/kg	0.25 mg/kg	0.20 mg/kg	0.25 mg/kg	9‖mg/m^2
Prednisone	days 1-4	days 1-5	days 1-4	days 1-4	days 1-4	days 1-4
	40 mg/m^2	1 mg/kg	2 mg/kg	2 mg/kg	100 mg	60 mg/m^2
	days 1-7	days 1-5	days 1-4	days 1-4	days 1-4	days 1-4
No. of cycles/interval (weeks)	6/4	8/4	12/6	12/6	Until plateau/6	8/6
Thalidomide, mg/day	100	200	100-400*	100	200-400	100
Duration	Until relapse	8 cycles	12 cycles	12 cycles	Until relapse†	8 cycles
Crossover to MPT from MP	No	No	No	No	No	18%
Second-line thalidomide after relapse, % of MP patients	34‡	57	38	45	45	7

HOVON indicates Hemato-Oncologie voor Volwassenen Nederland.
*Recommended dose was 200 mg/day with rapid increase if well tolerated, up to maximum 400 mg/day.
†A total of 200 mg/day from plateau until relapse.
‡Second-line thalidomide or bortezomib.

Figure 1 MPT vs MP in elderly trial characteristics (Fayers PM 2011)

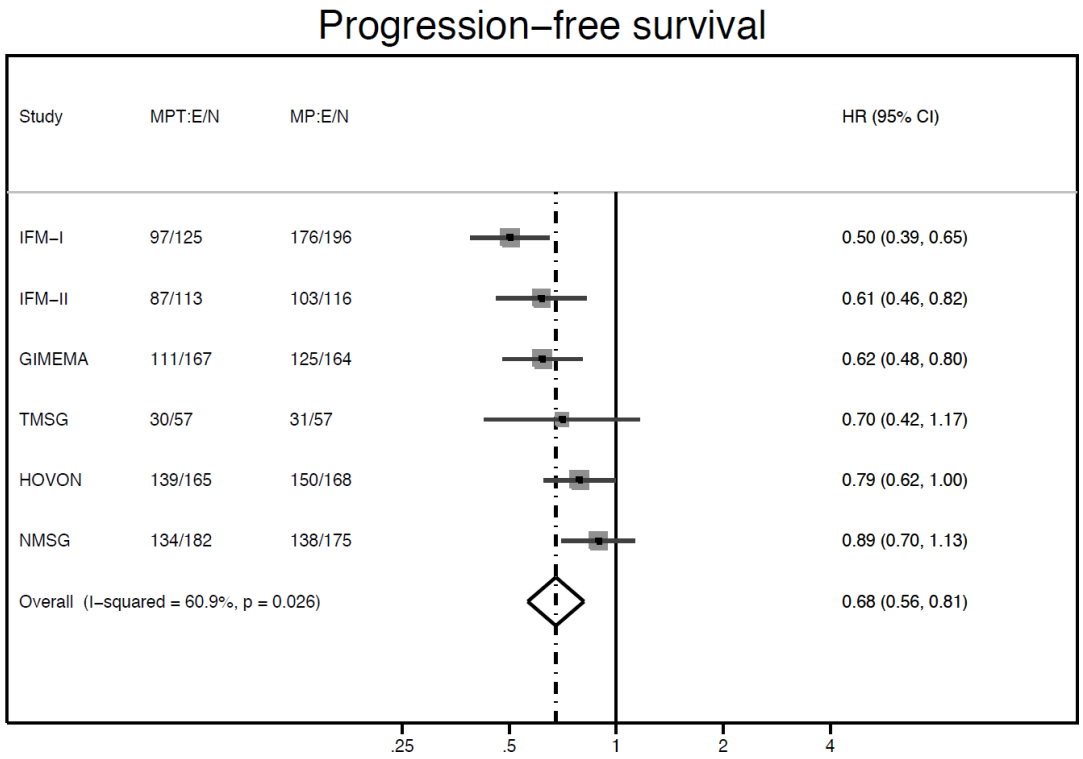

Figure 6. Forest plot: PFS HR of MPT versus MP, by study. The HR and 95% CI are shown for each study, and the overall HR (where the dotted line bisects the diamond) and 95% CI (indicated by left and right corners of the diamond), assuming a random effects model. For each treatment arm of each study, the number of events (deaths) and number of patients (E/N) is given. Overall test of HR = 1: $P < .0001$.

Figure 2 PFS MPT vs MP in elderly (Fayers PM 2011)

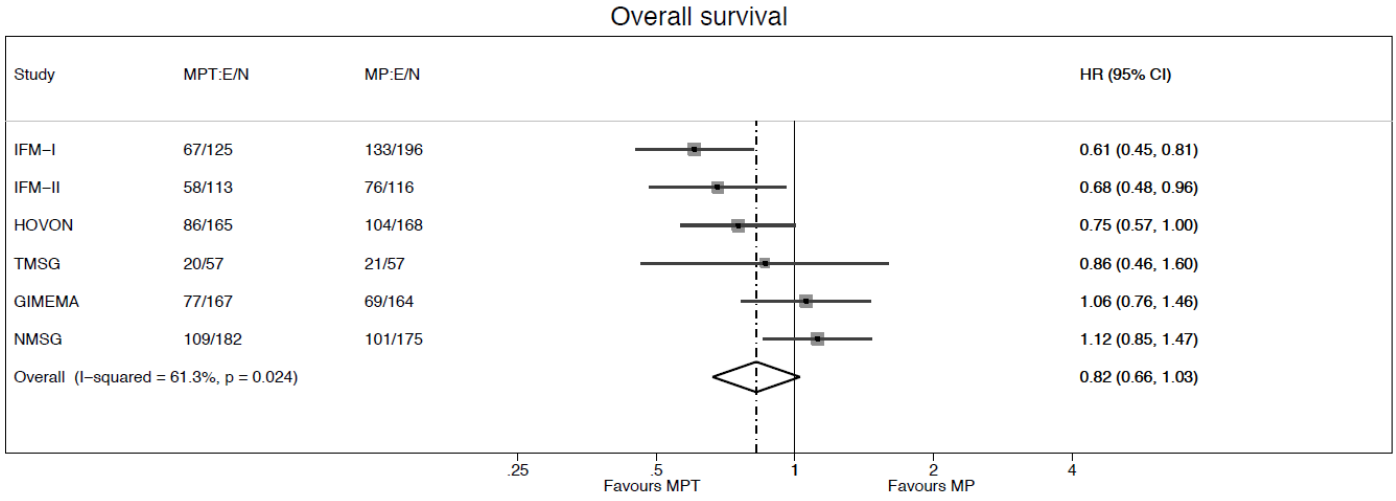

Figure 2. Forest plot: OS HR of MPT versus MP, by study. The HR and 95% CI are shown for each study, and the overall HR (where the dotted line bisects the diamond) and 95% CI (indicated by left and right corners of the diamond), assuming a random effects model. For each treatment arm of each study, the number of events (deaths) and number of patients (E/N) is given. There is evidence of heterogeneity ($I^2 = 61\%$) that may jeopardize the *P* value and CI of the estimated overall effect (0.82).

Figure 3 OS MPT vs MP in elderly (Fayers PM 2011)