

Table S1: Summary of recent reviewed studies related to age-standardized incidence/mortality rates of malignant mesothelioma

part 1a-Word publications (2010-2017)

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|-------------------------------|---------|--------------|--|----------------|--------------------------------|---|
| Bianchi et al. 2014 [10] | World | | Different sources | | Standard World population 2000 | <p>Countries at high incidence (> 2 among men) : UK, Australia, Netherlands, New Zealand, Belgium, Republic of Malta</p> <p>Countries with intermediate incidence rates (>1-2) : Denmark, Finland, Norway, Sweden, Iceland, Germany, France, Italy, Croatia, Austria, Cyprus, United States, Israel, South Africa</p> <p>Countries with low incidence rates (<1) or insufficient data : Central Europe, Spain, Ireland, Japan, Lebanon, Jordan, China, South Korea, Taiwan, Hong Kong, Singapore, India, Thailand, Middle East</p> |
| Delgermaa et al. 2011 [11] | World | 1994-2008 | World Health Organization Mortality Database | | Standard World population 2000 | <p>Mortality rate Overall : 0.49 Men : 0.9 Women : 0.19</p> <p>US : 0.5 UK and northern Ireland : 1.78 Japan : 3.2 Germany : 0.68 France : 0.76 Netherlands: 0.64 Australia: 1.65 Italy: 1.03 South Africa: 0.67 Spain: 0.39</p> |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|-----------------------------|---------|--------------|---|------------------------|--------------------------------|---|
| Kameda et al 2014 [14] | World | 1994-2012 | World Health Organization Mortality Database and searched PubMed or governmental websites | ICD-9 ICD-10 C45 | Standard World population 2000 | Countries with early asbestos ban = 0.94 Countries with late asbestos ban = 0.37 Countries with no asbestos ban = 0.32 All = 0.78 |
| Odgerel et al. 2017 [12] | World | 1994-2014 | WHO Mortality Database | C45 | Standard World population 2000 | Crude mortality rate for 104 countries : from 0.004(in Egypt) to 4.456(in the British Virgin Islands) Mean and median of mortality rates: 0.660 and 0.291 |
| Soberg et al. 2015 [15] | World | 2003-2007 | 10th volume of the Cancer Incidence in Five Continents (IARC) | ICD-10 C45 | SegiWorld population | Countries with a age-standardized incidence rate among men > 2.0 : Australia (all jurisdictions), Belgium, England, France (1 out of 11 jurisdictions reported), Germany (4 out of 9 jurisdictions reported), Italy(8 out of 33 jurisdictions reported), New Zealand, The Netherlands, Northern Ireland, Scotland, Switzerland (3 out of 9 jurisdictions reported), and Wales |
| Le et al. 2011 [16] | World | 1994-2008 | WHO Mortality Database | ICD-10 C45 | Standard World population 2000 | Age adjusted mortality rate highest for Cyprus (0.479), Israel(0.367) and Japan (0.325) Japan : linear increase of mesothelioma mortality since 1995 (peak use of asbestos : 1970-1990) Korea : increase in mesothelioma mortality that has slowly risen since 1995 (peak use of asbestos : 1975-1995) Singapore : sharp increase since 1995 (peak use of asbestos : 1975) |

Table S1: Summary of recent reviewed studies related to age-standardized incidence/mortality rates of malignant mesothelioma

Part 1b-countries reporting age-standardized incidence/mortality rates over 2/100,000 among men (2010-2017)

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|--------------------------------|-----------|--------------|---|-------------------|--------------------------------------|---|
| Fazzo et al. 2012 [17] | Italy | 1995-2002 | Death certificates | ICD-9 code 163 | Standard Italian population 2001 | 0-39 years men : 0.04 [0.03-0.05] women : 0.03 [0.02-0.05] 40-75 years men : 4.91 [4.71-5.11] women : 1.71 [1.60-1.82] 76-99 years men : 16.37 [15.61-17.15] women : 5.56 [5.23-5.90] |
| Marinaccio et al. 2012 [18] | Italy | 1993-2004 | Italian National Mesothelioma Register (ReNaM) | | Standard Italian population 2001 | Men : 3.49 Women : 1.25 |
| Korda et al. 2016 [19] | Australia | 1994-2011 | Australian Capital Territory (ACT) Cancer Registry (1982- 2014) Western Australia (WA) Cancer Registry Australian Cancer Database (1982- 2011) | ICD-O-3 | Standard Australian population | both sexes (crude rates) ACT 2009-2011 : 2.95 (2.02-4.17) Rest of Australia 2009-2011 : 2.94 (2.80-3.08) Rates increased 12% more in ACT than the rest of Australia Rose of incidence in ACT at least up to 2009-2011 |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|-----------------------------|-----------|--------------|---|--------------------------|--|---|
| Soeberg et al. 2016 [20] | Australia | 1972-2009 | New south wales cancer registry | ICD-10C45 ICD-O-3 | Australian 2001 World standard population Segi population | <p>Australian standardization 2009 : 2.6 (95%CI 2.3–3.0), men : 4.8 (95%CI 4.1–5.5) / women : 0.8 (95%CI 0.5–1.0)</p> <p>1994 : highestage-standardized incidence rate for men:5.7 (95%CI 4.7–6.6)</p> <p>2003 : highest age standardizedincidence rate for women : 1.1 (95%CI: 0.7–1.4)</p> |
| Soeberg et al. 2016 [21] | Australia | 1982-2009 | Population-based Australian Cancer database | ICD-10 C45 ICD-O-3 | Australian 2001 standard population SegiWorld population | <p>Men : 2.1 in 1982 Average percent of change (APC) : +3.4 (2.5-4.4) 1982-1994 : +6.8 (4.8-8.8) 1994-2009 : 0.8 (-0.1-1.7)</p> <p>Women : 0.3 APC : +4.9 (3.6-6.2) 1982-1994 : +6.7 (5.3-8.1) 1994-2009 : -0.2 (-3.5-3.3)</p> <p>peaked during 2005–2010 for MPM aged 65-74 years peak around 2020 for MPM aged 75 years or more</p> |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|------------------------------|------------------|--------------|-----------------------------|---|---------------------------------------|---|
| Krupoves et al. 2015 [22] | Quebec Canada | 2008-2034 | Canadian cancer registry | 1992-2007ICD- O- 3C38.4+M905C 38.8+M905198 4-1991ICD9 code 163+ ICD- O M905 | Standard Quebec population 1996 | <p>Quebec Men : 2.12 Women : 0.42</p> <p>Average annual rate of change Men 1984-2007 : +2.71% per year (+1.75-+3.67) 1984-1995 : +6.41 (+3.66-+9.22) 1996-2007 : +0.65 (-1.47-+2.81)</p> <p>Women 1984-2007 : +2.60 (+1.02-+4.20) 1984-1995 : +3.55 (-1.46-+8.82) 1996-2007 : -0.92 (-4.45-2.74)</p> <p>Rest of Canada Men : 1.46 Women : 0.21</p> <p>Average annual rate of change Men 1984-2007 : +2.00 (+1.19-+2.81) 1984-1995 : +3,06 (+1.31-+4.83) 1996-2007 : +0.33 (-1.42-+2.10)</p> <p>Women 1984-2007 : +2.53 (+1.13-+3.96) 1984-1995 : +0.14 (-4.22-+4.70) 1996-2007 :+2.84 (-0.45-+6.24)</p> |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|-----------------------------------|---------|--------------|--|--|-----------------------------------|---|
| Van den Borre et al. 2014 [23] | Belgium | 1994-2008 | Death certificates WHO mortality database | ICD-8code 163.0 ICD-9code 163ICD-10C45 | Standard World population 2000 | 0.96 Men: increased from 0.25 to 2.63 over the 40-year periods Increased annual rate of +6.65% Since 1983 : +5.44% Women increased from 0.16 to 0.41 over the 40-year period Increased annual rate of +3.04% Since 1983 : +2.80% |
| Tomasson et al. 2016 [24] | Iceland | 1965-2014 | Population-based Icelandic Cancer Registry National Cause of Death Registry National Register | ICD-10 C45 ICD-O-3 9050/3 9051/3 9052/3 9053/3 | - | Men 1965-1974 : 0.14 (0.01-0.71) 1975-1984 : 0.48 (0.15-1.16) 1985-1994 : 0.94 (0.46-1.72) 1995-2004 : 1.76 (1.09-2.69) 2005-2014 : 2.14 (1.44-3.07) Women 1965-1974 : 0.29 (0.05-0.96) 1975-1984 : - 1985-1994 : 0.31 (0.08-0.85) 1995-2004 : 0.37 (0.12-0.88) 2005-2014 : 0.56 (0.24-1.10) |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|-------------------------------|---------|--------------|---|----------------|--|---|
| Schonfeld et al. 2014 [25] | Germany | 2000-2010 | Death certificates WHO mortality database | ICD-10 C45 | Standard European population truncated to the age of 40 years and older (ASR40+) | <p>2000-2010</p> <p>Men : 3.9</p> <p>East Germany : 1.7</p> <p>annual percent of change <65 yrs : -4.0 (-8.2-0.5)</p> <p>annual percent of change 65+ yrs : 1.0 (-1.7-3.7)</p> <p>West Germany : 4.6</p> <p>annual percent of change <65 yrs : -5.5 (-6.8--4.3)</p> <p>annual percent of change 65+ yrs : 2.9 (2.1-3.7)</p> <p>Women : 0.8</p> <p>East Germany : 0.6</p> <p>annual percent of change <65 yrs : -2.5 (-9.2-4.6)</p> <p>annual percent of change 65+ yrs : -0.3 (-3.9-3.4)</p> <p>West Germany : 0.9</p> <p>annual percent of change <65 yrs : -2.8 (-5.4--0.1)</p> <p>annual percent of change 65+ yrs : -0.1 (-1.6-1.3)</p> <p>predicted peak in both regions around 2020</p> |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|--------------------------|----------|--------------|----------------------------------|----------------|---|---|
| Lehnert et al. 2017 [26] | Germany | 2009-2013 | Population-based cancer registry | ICD-10 C45 | Standard European population truncated to the age of 40 years and older (ASR40+) - Standard European population (EuPop) - World Segi - Standard world population 2000 | <p>ASR40+</p> <p>Men : 4.78 (4.64;4.90)</p> <p>Women : 0.98 (0.92-1.04)</p> <p>EuPop</p> <p>Men : 2.06 (2.00-2.12)</p> <p>Women : 0.43 (0.41-0.46)</p> <p>World Segi</p> <p>Men : 1.33 (1.30-1.37)</p> <p>Women : 0.29 (0.28-0.31)</p> <p>World WHO</p> <p>Men : 1.56 (1.52-1.60)</p> <p>Women : 0.33 (0.32-0.35)</p> <p>Significant downward slopes in men of -0.67 (95% CI -1.10; -0.24) for Bremen and -0.57 (95% CI -0.88;-0.26) for Hamburg, but not for the other federal states</p> <p>Annual rates for women varied without a clear trend</p> |
| Zadnik et al. 2017 [27] | Slovenia | 1961-2014 | Cancer Registry of Slovenia | ICD-10 | Segi World population | <p>2005-2009 (Men and women): 1.5</p> <p>Male: 2.3</p> <p>1998-2003: increased incidence : +13.5% (95%CI: 5.7-20.6)</p> <p>After 2004: -0.4% (-5.1- -3.9)</p> |

Table S1: Summary of recent reviewed studies related to age-standardized incidence/mortality rates of malignant mesothelioma:

Part 1c- countries reporting age-standardized incidence/mortality rates between 1/100,000 and 2/100,000 among men (2010-2017)

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|----------------------------|-------------------|--------------|---|--|--------------------------------|--|
| Glynn et al. 2017 [28] | United- States | 1973-2012 | SEER registries | ICD-10Code C45/C38.4 | Standard US population 2000 | <p>Men Urban: 1.72 increase of incidence rates by 4.16% (95% CI: 3.01, 5.31) per year from 1973 to 1992 and decrease by 1.89% (95% CI: –2.60, –1.17) per year after 1992</p> <p>Rural: 0.2 increase of incidence rates by 23.8% (95% CI: 7.28, 42.8) per year from 1973 to 1980 and constant annual incidence rate through 2012</p> <p>Women Urban: 1.14 increase of incidence rate by 2.82% (95% CI: 1.34, 4.32) per year from 1973-1993 and constant annual incidence rate through 2012</p> <p>Rural: 0.265 Stable trend from 1973-2012: 1.05%; 95% CI: –0.0189, 2.14)</p> |
| Henley et al. 2013 [29] | United- States | 2003-2008 | National Program for Cancer Registries and the Surveillance, Epidemiology, and End Results registries | ICD-O C38.4 C48 Other mesothelioma | Standard US population 2000 | <p>2003-2008 : 1.05 (95% CI: 1.03–1.06) Men : 1.93 (95% CI: 1.90-1.97) Decrease of incidence rate by 2.6%</p> <p>Women : 0.41 (95%CI: 0.41-0.43) Stability of incidence rate</p> <p>State rates from 0.58 to 1.65</p> |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|--------------------------------|---------------|--------------|---|---|--------------------------------|--|
| Mokdad et al. 2017 [30] | United-States | 1980-2014 | National Center for Health Statistics (NCHS) Human Mortality Database | Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) | Standard US population 2000 | 1.0 |
| Helland et al. 2012 [31] | Norway | 1970-2009 | Cancer Registry of Norway | | Standard World population 2000 | Men Rates in 1970-1974 : 0.3 Rates in 2000-2004 : 1.6 Rates in 2005-2009 : 1.5 Age-adjusted annual increase : 4.2% Women Rates in 1970-1974 : 0.1 Rates in 2000-2004 : 0.2 Rates in 2005-2009 : 0.3 Age-adjusted annual increase : 2.9% |
| Kielkowski et al. 2011 [32] | South Africa | 1995-2007 | Death certificate | ICD-9code 509 (Own code of Stats SA) ICD-10code C45 | Standard World population 2000 | Men 1995 : 1.5 (1.2-1.7) 2000 : 1.1 (0.9-1.3) 2005 : 1.2 (1.0-1.4) 2007 : 1.3 (1.1-1.5) No statistically significant trend Women 1995 : 0.4 (0.3-0.5) 2000 : 0.4 (0.3-0.5) 2005 : 0.3 (0.2-0.3) 2007 : 0.3 (0.3-0.5) No statistically significant trend |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|------------------------------|---------|--------------|---|----------------|------------------------------------|---|
| Jennings et al. 2014 [33] | Ireland | 1994-2009 | National Cancer Registry of Ireland | | Standard European population | <p>Men</p> <p>1994-1997 : 0.908 1998-2001 : 0.802 2002-2005 : 1.235 2006-2009 : 1.311 1994-2009 : 1.064</p> <p>Women</p> <p>1994-1997 : 0.089 1998-2001 : 0.205 2002-2005 : 0.133 2006-2009 : 0.136 1994-2009 : 0.141</p> |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|--------------------------------|---------|--------------|---|----------------------------|--------------------------------|--|
| Le Stang et al. 2010 [34] | France | 1980-2003 | National French mesothelioma surveillance program | ICD-O-3C38.4 | Standard World population 2000 | <p>Men</p> <p>FRANCIM</p> <p>1980 : 0.8</p> <p>1990 : 1.3</p> <p>2000 : 1.4</p> <p>2005 : 1.2</p> <p>Evolution rate 1980-2005 : 1.7</p> <p>2000-2005 : 3.4</p> <p>PNSM</p> <p>1998 : 1.11</p> <p>2005 : 0.93</p> <p>Slight falling trend</p> <p>Women</p> <p>FRANCIM</p> <p>1980 : 0.2</p> <p>1990 : 0.3</p> <p>2000 : 0.3</p> <p>2005 : 0.4</p> <p>Evolution rate</p> <p>1980-2005 : 3.1</p> <p>2000-2005 : 1.8</p> <p>PNSM</p> <p>1998 : 0.18</p> <p>2005 : 0.29</p> |
| Skammeritz et al. 2013 [35] | Denmark | 1943-2009 | Danish Cancer Registry | ICD-7 ICD-10 ICD-O-3 | Standard World population 2000 | <p>Men</p> <p>Increase of incidence over the period</p> <p>2008-2009 : 1.76</p> <p>Women</p> <p>Steady incidence since 1990 around 0.3</p> |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|--------------------------|---------|--------------|----------------------------------|--------------------------------------|--|--|
| Järholm et al. 2015 [36] | Sweden | 1995-2013 | National Swedish Cancer Registry | ICD-7 1622 histo : Code 776 | Standard Swedish population 2000 | Men Decrease of age-adjusted incidence rate: -1.3% Women No clear trend of age-adjusted incidence rate: +0.6% |
| Zhao et al. 2017 [37] | China | | National central cancer registry | ICD-10 C45 | Segi World population | 2013 Male: 1.19 Female: 0.87 2000-2012 Male: 0.2 (95% CI: -2.5-2.9) Female: -1.8 (95 %CI: -3.5-0.0) |

Table S1: Summary of recent reviewed studies related to age-standardized incidence/mortality rates of malignant mesothelioma

Part 1d- countries reporting age-standardized incidence/mortality rates under 1/100,000 among men (2010-2017)

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|------------------------------|----------------|--------------|--|-------------------------|--|---|
| Algranti et al. 2015 [38] | Brazil | 2000-2012 | Death certificates | ICD-10Code C45/C38.4 | Standard Brazilian population 2010 | C45 Brazil : 0.07-0.1 No significant trend São Paulo : 0.1-0.21 Significant linear trend C38.4 Brazil : 0.1-0.16 No significant trend São Paulo :0.08-0.19 No significant trend Incidence peak around 2021-2026 |
| Jung et al. 2012 [39] | Korea | 2001-2010 | Korean mesothelioma surveillance system | | - | 2001 : 0.027 2005 : 0.075 2008 : 0.125 2010 : 0.087 Gender ratio over the decade : 1.96 |
| Kwak et al. 2017 [40] | South Korea | 1994-2013 | Korea Central Cancer Registry (KCCR) | ICD-10 C45 | Standard World population 2000 | Men 2009-2013 : 0.228 Increase continuously and slowly until 2019±2023 Women 2009-2013 : 0.113 Increase continuously and slowly until 2019±2023 |

| Author | Country | Study period | Data | Classification | Standardization | Age-adjusted incidence (mortality) rate / 100,000 |
|----------------------------------|-----------|--------------|---|--|--------------------------------|---|
| Lee et al. 2010 [41] | Taiwan | 1979-2005 | Population-based Taiwan Cancer Registry | ICD-0 Codes 163 and 158 9050/3, 9051/3, 9053/3 | Standard World population 2000 | Increased age-standardized incidence rate over the period 1979-2005 Men - 2005 : approximatively 0.16 Women - 2005 : approximatively 0.1 |
| Tse et al. 2010 [42] | Hong-Kong | ? | Hong Kong cancer registry | ICD-10 C45 | World standard population 1966 | Men Before 1993–1994, the moving average of ASIRs : 0.016–0.073 1993–1994 : 0.125–0.156 peak in 2004 : 0.386 2006: 0. 347 (slight decrease) Women Similar trend until 1992 Incidence stable since 1994, may be a slight decrease |
| López-Abente et al. 2013 [43] | Spain | 1976-2010 | Death certificates | ICD-9Code 163ICD-10C38,4, C45,0 | European Standard population | Men 1976-1980 : 0.347 1991-1995 : 0.566 2006-10 : 0.644 levelling-off from the period 2001–2005 Prediction for 2011-15: 0.620 Prediction for 2016-20: 0.577 Women 1976-1980 : 0.233 1991-1995 : 0.219 2006-10 : 0.196 gradual decline from the 1980s Prediction for 2011-15: 0.177 Prediction for 2016-20: 0.163 |

Table S2: Summary of recent reviewed studies related to population attributable risk of asbestos exposure for malignant mesothelioma (2010-2017).

| Authors | Country | Period | Exposure | Design | Cases enrolment | Controls enrolment | Diagnostic | Questionnaire | Exposure assessment | Population attributable fraction |
|--------------------------------|---------|-----------|-----------------------|-----------------------------------|--|---|---------------------------------|---|--|----------------------------------|
| Aguilar-Madrid et al 2010 [49] | Mexico | 2004-2006 | Occupational exposure | Hospital-based case-control study | Insured workers with suspected diagnosis MPM n=119 | Hospital controls randomly selected from the insured-worker population data Frequency-matched on sex, age (+/- 5 years), insurance type and geographical area n=353 | Immuno-histopathology confirmed | Standardized questionnaire Face to face interviews | Expertise certain/likely/possible | 44% |
| Rushton et al 2010 [50] | UK | 2005 | Occupational exposure | Cross-sectional | National data sources: Carcinogen Exposure database UK labour force survey Census employment UK mesothelioma studies | | ICD-10 C45 | | CAREX | Men: 97.0% Women: 82.5% |

| Authors | Country | Period | Exposure | Design | Cases enrolment | Controls enrolment | Diagnostic | Questionnaire | Exposure assessment | Population attributable fraction |
|--------------------------|---------|-----------|--|-------------------------------------|---|--|---|---|---|---|
| Lacourt et al 2014 [51] | France | 1998-2002 | Occupational and non-occupational exposure | Population based case-control study | Incident cases identified through the PNSM n=437 (362 men and 75 women) | General population, 2 controls/case Matched on sex, age (± 5 years) and district of residence. N= 874 (724 men, 150 women) | Certified by a standardised diagnostic confirmation procedure | Standardized questionnaire Face-to-face interviews | Expertise Not exposed/ Possible/ Probable Cumulative exposure index (f/ml-yr) : <0,1/ 0,1-1/ 1-10 / >10 Occupational only/ Non occupational only/ both | Occupational exposure: Men: 83.1% Women: 41.7% Non-occupational exposure: Men: 20.0% Women: 38.7% All exposure: Men: 87.3% Women: 64.8% |
| Ferrante et al 2016 [52] | Italy | 2001-2006 | Occupational and non-occupational exposure | Population-based case-control study | Incident cases identified in different units of the hospitals serving the study area n=223 | General population Matched by date of birth (± 18 months) and gender n=552 | Histological and/or cytological confirmation | Standardized questionnaire Face-to-face interviews | Expertise Cumulative exposure index : background level (<0,1)/ 0,1-1/ 1-10 / >10 | All subjects : 89.4% Non-occupationally exposed only : 82.1% |

Table S3: Summary of recent reviewed studies related to the relationship between non-occupational asbestos exposure and pleural mesothelioma (2010-2017).

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|-------------------------|---------------|-----------------------------|------------------------------|-----------|--|--|---|---|
| Baumann et al 2011 [55] | New Caledonia | Natural sources of asbestos | Cluster and ecological study | 1984-2008 | Histologically confirmed cases (n=109) Comparison of 100 tribes: tribes with MM cases (n = 34) and without MM cases (n = 48). | Cancer Registry of New Caledonia ; Questionnaire: cases or two of their closest relatives | self-report Identification and characterization of sources of natural asbestos | Age-standardized incidence: Noumea: 0.64 (95% CI: 0.13-1.88) Houaïlou: 128.66 (95% CI: 70.41-137.84) Koné: 25.46 (95% CI: 14.25-41.98) Poindimié: 15.37 (95% CI: 3.17-44.92) Identification of a spatial cluster grouping 18 tribes (31 observed cases vs 8 expected) Serpentine on roads : OR=13.0 (95% CI: 10.2-16.6) Increased risk with serpentine surface, proximity to serpentine quarries, and distance to the peridotite massif No significant association with whitewash |
| Berk et al 2014 [56] | Turkey | Environmental exposure | Case series | 1993-2010 | Confirmed cases diagnosed in Sivas (n=219, 126 men, 93 women) | Hospital records | Rock, soil and house plaster samples | Male:female ratio: 1.4:1 1.8 % patients with an occupational history with a potential risk for asbestos exposure 86 % patients with a history of living in a house containing asbestos-contaminated soil |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|---------------------------|---------|------------------------|------------------------------|-----------|--|--|---|---|
| Bourgault et al 2014 [57] | Quebec | Environmental exposure | | | General population of Thetford Mines | Mortality data from the Ministry of Health and Social Services of the Province of Quebec, covering the 2000–2003 period Potency factors calculated by Berman and Crump for the Quebec mining and milling cohort | Indoor and outdoor measurements lifetime exposure concentration: sum of the average indoor and outdoor exposures concentrations, weighted by the respective proportion of the time spent indoors and outdoors | Lifetime mortality risk (/100000) from environmental exposure to asbestos fibers in Thetford Mines : 0.7-2.3 Health's Canada threshold for considering a lifetime cancer risk as negligible: 1/100 000 |
| Corfiati et al 2015 [58] | Italy | All types | Population-based case series | 1993-2008 | Histologically confirmed cases (n=15322) | Italian national mesothelioma registry (ReNaM) Interviews | Expertise: - Occupational: definite, probable, possible - Familial - Environmental - Other non-occupational | Identification of 32 clusters mostly located in southern Italy Main source of asbestos exposure : asbestos cement manufacturing industries, shipbuilding and repair facilities Cases for which environmental exposure was ascertained are mostly concentrated in clusters where asbestos cement plants were located |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|---------------------------|-------------|---|------------------------------|-----------|--|--|--|--|
| D'Agostin et al 2017 [59] | Italy | Para-occupational | Population-based case series | 1995-2014 | Histologically confirmed mesothelioma cases (n=1063) | Friuli Venezia Giulia Mesothelioma Register Interview | Self-report and expertise | Para-occupational exposure : 35 cases (33 women and 2 men) |
| Driece et al 2010 [60] | Netherlands | Environmental exposure (asbestos pollution of friable and non-friable waste products) | Ecological study | 1960–2007 | Resident of municipality Hof van Twente | Demographic and mortality databases | Number and size of polluted sites per postal code Number of exposed households per postal code Historical measurements | 416 sites with asbestos pollution were identified High exposure category - Site approach: 78 extra cases - maximum : 431 cases during the 48-year period with asbestos contamination in the region - Household approach: 42 extra cases - maximum : 231 cases Intermediate exposure category - Site approach: 2.8 extra cases - maximum : 15.4 cases - Household approach: 1.7 extra cases - maximum: 9.1 cases Low exposure category - Site approach: 3.1 extra cases - maximum : 16.9 cases - Household approach: 1.5 extra cases - maximum : 8.0 cases |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|------------------------------|---------|--|------------------|-----------|--|--|--------------------------------------|--|
| Fazzo et al 2014 [61] | Italy | Environmental exposure (asbestos-cement plant) | Ecological study | 2001-2007 | Residents of Coroglio-Bagnoli in Naples (n= 174682; 132 881 in subarea 1 and 41 801 in subarea 2) | Demographic database Italian national mesothelioma registry (ReNaM) | SIG Expertise and company records | 34 men and 12 women cases Study area vs Campania Region SIR=2.30 95%CI : 1.59-3.21 for men SIR=2.26 95%CI : 1.17-3.95 for women subjects non occupationally exposure to asbestos Men (n=19) : SIR = 2.48; 95% CI: 1.49-3.88 Women (n=11) SIR = 1.34; 95% CI: 0.67-2.40 |
| Ferrante et al. 2016 [52] | Italy | Occupational and non-occupational exposure | Case-control | 2001-2006 | 223 confirmed cases 552 Controls were randomly selected from the population rosters of the LHA of Casale Monferrato | Standardized questionnaire administered face-to-face by trained interviewers | Expertise | Subjects non-occupationally exposed Background level : OR=1 >=0.1-1 : OR=3.8 (95%CI:1.3-11.1) >=1-10: OR= 14.8 (95%CI:5.7-38.6) >=10: OR=23.3 (95%CI:2.9-186.9) Having an exposed family members: OR=2.4 (95%CI: 1.3-4.4) |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|---------------------------|---------|--|--------|-----------|--|--|--|--|
| Gogali et al 2012 [62] | Greece | Domestic exposure (tremolite-containing whitewash) | cohort | 1980-2009 | Residents of Metsovo municipality (n=4,417) Histologically confirmed cases (n=26) | Hospital and medical records Death certificates | no history of asbestos-related occupation or radiation treatment | <p>Cumulative incident rate 1980-2009: 2.04/10 000 person-yrs</p> <p>Analyses by 15 years intervals (no statistical difference) 1980-1994: 2.2/10 000 person-yrs 1994-2009: 1.8/1 0000 person-yrs</p> <p>Analyses by decades 1980-1989: 2.6/10 000 person-yrs 1990-1999: 2.4/10 000 person-yrs 2000-2009: 1.1/10 000 person-yrs</p> <p>Metsovo population: 2.04/10 000 person-yrs Loannina population outside Metsovo: 1.48 per 1,000,000 person-yrs</p> <p>Abandonment of tremolite-containing whitewash associated with a drop of mesothelioma incidence</p> |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|--------------------------|---------|--|------------------------------|-----------|--|--|---|---|
| Goldberg et al 2010 [63] | France | All types | Population-based case series | 1998-2008 | Histologically confirmed cases residents of 26 French geographical districts (n=1937 ; 21.2% women) | Death certificates National Mesothelioma Surveillance Program | Questionnaire and expertise (occupational and non-occupational) | <p>Mortality rates spatially heterogeneous 0.84-5.08 per 100 000 men 0.11-1.62 per 100 000 women</p> <p>Correlations between men and women SMRs r=0.76 (95% CI 0.31 to 0.84)</p> <p>Correlation between men and women SIRs r=0.80 (95% CI: 0.49-0.87)</p> <p>Burden of environmental asbestos exposure in industrialized countries non negligible</p> |
| Goswami et al 2013 [64] | | Domestic exposure | Meta-analyses | 1960-2012 | Published literature related to domestic exposure 12 cohort and case-control studies | | | <p>Summary relative risks estimates Overall= 5.02 (95% CI: 2.48-10.13) Case control studies without occupational exposure=3.11 (95% CI: 1.64-5.9)</p> |
| Lacourt et al 2014 [51] | France | Occupational and non-occupational exposure | Case-control | 1998-2002 | <p>437 confirmed cases identified through the PNSM</p> <p>874 controls, selected from the general population, were matched with cases for sex, age (± 5 years) and district of residence.</p> | Questionnaire | Expertise | <p>Among subjects non-occupationally exposed to asbestos (9 male and 36 female cases / 18 male and 72 female controls) OR for non-occupational asbestos exposure Men: 2.4 (95% CI: 0.2-26.7) Women: 4.3 (95% CI: 1.2-15.1)</p> |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|------------------------------|---------|---|------------------|-----------|---|-------------------------------------|---------------------|---|
| Langhoff et al 2014 [65] | Denmark | Para-occupational | Case series | 1996-2012 | Histologically confirmed female cases diagnosed at Aalborg University hospital (n=24) | Hospital records | Expertise | Domestic exposure identified in 46% (11/24) of cases through their husbands or sons |
| Lopez-Abente et al 2012 [66] | Spain | Environmental exposure (Industrial pollution) | Ecological study | 1997-2006 | Residents of 8,098 Spanish municipalities | Demographic and mortality databases | SIG | <p>Populations residing ≤ 2 km from pollutant facilities faced a higher risk than did unexposed or distant populations</p> <p>Statistically significant RRs in both sexes in the vicinity of 7 of the 24 industrial groups studied (RR, 95% CI)</p> <ul style="list-style-type: none"> - biocide facilities (2.595, 1.459–4.621) - ship-building (2.321, 1.379–3.918) - glass and mineral fiber production (1.667, 1.041–2.665) - non-hazardous waste treatment (1.737, 1.077–2.799) - galvanizing (1.637, 1.139–2.347) - organic chemical plants (1.386, 1.075–1.782) - food and beverage sector (1.255, 1.006–1.562) |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|----------------------------|---------|------------------------------------|------------------------------|-----------|--|---|---------------------|---|
| Marinaccio et al 2015 [67] | Italy | Non-occupational asbestos exposure | Population-based case series | 1993-2008 | Histologically confirmed cases (n=15845) | Italian national mesothelioma registry (ReNaM) Questionnaire | Expertise | <p>15 845 cases of MM were identified</p> <p>SIR in 2008 Men: 3.84 cases per 100 000 inhabitants Women: 1.45 cases per 100 000 inhabitants</p> <p>Proportion of MM cases due to non-occupational asbestos exposure (familial, environmental or related to leisure activities) : 10.3%</p> <p>Female/male ratio - population with non-occupational exposure: 2.3:1 - population with familial modalities of exposure 5.9:1</p> <p>Clusters of cases due to environmental exposure: - asbestos-cement industry plants (Casale Monferrato, Broni, Bari) - shipbuilding and repair activities (Monfalcone, Trieste, La Spezia, Genova) - soil contamination (Biancavilla in Sicily)</p> |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|---------------------------|---------|--|------------------------------|-----------|---|---|--|---|
| Mensi et al 2015 [68] | Italy | Occupational Para-occupational Environmental | Population-based case series | 2000-2011 | Histologically confirmed cases living in Lombardy (n=147) | Lombardy Mesothelioma Registry Questionnaire | Self-report and expertise | 147 MM cases versus 17.45 expected Past-occupational asbestos exposure at the asbestos cement factory : 38 cases (2.33 expected), 32 were men 6 women In Family of Broni factory workers: 37 cases (4.23 expected), 5 men and 32 women Residents of Broni or adjacent towns: 72 cases (10.89 expected) 23 men and 49 women |
| Mirabelli et al 2010 [69] | Italy | Para-occupational Environmental | Population-based case series | 1993-2001 | Histologically confirmed cases n=(3746 men, n=1427 women) | Italian national mesothelioma registry (ReNaM) Questionnaire | SIG and Expertise (available for 3352 cases) | 294 cases without occupational exposure (8.3%) and : - environmental exposure (living in the vicinity of industrial or natural sources) : 144 cases - para-occupational exposure : 150 cases Women: 51% of all cases with environmental exposure and 84% of those with familial exposure. |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|-----------------------|-----------|--|------------------------------|-----------|--|---|--------------------------------|---|
| Olsen et al 2011 [70] | Australia | Home renovation | Population-based case series | 1960-2008 | Confirmed cases diagnosed in western Australia (n=1631, 1408 men, 223 women) | Western Australia mesothelioma register Questionnaire Medical records | Expertise | Occupational asbestos exposure : 82.8% of male cases / 16.6% of female cases 195 cases associated with non-occupational exposure (6.8% of male cases and 44.4% of female cases) Between 2005-2008 : 8.4% of male cases and 35.7% of female cases attributed to home renovation |
| Reid et al 2013 [71] | Australia | Environmental exposure (living in an asbestos mining town) | Cohort | 1950-2007 | former residents' cohort of Wittenoom who had lived in the town but who had not worked for the asbestos company (4,768 people ; 2,608 females) | Cancer registries Death certificates Demographic registry | Outdoor historical measurement | Women who first arrived at Wittenoom aged <15 years (n=13) SIR=70.05 (95% CI 36.20-122.37) SMR =75.6 (95% CI: 34.6–143.6) Men who first arrived at Wittenoom aged <15 years (n=29) SIR=44.54 (295% CI 9.83-63.98) SMR= 56.5 (95% CI: 35.8–84.8) No consistent trend on MM for age of arrival at Wittenoom Exposure to blue asbestos in childhood is associated with an increased risk of mesothelioma in adults |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|----------------------------|---------|--|--------|-----------|---|--|---------------------|--|
| Salerno et al 2013 [72] | Italy | Environmental exposure (near an oil refinery plant) | Cohort | 2003-2009 | All residents in Cerano during the time period 2003-2009 | Piedmont Region database Hospital records | | <p>4 cases in women, 2 in men</p> <p>women SIR = 9.09; (95%CI:6.13-12.0) with the district of the Local Health Authority of Novara population SIR =7.01; (95%CI: 4.41-9.60) with population in Turin</p> <p>men : SIR = 1.11; (95%CI: 0.0-2.57) with the district of the Local Health Authority of Novara population SIR =2.17; (95%CI: 0.13-4.21) with population in Turin</p> <p>RR=2.32 (95%CI: 0.04-3.98) among born/resident in Cerano and residents not born in Cerano</p> |
| Tarrés et al 2013 [73] | Spain | Environmental exposure (industrial source of asbestos) | Cohort | 2000-2009 | Histologically confirmed cases who had been living in the area around an asbestos cement plant in the province of Barcelona for some time while the plant was functioning (1907–1997) and up to the time of the diagnosis | medical records | SIG | <p>24 pleural mesotheliomas</p> <p>Incidence rate ratio for living <500 m to asbestos plant: 56.5 (Ref residence >2000-10000m of the asbestos plant) highest incidence rate ratio for pleural mesothelioma (161.9) found in the southeast quadrant of the 500-m area, coinciding with the predominant wind direction</p> |

Non-occupational asbestos exposure

| Author | Country | Exposure type | Design | Period | Study population | Data Sources | Exposure assessment | Results |
|---------------------|---------|---|--------|-----------|---|--|---------------------|--|
| Wei et al 2012 [74] | China | Environmental exposure (Naturally occurring asbestos) | Cohort | 2007-2010 | Confirmed deceased cases in Dayao from 2007 to 2010 | Center for Disease Control database Prevention of Dayao County database | SIG | higher mortality rates of mesothelioma and other cancer in Area I implying that environmental exposure to asbestos derived from outcropped asbestos in soil and rocks in the area may elevate mortality rates of cancers |

Table S4: Summary of recent reviewed studies related to the relationship between other elongated mineral particles exposure and pleural mesothelioma (2010-2017).

| Authors | Country | Exposure | Study Period | Study design | Study population | Mesothelioma cases | Data collection | Exposure assessment | Results |
|----------------------------------|---------------|-------------|--------------|-----------------|---|--|---|---|--|
| Erionite | | | | | | | | | |
| Metintas et al. 2010 [75] | Turkey | Erionite | 1990-2006 | cross-sectional | Population of Karain Village (n=322) (ref world population) | Death certificates (n=52) | Clinical and medical records Death certificates Interviews of residents | Samples from houses and analyses | SMR Men: 687.5 (95%CI 447.6-1032.5) Women: 1666.7 (95%CI 1134.1-2319.7) |
| Ortega-Guerrero et al. 2014 [76] | Mexico | Erionite | 2000-2012 | cross-sectional | Population of Tierra Blanca (n=254) (ref population of Guanajuato) | Histologically confirmed cases in Terra Blanca (n=4) | Clinical and medical records Mortality database Interview of family members | Mineralogical and chemical characterization of 206 samples of rocks, soils and building materials | Age-specific mortality rate / 1000 persons/year Men : 2.48 (95% CI 0.49 to 8.90) Women: 1.05 (95% CI 0.03 to 6.26) |
| Vermiculite | | | | | | | | | |
| Dunning et al. 2012 [77] | United States | Vermiculite | 1980-2011 | Cohort | Workers (white men) from an Ohio manufacturing facility (n=465) (ref US population) | Death certificates (n=2; 1.5%) | Questionnaire : work history, asbestos exposure | Historical measurement | SMR = 10.5 (95% CI 1.3-38.0) |
| Larson et al. 2010 [78] | United States | Vermiculite | 1960-2006 | Cohort | 1862 vermiculite workers cohort (ref US population) | Death certificates (n=19) | Company records | Historical measurement Expertise | SMR = 94.8 (95%CI 57.0-148.0) Dose-response relationship with cumulative exposure |

OtherEMPs

| Authors | Country | Exposure | Study Period | Study design | Study population | Mesothelioma cases | Data collection | Exposure assessment | Results |
|----------------------------|---------------|----------------|--------------|-----------------|--|---|---|---------------------|---|
| Moolgavkaret al. 2010 [79] | United States | Vermiculite | 1982-2001 | Cohort | 1,662 white male subjects enumerated in 1982 who had worked as vermiculite miners, millers, and processors at Libby, Montana (ref US population) | Death certificates (n=6) | Company records | Job exposure matrix | Km= 0.5×10^{-8} , 95% CI = [0.3×10^{-8} , 0.8×10^{-8}]. |
| Fluoro-edenite | | | | | | | | | |
| Bruno et al. 2014 [80] | Italy | Fluoro-edenite | 1998-2011 | Case cohort | Population of Biancavilla municipality (ref regional population) | cases classified as "certain" (histologically confirmed), "probable" or "possible" (n=45) | ReNaM registry Medical records Interview of cases or next-of-kins | Expertise | SIR Total : 5.76 (95% CI 3.76-8.44) Men : 3.69 (95% CI 1.97-6.32) Women : 13.08 (95% CI 6.97-22.00) |
| Conti et al. 2014 [81] | Italy | Fluoro-edenite | 2003-2010 | cross-sectional | Biancavilla residents (ref Sicilian population) | Death certificates (n=5) Hospitalization records (n=7) | Medical records Mortality database Demographic database | | SMR Men : 379 (90% CI 149-797) Women : 1128 (90% CI 491-2226) Standardized hospitalization ratio Men: 261 (90% CI 122-489) Women : 780 (90% CI 366-1464) |
| Other EMPs | | | | | | | | | |

| Authors | Country | Exposure | Study Period | Study design | Study population | Mesothelioma cases | Data collection | Exposure assessment | Results |
|--------------------------|---------------|-------------------------------|--------------|-----------------|--------------------------|--|---|---|---|
| Abakay et al. 2016 [82] | Turkey | Ophiolites | 2008-2013 | cross-sectional | Population of Diyarbakir | Histologically confirmed cases (n=180) | Medical records Interview with subjects | SIG | Mean incidence /100 000 In Naturally occurring asbestos area (NOA) : 1059.5 <10 km from NOA area : 499.2 >10 km from NOA area : 240.1 |
| Bayramet al. 2013 [83] | Turkey | Ophiolites | 2000-2010 | Case-Control | Population of Sivas | Cases identified from the cancer registry (n=100) Cancer controls (n=161) | Cancer registry Demographic database | SIG | OR for distance of birthplaces to ophiolites units Men: 1.68, IC95% CI 1.39-2.04 Women: 2.15 IC95% CI 1.69-2.74 |
| Baumann et al. 2015 [84] | United States | Naturally occurring amphibole | 1999-2010 | Case cohort | Population of Nevada | Death certificates (n=31526) | Demographic database | Published data describing the presence of fibrous mineral in Nevada | MM sex-ratio M:F In southern Nevada counties of Clark and Nye: 2.69:1 In all Nevada counties, excluding the southern Nevada counties of Clark and Nye: 6.33:1 In all other US counties : 4.97:1 Proportion of young cases In southern Nevada counties of Clark and Nye: 11.28% In all Nevada counties, excluding the southern Nevada counties of Clark and Nye: 9.09% In all other US counties : 6.21% |

OtherEMPs

| Authors | Country | Exposure | Study Period | Study design | Study population | Mesothelioma cases | Data collection | Exposure assessment | Results |
|------------------------------|---------------|----------|--------------|---------------------|---|---|---------------------------------------|---|--|
| Allen et al 2014 [85] | USA | Taconite | 1960-2010 | Cohort | Minnesota taconite mining workers employed in 1983 for at least 1 year (n=68737) (ref Minnesota population) | Death certificates (n=30) | Company records | Duration of employment 1 year/ 2–5 years/ 6–14 year/ 15+ years | SMR=2.77 (95% CI 1.87- 3.96) |
| Lambert, C. et al 2016 [86] | USA | Taconite | | Nested case–control | Minnesota taconite mining workers employed in 1983 for at least 1 year (n=68737) | Deceased cases (n=80 men) 4 controls matched controls by age (n=315) | Company records | Historical measurement Job exposure matrix | Duration of employment RR=1.03 (95%CI 1.00-1.06) Cumulative EMP RR=1.10 (95%CI 0.97-1.24) |
| Finkelstein et al. 2012 [87] | United States | Talc ore | 1990-2007 | cohort | New York Talc mining and milling workers who worked at least 1 day from 1948-1989 (n=782) | Death certificates | Company records Personal interview | | Incidence rates at least 5 (1.6-11.7) times the rate in the general population |
| Synthetic fibers | | | | | | | | | |

| Authors | Country | Exposure | Study Period | Study design | Study population | Mesothelioma cases | Data collection | Exposure assessment | Results |
|-----------------------------|---------------|---------------------------|--------------|--------------|--|--------------------|---------------------------------------|---|---|
| Walker et al. 2012 [88] | United States | Refractory ceramic fibers | 1970-2008 | Cohort | Workers employed in RCF factories since 1950 (n=605) 605 cohort members engaged in the manufacture of RCF and followed since 1987 to cancer rates | Death certificates | Company records Personal interview | Historical measurement Job exposure matrix | No deaths from mesothelioma as compared to 4.9 anticipated under a crocidolite-like hypothesis ($p = 0.007$), 1.0 for amosite ($p = 0.38$) and 0.05 for chrysotile ($p = 0.95$) |
| Lemastrers et al. 2017 [89] | United States | Refractory ceramic fibers | 1987-2014 | Cohort | Workers employed at five RCF facilities from 1987-1999 (n=1119) | Death certificates | Company records Personal interview | Historical measurement Job exposure matrix | 1 mesothelioma death SMR=2.86 (95% CI: 0.07-15.93) |

Table S5: Biomarkers and pleural mesothelioma in retrospective studies: diagnostic value. Selection of initial studies, recent studies and meta-analysis.

| Study (country) | Population (type, number of subjects) | Biomarker (in serum or plasma) | cut off value | Se | Sp | Comments |
|---|--|---|--|----------------|----------------|---|
| Mesothelin and related peptides (including megakaryocyte potentiating factor) | | | | | | |
| Robinson et al 2003 [130] (Australia) | <ul style="list-style-type: none"> • 44 MM (39 men, 5 woman) • 68 healthy controls (40 asbestos-exposed and 28 non asbestos-exposed) • 38 non mesothelioma pleural diseases (16 pleural plaques) • 30 malignant non-pleural diseases • 92 inflammatory non-pleural lung disease | Mesothelin (serum) (specific ELISA with OV569 and 4H3 monoclonal antibodies) | Absorbance ≥ 0.218 (mean value of non asbestos-exposed healthy subjects +3SD) | 84% (a) | 95% (a) | <ul style="list-style-type: none"> - 3 of the 7 positive asbestos-exposed control developed mesothelioma within 1-5 years - None of the 33 negative asbestos controls developed mesothelioma during an 8 years follow-up - Se and Sp were calculated here comparing MM cases (n=44) to a group including all other subjects except non asbestos healthy subjects (n=200). Sp value was 82.5% when controls were restricted to asbestos-exposed healthy subjects. |
| Hollevoet et al 2010 [131] (Belgium) | Six cohort of subjects <ul style="list-style-type: none"> • 85 MPM (median age = 65 years) • 101 healthy unexposed controls (median age = 56 years) • 89 healthy asbestos-exposed (median age = 52 years) • 123 benign asbestos-related disease (median age = 64 years) • 46 benign respiratory disease (median age = 62 years) • 63 lung cancer (median age = 65 years) | Megakaryocyte potentiating factor (MPF) ELISA Kit (serum) Soluble mesothelin (Mesomark Cis bio ELISA Kit) in serum | 13.46 ng/mL 1.89 nmol /L | 68% 66% | 97% 94% | <ul style="list-style-type: none"> - MPF and soluble mesothelin have an equivalent diagnostic performance - MPF and soluble mesothelin levels highly correlated |
| Bayram et al 2014 * [132] (Turkey) | <ul style="list-style-type: none"> • 24 MPM (mean age = 57.8 ± 12.7 years) • 279 pleural plaques (mean age = 63.1 ± 11.5 years) • 123 healthy exposed (mean age = 63.3 ± 9.8 years) • 120 controls (mean age = 61.6 ± 10.8 years) | Mesothelin (serum) (Fujirebio ELISA Kit) | 1.63 ng/L | 58% | 83% | <ul style="list-style-type: none"> - Se and Sp evaluated when mesothelioma subjects were compared to the 3 other groups |

Biomarkers

| | | | | | | |
|--|---|---|---|------------------------------|------------------------------|--|
| Creaney et al 2014 [133] (Australia) | <ul style="list-style-type: none"> • 82 MPM (mean age = 70 years) • 49 benign asbestos related pulmonary diseases (mean age = 77 years) • 35 non-malignant effusions (mean age = 68 years) • 36 malignant effusions (mean age = 67 years) | Mesothelin (plasma) (Mesomark Fujirebio ELISA Kit) Fibulin 3 (plasma) (USCN Life Science Inc ELISA Kit) | 2.5 nM/mL 53 ng/mL | 56% 22% | 96% 95% | <ul style="list-style-type: none"> - MPM compared to the 3 others groups - Mesothelin remains the clinically useful mesothelioma biomarker - MPM compared to the 3 others groups |
| Luo et al 2010 [134] (several countries) | <i>Meta-analysis (11 studies until march 2008)</i> <ul style="list-style-type: none"> • 717 MM • 2,851 controls (with various histories of asbestos exposure and/or asbestos-related disease) | <i>SMRP (ELISA) (8 studies on soluble mesothelin, 3 on megakaryocyte potentially factor)</i> | <i>Various values among the studies included in the meta-analysis</i> | <i>64% [95%CI = 61%-68%]</i> | <i>89% [95%CI = 88%-90%]</i> | <ul style="list-style-type: none"> - Significant heterogeneity between studies (Se ranging from 41% to 91%, Sp from 73% to 100%). |
| Hollevoet et al 2012 [135] Several countries) | <i>Meta-analysis on 4,491 patients (median age = 62 years)</i> <ul style="list-style-type: none"> • 1,026 MPM (median age = 66 years) • 778 lung cancer (median age = 65 years) • 267 benign respiratory disease (median age = 65 years) • 736 benign asbestos-related disease (median age = 63 years) • 775 healthy asbestos-exposed (median age = 54 years) • 909 healthy (median age = 56 years) | <i>Mesothelin (serum) (MesomarkFujirebio ELISA Kit)</i> | <i>2nmol/L</i> | <i>47%</i> | <i>96%</i> | <i>When applying a common threshold of 2nmol/L; sensitivities varied from 19% to 68% according to the studies, and specificities from 88% to 100% At a selected specificity of 95%, sensitivity was 32% (95% CI = 26% to 40%) when analysis was restricted to 217 subjects with early diagnosis of MM (stage I or II, epithelioid or biphasic type) and 1,612 symptomatic or high risk controls.</i> |
| Osteopontin | | | | | | |
| Pass et al 2005 [136] (USA) | <ul style="list-style-type: none"> • 76 MPM (mean age = 65 ±1 year) • 69 asbestos-related non malignant pulmonary disease (mean age = 65±1 year) • 45 subjects without exposure | Osteopontin (ELISA Assay) | 48.3 ng/mL | 77.6% | 85.5% | Se and Sp were calculated comparing MM cases and the group exposed to asbestos |

Biomarkers

| | | | | | | |
|--|--|---|--|-----------------------|-----------------------|--|
| Bayram et al 2014 * [132] (Turkey) | <ul style="list-style-type: none"> • 24 MPM (mean age = 57.8 ± 12.7 years) • 279 pleural plaques (mean age = 63.1 ± 11.5 years) • 123 healthy exposed (mean age = 63.3 ± 9.8 years) • 120 controls (mean age = 61.6 ± 10.8 years) | Osteopontin (serum) (Ray bio ELISA Kit) | 17.273 ng/L | 75% | 86% | - Se and Sp evaluated when mesothelioma subjects were compared to the 3 other groups |
| Hu et al 2014 [137] (several countries) | <p><i>Meta-analysis (6 studies until march 2013)</i></p> <ul style="list-style-type: none"> • 356 MPM • 546 controls (with various histories of asbestos exposure and/or asbestos related diseases. Some were healthy controls without asbestos exposure). | <i>Osteopontin (In serum and / or plasma)</i> | <i>Various values among the studies included in the meta-analysis.</i> | 65% [95%CI = 60%-70%] | 81% [95%CI = 78%-85%] | <ul style="list-style-type: none"> - <i>Diagnostic accuracy of serum and plasma osteopontin was comparable</i> - <i>Great heterogeneity among the included studies (Se ranging from 41% to 96%, Sp from 26% to 96%)</i> |
| Fibulin3 | | | | | | |
| Pass et al 2012 [138] (USA and Canada) | <p>Three cohorts originating from Detroit, New-York and Toronto.</p> <p>Total of patients :</p> <ul style="list-style-type: none"> • 92 MM patients (USA) • 136 asbestos-exposed subjects without cancer • 93 patients with effusions (not mesothelioma) • 43 healthy controls | Fibulin-3 (plasma) (ELISA USCN life Science) | 52.8 ng/mL | 96.7% | 95.5% | <ul style="list-style-type: none"> - No variation of plasma fibulin-3 level according to age, sex, duration of asbestos exposure or radiographic changes - Se and Sp calculated when MM patients (n = 92) were compared to other cohorts (n = 290) - Validation cohorts were used: serum samples (no plasma available) from 49 asbestos-exposed subjects in whom mesothelioma developed and 96 asbestos-exposed cancer-free controls from Carotene and Retinol Efficacy Trial (CARET), and also 48 plasma samples of mesothelioma patients and 96 asbestos-exposed cancer-free persons from Toronto Princess Margaret Hospital. <p>No discrimination between MPM patients and controls in the CARET serum old archived samples.</p> <p>In the Canadian population, at a cut-off value of 28.96ng/mL, Se was 72.9% and Sp 88.56%</p> |

Biomarkers

| | | | | | | |
|--|---|--|--|--|--|--|
| Pei et al 2017 [139] (several countries) | <p>Meta-analysis (7 studies)</p> <ul style="list-style-type: none"> • 468 MPM • 664 controls (cancer-free individuals, but with various asbestos exposure and/or diseases) | <p>Fibulin-3 (all samples)</p> <p>(serum)</p> <p>(plasma)</p> | <p>Various values according to studies and type of biological sample</p> | <p>62% [95%CI = 45%-77%]</p> <p>77% [95%CI = 71%-83%]</p> <p>54% [95%CI = 50%-58%]</p> | <p>82% [95%CI = 73%-89%]</p> <p>85% [95%CI = 79%-90%]</p> <p>77% [95%CI = 74%-80%]</p> | <ul style="list-style-type: none"> - Heterogeneity between the studies. - Role of the test matrix : studies with serum-based analysis harbored better accuracy than those with plasma-based analysis |
| Micro RNA | | | | | | |
| Kirschner et al 2012 [140] (Australia) | <p>Test cohort</p> <ul style="list-style-type: none"> • 15 MM • 14 healthy controls <p>Validation cohort</p> <ul style="list-style-type: none"> • 30 MM • 10 asbestosis | 854 mi RNA | | | | <ul style="list-style-type: none"> - miR-625-3p significantly elevated in the serum of MM patients compared with asbestosis controls in the validation cohort |
| Santarelli et al 2015 [141] (Italy) | <ul style="list-style-type: none"> • 45 MPM patients (mean age = 69 ± 8 years) • 99 asbestos exposed subjects (mean age : 64 ± 10 years) • 44 healthy controls (mean age = 68 ± 6 years) | <p>miRNA-126</p> <p>methyated thrombomodulin promoter (Met-TM)</p> | | <p>75%</p> <p>-</p> | <p>54%</p> <p>82%</p> | <p>Combination of miR-126 with Met-TM and SMRP allowed better differentiation of the subjects having MM and control group.</p> <p>The biomarkers were independent of age, gender, smoking and duration of exposure.</p> <p>A validation cohort was used = 18 patients with MM, 50 asbestos exposed subjects, 20 controls and 42 lung cancer cases.</p> |
| Bononi et al 2016 [142] (Italy) | <ul style="list-style-type: none"> • 10 MPM • 10 healthy exposed • 10 controls | Micro RNA (1,201 miRNA assessed) | | - | - | miR-197-3p, miR-1281 and miR-32-3p are up-regulated in MPM subjects |
| Weber et al 2017 [143] (Germany) | <p>Discovery phase</p> <ul style="list-style-type: none"> • 21 male patients with MPM (median age = 72 years) • 21 cancer-free male exposed to asbestos <p>Verification phase</p> <ul style="list-style-type: none"> • 22 MPM • 44 controls exposed to asbestos | <p>miRNA (plasma)</p> <p>Specific study of miR-16, miR-24, miR-28-3p, miR-126 miR-132-3p, miR-146b-5p, miR-625-3p, U6 snRNA</p> <p>miR-132-3p</p> <p>miR-132-3p and miR126</p> | | <p>86%</p> <p>77%</p> | <p>61%</p> <p>86%</p> | <p>MPM and controls were matched for age and smoking status.</p> <p>miR-132-3p shows different expression levels in plasma between MPM subjects and cancer-free controls formerly exposed to asbestos</p> |

Biomarkers

| HMGB1 | | | | | | |
|---|--|---|----------------------------|-------------------|------------------|--|
| Napolitano et al 2016 [144] (USA and UK) | <ul style="list-style-type: none"> • 22 MM patients (mean age = 66 years) • 20 asbestos exposed insulators subjects • 13 benign pleural effusions • 25 malignant pleural effusions • 20 healthy controls from UK | Total HMGB1 (serum and plasma) Hyper acetylated HMGB1 | 15.75 ng/mL 2 ng/mL | 72.3% 100% | 100% 100% | <ul style="list-style-type: none"> - Se and Sp calculated for comparison of MM with asbestos exposed subjects healthy controls - Total HMGB1 and hyper-acetylate HMGB1 also differentiated MM patients from individuals with pleural effusions due to other causes (but with different cut-off values) - Total and hyper-acetylated HMGB1 did not correlated with any of the other biomarkers tested (mesothelin, osteopontin, fibulin-3) among MM patients - Combining HMGB1 and fibulin-3 provided increased sensitivity and specificity in differentiating MM patients from patients with benign or malignant non MM pleural effusion |
| Ying et al 2017 [145] (China) | 497 subjects <ul style="list-style-type: none"> • 15 MPM (median age = 66 years) • 71 healthy without any asbestos exposure (median age = 67 years) • 170 exposed to asbestos < 10 years with normal chest X-ray (median age = 66 years) • 129 exposed to asbestos > 10 years with normal chest X-ray (median age = 67 years) • 81 pleural plaques (median age = 68 years) • 31 asbestosis (median age = 73 years) | HMGB1 (Cloud Clone Corp ELISA Kit) (serum) | 52.29 ng/mL 52.39 ng/mL | 100% 100% | 57.6% 57.4% | <ul style="list-style-type: none"> - Se and Sp on the two lines are reported for cut-off values when comparing MPM subjects with asbestos-exposed subjects during less than 10 years and more than 10 years, respectively. - Even if mean HMGB1 levels were significantly higher in asbestosis and MPM groups than in other groups, there was a large overlap of individual values of serum HMGB1 levels, in the six groups of subjects |
| Other tests | | | | | | |
| Onda et al 2006 [146] (USA) | <ul style="list-style-type: none"> • 56 MM (all of epithelial type) (median age = 57 years) • 70 healthy controls (median age = 39 years) | Megakaryocyte potentiation factor (MPF) (serum) Construction of a new specific ELISA test | Absorbance \geq 0.034 | 91% | 100% | <ul style="list-style-type: none"> - Initial methodological study : - 56 cases with MM had advanced disease. |
| Ostroff et al 2012 [147] (USA) | Case-control design <ul style="list-style-type: none"> • 117 MM (median age = 64 years) • 142 asbestos-exposed controls (including subjects with asbestosis, pleural plaques) | SOMAscan proteomic assay = Slow Off-rate Modified Aptamers quantification of proteins in biological samples (1045 proteins) | | | | <ul style="list-style-type: none"> - 60 cases and 60 controls for training, 19 cases and 20 controls for validation, 38 cases and 62 controls for validation - Identification of 64 candidate biomarkers. 13 biomarkers retained in the validation assay |

Biomarkers

| | | | | | | |
|---|---|---|--------------------------------|----------------|----------------|--|
| Watzka et al 2013 [148] (USA) | <ul style="list-style-type: none"> • 101 MPM (73 epithelioid type) • 96 asbestos-exposed healthy insulation male workers | Integrin linked Kinase (ILK) (serum) ELISA assay | 4.49 ng/mL | 61.4% | 80.2% | No influence of the histological type of MPM on the level of ILK serum concentration |
| Xu et al 2015 [149] (Japan) | <ul style="list-style-type: none"> • 10 mesothelioma (mean age = 69.9 ± 5.6 years) • 172 healthy subjects possibly exposed to asbestos (mean age = 65.7 ± 8.8 years) • 76 healthy subjects unexposed to asbestos (mean age = 50.9 ± 7.7 years) • 532 subjects possibly exposed to asbestos • 412 pleural plaques • 10 benign hydrothorax • 86 asbestosis • 17 lung cancer | CCL3 (Chemokine ligand 3) (serum) (Quantikine Human CCL3 / MIP-1a Immunoassay Kit, (R&D Systems)) | 7.8 pg/mL (limit of detection) | - | - | <ul style="list-style-type: none"> - No significant difference in the level of CCL3 in the unexposed group and the healthy asymptomatic subjects possibly exposed to asbestos where CCL3 was detectable in 6.6% and 30.2% respectively. - Very high level of CCL3 in 3 subjects with mesothelioma (CCL3 detectable in 9 out of 10 subjects with mesothelioma). |
| Demir et al 2016 [150] (Turkey) | <ul style="list-style-type: none"> • 42 MPM (mean age = 60.7 ± 11.4 years) • 48 asbestos exposed subjects (mean age = 59.1 ± 13.3 years (27 with pleural plaques)) | Thioredoxin1 (TRX, serum) Epidermal growth factor receptor (EGFR, serum) | 156,67 ng/mL 19.96 ng/mL | 92.9% 90.5% | 77.6% 64.4% | - The MPM group had significantly higher levels of EGFR, TRX, SMRP and fibulin-3 levels than other groups |
| Morré et al 2016 [151] (Australia) | <ul style="list-style-type: none"> • 17 MPM (mean age = 67 years) • 15 asbestos exposed (pleural plaques or asbestosis) (mean age = 72 years) | Ecto-nicotinamide adenine nucleotide oxidase disulfide-thiol exchanger 2 (ENOX2) transcripts | | | | - ENCX2 protein transcript variants were present in serum 4 to 10 years before clinical symptoms of mesothelioma |
| Johnen et al 2017 [152] (Australia and Germany) | <ul style="list-style-type: none"> • 163 + 36 MPM • 163 + 72 controls (asbestosis or pleural plaques) | Calretinin (plasma and serum) | 0.85 ng/mL | 71% | 95% | <ul style="list-style-type: none"> - Calretinin is specific for epithelioid and biphasic MPM - Performance was roughly similar to mesothelin (Se 69%, Sp 95%) in this series for non-sarcomatoid MPM |

n : number

MPM : malignant pleural mesothelioma ; MM : malignant mesothelioma ; Se : sensibility ; SMRP : soluble mesothelin related peptide ; Sp : specificity ;

Table S6: Biomarkers and screening of mesothelioma: Follow-up studies of asbestos exposed cohorts

| Study (country) | Population (type, number of subjects, age, period/duration of follow-up) | Biomarker (in serum or plasma) | Threshold cut off value | Positive samples | Se | Sp | NPV | PPV | Comments |
|--------------------------------------|--|--|---|------------------------------------|-------------------------------------|---|---|--|--|
| Park et al 2008 [158] (Australia) | n = 538 subjects (mean age = 66.9 years) <ul style="list-style-type: none"> 20 silicosis 24 asbestosis 113 DPT 142 pleural plaques 13 asbestosis + DPT Follow-up = 1 year | Mesothelin (serum) (MesomarkFujirebio ELISA assay) | 2.5 nM/L | n = 15 | Not evaluable (a) | 97.2% (a) | 100% (a) | 0% (a) (0/15) | No mesothelioma case 15 false positive cases i.e (100% positive cases) |
| Hollevoet et al 2011 [159] (Belgium) | n = 215 asbestos exposed workers (mean age = 55.7 years) <ul style="list-style-type: none"> 71 pleural plaques 39 DPT 16 others (asbestosis++) 89 healthyasbestosexposed Follow-up = 2 years | Mesothelin (serum) (Mesomark Cis bio ELISA assay) MPF (Medical and Biological Laboratories Nagano ELISA Assay) | 2.10 nM/L 13.1 ng/mL | n = 20 n = 21 | 0% (a) 0% | 91% (a) 90.6% | 99.5% (a) 99.5% (a) | 0% (a) (0/20) 0% (0/21) (a) | - Longitudinal biomarker analysis performed in a subgroup, showing that biomarker levels increased during follow-up (role of age and glomerular filtration rate) - 14 subjects having both mesothelin and MPF markers elevated at baseline - 1 mesothelioma during follow-up (subject with pleural plaques) - 100% false positives for both markers |
| Gube et al 2011 [160] (Germany) | n = 626 asbestos exposed workers (mean age = 63 years) Mean follow-up (mortality study) : 10 to 14 years all previously exposed to asbestos | Mesothelin (serum) (Mesomark Fujirebio ELISA Kit) CYFRA21-1 (Elecsys 2010 System, Roche) CA125 (ADVIA Centaur System, Bayer) | 1.5 nM/L 3.3 ng/mL 34 KIU/L | n = 52 n = 10 n = 26 | 10% (a) 0% (a) 5% (a) | 91.8% (a) 98.4% (a) 95.9% (a) | 96.9% (a) 96.8% (a) 96.9% (a) | 3.9% (a) 0% (a) 3.9% (a) | - Subjects recruited between 1993 and 1997, mortality follow-up until April 30 2007. Mean duration of asbestos exposure = 25 years (minimum = 3, maximum = 45) - Archived serum samples collected between 1993 and 1997 - 20 mesothelioma cases and 12 lung cancer cases - Combination of biomarkers increased sensibility up to 15% (mesothelin + CA125) but with low PPV and high number of false positive cases (n = 71) |

Biomarkers

| | | | | | | | | | |
|---|--|--|----------------------------------|--|------------------------------|---------------------------------|-----------------------------------|-------------------------------|--|
| <p>Felten et al 2014 [161] (Germany)</p> | <p>n = 2,262 (mean age : 59 years)</p> <ul style="list-style-type: none"> • 1894 asbestos exposed power industry workers • 266 subjects with unknown history of asbestos exposure • 102 controls (unexposed to asbestos) <p>Follow-up = 7 months to 4 years</p> | <p>Mesothelin (serum) (Mesomark CIS Bio ELISA Kit)</p> <p>Osteopontin (IBL ELISA Kit, Hamburg)</p> | <p>1.4 nM/L</p> <p>900 ng/mL</p> | <p>n = 134 in exposed workers</p> <p>n = 43 in exposed workers</p> | <p>20% (a)</p> <p>0% (a)</p> | <p>93.2% (a)</p> <p>98% (a)</p> | <p>99.7% (a)</p> <p>99.7% (a)</p> | <p>0.7% (a)</p> <p>0% (a)</p> | <ul style="list-style-type: none"> - Blood samples collected between October 2005 and May 2009 - Several samples obtained in some participants. - Follow-up until the end 2009 - Influence of age on markers level. No effect of duration of asbestos exposure or presence of benign pleural disease - Fixed cut-off values for evaluated biomarkers appeared inadequate - 5 mesothelioma cases in power industry workers (and 11 cases of lung cancer) - High number of false positive cases (133 for mesothelin, 43 for osteopontin) - Some indication of increase of mesothelin level 6 to 18 months before clinical symptoms of mesothelioma |
| <p>Filiberti et al 2014 [162] (Italy)</p> | <p>N = 1,714 asbestos exposed subjects (dock/shipyard, iron and steel-mill industries) (mean age = 62.2 years)</p> <p>Median follow-up 47.1 months (range 5 – 58.6 months)</p> <ul style="list-style-type: none"> • 1,227 healthy subjects • 152 asbestos-related pleural lesions • 24 asbestosis • 182 other benign diseases • 118 cancers | <p>Mesothelin (serum) (Mesomark Fujirebio ELISA Kit)</p> | <p>1.5 nM/L</p> | <p>40</p> | <p>0% (a)</p> | <p>97.8% (a)</p> | <p>99.8% (a)</p> | <p>0% (a) 0/40</p> | <ul style="list-style-type: none"> - Duration of asbestos exposure ≥ 1 year - Blood sampling at 1 and 2 years of follow-up in 1,629 subjects - 3 mesothelioma cases during follow-up + 1 case diagnosed at first visit - Correlation between age and mesothelin level, and inverse correlation between body mass index and mesothelin level |

Biomarkers

| | | | | | | | | | |
|------------------------------------|---|----------------------------------|---------|--|----------------|----------|----------|------------------|--|
| Hirohashi et al 2014 [163] (Japan) | 5 years screening of Tokyo general construction workers n = 40,000 | N-ERC / mesothelin (ELISA assay) | 8 ng/mL | | 100% (2/2) (a) | 100% (a) | 100% (a) | 0.2% (2/714) (a) | <ul style="list-style-type: none"> - As of September 26, 2010, 40,000 participants and 124,288 blood samples collected and analyzed 1,603 with abnormal values. 714 samples confirmed after reanalysis. Finally, 62 participants identified as "high risk population" by the case review committee : i.e : <ul style="list-style-type: none"> i) level NERC/mesothelin > 8ng/mL and ii) age ≥ 35 years, iii) absence of renal dysfunction, iv) human anti-mouse antibody not detected. - Low risk population N-ERC / mesothelin measurements with no abnormal values at least twice. n = 7850 subjects - 2 cases of mesothelioma in the high risk group - PPV was 3.2% when analysis was restricted to participants identified as "high risk population" according to the criteria of the case review committee. |
|------------------------------------|---|----------------------------------|---------|--|----------------|----------|----------|------------------|--|

n : number ;

(a) Calculated from data of the original manuscript

DPT : Diffuse pleural thickening ; MPF : megakaryocyte potentiating factor ; NPV : Negative predictive value ; PPV : positive predictive value ; Se : sensibility ; SMRP : soluble mesothelin related peptide ;

Sp : specificity

Table S7: Biomarkers and early detection of mesothelioma in other retrospective case-control studies based on archived samples with longitudinal survey

| Study (country) | Population (type, number of subjects, age, period/duration of follow-up) | Biomarker (in serum or plasma) | Threshold cut off value | Positive samples | Se | Sp | NPV | PPV | Comments |
|--------------------------------------|---|--|-------------------------|------------------------------|---------|-----------|-----|---------------|--|
| Creaney et al 2010 [164] (Australia) | Retrospective longitudinal evaluation <ul style="list-style-type: none"> • 106 mesothelioma (87 MPM) with serum samples available before diagnosis (mean age = 66 years) Median timing of sample = 8 months before diagnosis • 99 asbestos exposed subjects (0.1 to 253 f-years/ml) • 109 non asbestos exposed healthy subjects (controls have follow-up of 10 years malignancy free period) | Mesothelin (serum) (Mesomark, Fujirebio ELISA Kit) | 2.5 nM | 17 1 (a) 3 (a) | 16% (a) | 98.1% (a) | 71% | 80.9% (17/21) | <ul style="list-style-type: none"> - No correlation between mesothelin concentration and degree of asbestos exposure in asbestos-exposed subjects - 17 subjects of the 106 mesothelioma cases had elevated mesothelin levels before pathologic diagnosis. No link with sex, age, histology, site of tumor, radiological changes in these mesothelioma subjects. - Elevated mesothelin in one asbestos exposed subject was related to renal dysfunction. |

n : number ;

(a) Calculated from data of the original manuscript

DPT : Diffuse pleural thickening ; MPF : megakaryocyte potentiating factor ; NPV : Negative predictive value ; PPV : positive predictive value ; Se : sensibility ; SMRP : soluble mesothelin related peptide ; Sp : specificity

Table S8: Simulations of the expected number (%) of false positive tests and false negative tests from real-life use of biological markers according to a specificity of 95%, different scenario of sensitivity (32%, 50%, 60%, 70%) and several lifetime risks of mesothelioma (15%, 10%, 5%, 2.5%, 2%, 1.5%, 1%, 0.5%).

| | Se=0.32 / Sp=0.95 | | | Se=0.50 / Sp=0.95 | | | Se=0.60 / Sp=0.95 | | | Se=0.70 / Sp=0.95 | | |
|--|--------------------------|-------------|--------|--------------------------|-------------|--------|--------------------------|-------------|--------|--------------------------|-------------|--------|
| | <u>Mesothelioma</u> | | | <u>Mesothelioma</u> | | | <u>Mesothelioma</u> | | | <u>Mesothelioma</u> | | |
| | Yes | No | Total | Yes | No | Total | Yes | No | Total | Yes | No | Total |
| Lifetime risk of mesothelioma: 15% | | | | | | | | | | | | |
| Test + | 480 | 425 | 905 | 750 | 425 | 1,175 | 900 | 425 | 1,325 | 1,050 | 425 | 1,475 |
| Test- | 1,020 | 8,075 | 9,095 | 750 | 8,075 | 8,825 | 600 | 8,075 | 8,675 | 450 | 8,075 | 8,525 |
| Total | 1,500 | 8,500 | 10,000 | 1,500 | 8,500 | 10,000 | 1,500 | 8,500 | 10,000 | 1,500 | 8,500 | 10,000 |
| False positive (%) | | 47.0 | | | 36.2 | | | 32.1 | | | 28.8 | |
| False negative (%) | | 11.2 | | | 8.5 | | | 6.9 | | | 5.3 | |
| Lifetime risk of mesothelioma: 10% | | | | | | | | | | | | |
| Test + | 320 | 450 | 770 | 500 | 450 | 950 | 600 | 450 | 1,050 | 700 | 450 | 1,150 |
| Test- | 680 | 8,550 | 9,230 | 500 | 8,550 | 9,050 | 400 | 8,550 | 8,950 | 300 | 8,550 | 8,850 |
| Total | 1,000 | 9,000 | 10,000 | 1,000 | 9,000 | 10,000 | 1,000 | 9,000 | 10,000 | 1,000 | 9,000 | 10,000 |
| False positive (%) | | 58.4 | | | 47.4 | | | 42.9 | | | 39.1 | |
| False negative (%) | | 7.4 | | | 5.5 | | | 4.5 | | | 3.4 | |
| Lifetime risk of mesothelioma: 5% | | | | | | | | | | | | |
| Test + | 160 | 475 | 635 | 250 | 475 | 725 | 300 | 475 | 775 | 350 | 475 | 825 |
| Test- | 340 | 9,025 | 9,365 | 250 | 9,025 | 9,275 | 200 | 9,025 | 9,225 | 150 | 9,025 | 9,175 |
| Total | 500 | 9,500 | 10,000 | 500 | 9,500 | 10,000 | 500 | 9,500 | 10,000 | 500 | 9,500 | 10,000 |
| False positive (%) | | 74.8 | | | 65.5 | | | 61.3 | | | 57.6 | |
| False negative (%) | | 3.6 | | | 2.7 | | | 2.2 | | | 1.6 | |
| Lifetime risk of mesothelioma: 2.5% | | | | | | | | | | | | |
| Test + | 80 | 488 | 568 | 125 | 488 | 613 | 150 | 488 | 638 | 175 | 488 | 663 |
| Test- | 170 | 9,263 | 9,433 | 125 | 9,263 | 9,388 | 100 | 9,263 | 9,363 | 75 | 9,263 | 9,338 |
| Total | 250 | 9,750 | 10,000 | 250 | 9,750 | 10,000 | 250 | 9,750 | 10,000 | 250 | 9,750 | 10,000 |
| False positive (%) | | 85.9 | | | 79.6 | | | 76.5 | | | 73.6 | |
| False negative (%) | | 1.8 | | | 1.3 | | | 4.1 | | | 0.8 | |

Table S8 (continue): Simulations of the expected number (%) of false positive tests and false negative tests from real-life use of biological markers according to a specificity of 95%, different scenario of sensitivity (32%, 50%, 60%, 70%) and several lifetime risks of mesothelioma (15%, 10%, 5%, 2.5%, 2%, 1.5%, 1%, 0.5%).

| | Se=0.32 / Sp=0.95 | | | Se=0.50 / Sp=0.95 | | | Se=0.60 / Sp=0.95 | | | Se=0.70 / Sp=0.95 | | |
|--|--------------------------|-------------|--------|--------------------------|-------------|--------|--------------------------|-------------|--------|--------------------------|-------------|--------|
| | Mesothelioma | | | Mesothelioma | | | Mesothelioma | | | Mesothelioma | | |
| | Yes | No | Total | Yes | No | Total | Yes | No | Total | Yes | No | Total |
| Lifetime risk of mesothelioma: 2% | | | | | | | | | | | | |
| Test + | 64 | 490 | 554 | 100 | 490 | 590 | 120 | 490 | 610 | 140 | 490 | 630 |
| Test- | 136 | 9,310 | 9,446 | 100 | 9,310 | 9,410 | 80 | 9,310 | 9,390 | 60 | 9,310 | 9,370 |
| Total | 200 | 9,800 | 10,000 | 200 | 9,800 | 10,000 | 200 | 9,800 | 10,000 | 200 | 9,800 | 10,000 |
| False positive (%) | | 88.4 | | | 83.0 | | | 80.3 | | | 77.8 | |
| False negative (%) | | 1.4 | | | 1.1 | | | 0.8 | | | 0.6 | |
| Lifetime risk of mesothelioma: 1.5% | | | | | | | | | | | | |
| Test + | 48 | 493 | 541 | 75 | 493 | 568 | 90 | 493 | 583 | 105 | 493 | 598 |
| Test- | 102 | 9,358 | 9,460 | 75 | 9,358 | 9,433 | 60 | 9,358 | 9,418 | 45 | 9,358 | 9,403 |
| Total | 150 | 9,850 | 10,000 | 150 | 9,850 | 10,000 | 150 | 9,850 | 10,000 | 150 | 9,850 | 10,000 |
| False positive (%) | | 91.1 | | | 86.8 | | | 84.5 | | | 82.4 | |
| False negative (%) | | 1.1 | | | 0.8 | | | 0.6 | | | 0.5 | |
| Lifetime risk of mesothelioma: 1% | | | | | | | | | | | | |
| Test + | 32 | 495 | 527 | 50 | 495 | 545 | 60 | 495 | 555 | 70 | 495 | 565 |
| Test- | 68 | 9,405 | 9,473 | 50 | 9,405 | 9,455 | 40 | 9,405 | 9,445 | 30 | 9,405 | 9,435 |
| Total | 100 | 9,900 | 10,000 | 100 | 9,900 | 10,000 | 100 | 9,900 | 10,000 | 100 | 9,900 | 10,000 |
| False positive (%) | | 93.9 | | | 90.8 | | | 89.2 | | | 87.6 | |
| False negative (%) | | 0.7 | | | 0.5 | | | 0.4 | | | 0.3 | |
| Lifetime risk of mesothelioma: 0.5% | | | | | | | | | | | | |
| Test + | 16 | 498 | 514 | 25 | 498 | 523 | 30 | 498 | 528 | 35 | 498 | 533 |
| Test- | 34 | 9,453 | 9,487 | 25 | 9,453 | 9,478 | 20 | 9,453 | 9,473 | 15 | 9,453 | 9,468 |
| Total | 50 | 9,950 | 10,000 | 50 | 9,950 | 10,000 | 50 | 9,950 | 10,000 | 50 | 9,950 | 10,000 |
| False positive (%) | | 96.9 | | | 95.2 | | | 94.3 | | | 93.4 | |
| False negative (%) | | 0.4 | | | 0.3 | | | 0.2 | | | 0.2 | |

Table S9. Immunohistochemical analysis in epithelioid mesothelioma

| Mesothelial Markers | sensitivity | Specificity versus lung adenocarcinoma |
|--|-------------|--|
| Calretinin (poly) | >90% | 90-95% |
| WT1 (cl 6FH2) | 70-75% | ~100% |
| CK5/6 | 75%–100% | 80%–90% |
| D240 (Cl.D2-40)) | | |
| EMAm (cl E29) | 77% | 77% |
| Mesothelin (cl.A103) | 88% | 73% |
| Adenocarcinoma markers (positive epithelial markers) | | |
| B72.3 (cl) | 25-85% | 95% |
| BerEP4(Cl) | 95-100% | 74-87% |
| BG8 (cl) | 90-100% | 93-97% |
| ACE moabs | 80-100% | >95% |
| Organ specific markers Lung | | |
| TTF-1 (cl.8G7G3/1) | ~80% | High |
| Napsin A | ~80% | High |
| Organ specific –Breast carcinoma metastasis | | |
| Estrogen receptor α (cl.EP1)) | NA | NA |
| Progesterone receptor | NA | NA |
| GCDFP15 | 30-40% | High |
| Mammaglobin | 50-85% | High |
| Organ specific –Renal carcinoma metastasis | | |
| PAX8 (Poly) | 70-100% | Unknown |
| PAX2 | 80% | Unknown |
| RCC (cl.PN-15) | <85% | 75-95% |
| CD15 | 60% | High |
| BAP-1 | ~50-70% | NA |

Adapted from Travis 2015 [297] and Righi 2016 [298] ; variable by subtype; NA=Not available

Table S10. Immunohistochemical analysis in sarcomatoid mesothelioma

| Mesothelial markers | % of positivity in Sarcomatoid mesothelioma |
|-------------------------------|---|
| Keratin AE1/AE3 | ~90% |
| CAM5.2 | ~90% |
| CK5/6 | ~30% |
| Calretinin (nuclear staining) | ~50% often focal |
| WT1 | ~45% |
| D240 | >70% |
| GATA3 | 85% sensitivity and 100% specificity |
| BAP1 | 22% |

Adapted from Travis 2015 [297], Righi 2016 [298] et Marchevsky 2017 [299].

Table S11. Immunohistochemical analysis in sarcomatoid carcinoma metastatic to the pleura

| Mesothelial markers | % of positivity in sarcomatoid carcinoma |
|----------------------|--|
| Keratin AE1/AE3 | ~88% |
| CAM 5.2 | ~91% |
| Calretinin | <40% |
| TTF-1 (cl. 8G7G3/1) | ~17% |
| P40 (cl.BC28) | 0 |
| BAP1 (cl.C-4) | <1% |

Table S12. Characteristics of studies assessing first-line treatments in malignant pleural mesothelioma.

| Reference | Design | N pts | Treatment | Results based on primary endpoint | Conclusion |
|--------------------------------------|------------|-------|-------------------------|--|---|
| Targeted therapies | | | | | |
| Laurie, 2011 [249] | Phase II | 18 | Sunitinib | 1 response among 18 pts. | Negative |
| Buikhuisen, 2013 [250] | Phase III | 222 | Maintenance thalidomide | PFS: median 3.6 months (thalidomide) versus 3.5 months (HR=0.95; 95% CI: 0.73-1.20; p=0.72) | Negative |
| Buikhuisen, 2016 [251] | Phase II R | 25 | CDDP-PEM +/- Axitinib | 11/11 and 16/20 had second thoracoscopy (No difference for RR, PFS, survival) | Negative (for common clinical criteria) |
| Dubey, 2010 [252] | Phase II | 20 | Sorafenib | RR 10% | Negative |
| Fennell, 2012 [253] | Phase II | 10 | Bortezomib | RR 0% | Negative |
| Hassan, 2014 [254] | Phase II | 99 | CDDP-PEM + Amatuximab | PFS rate at 6 months 51.3% | Negative |
| Jahan, 2012 [255] | Phase II | 47 | Vatalanib | PFS rate at 3 months 55% | Negative |
| Krug, 2014 [256] | Phase II R | 65 | CDDP-PEM +/- CBP501 | PFS rate at 4 months 25/40 (63%) versus 9/23 (39%) | Positive |
| O'Brien, 2013 [257] | Phase II | 82 | CDDP-Bortezomib | PFS rate at 18 weeks 53% | Negative |
| Conventional chemotherapy | | | | | |
| Ralli, 2009 [258] | Phase II | 25 | GEM-DOC | No clear primary endpoint RR 28%, median overall survival 15 months (range: 12.4-17.5 months) | Positive (?) |
| Arrieta, 2012 [259] | Phase II | 38 | CDDP-liposomal DOX | No clear primary endpoint RR 38.9%, median PFS 4.6 months, median survival 19.6 months | Positive (?) |
| Habib, 2013 [260] | Phase II R | 36 | CDDP-GEM vs CBDCA-PEM | No clear primary endpoint RR 10% vs 15% (p=0.041) | ? |
| Katirtzoglou, 2010 [261] | Phase II | 62 | CBDCA-PEM | RR 29% | Positive |
| Kovac, 2012 [262] | Phase II | 78 | CDDP-GEM | Survival: median 17 months | Positive |
| Kuribayashi, 2013 [263] | Phase II | 21 | MTX-GEM | No clear primary endpoint (RR 38.1%, median survival 19.4 months) | Positive (?) |
| Bevacizumab-based combination | | | | | |
| Zalcman, 2016 [264] | Phase III | 458 | CDDP-PEM +/- Bev | Survival: median 18.8 months vs 16.1 months (p = 0.0167) | Positive |
| Ceresoli, 2013 [265] | Phase II | 76 | CBDCA-PEM- | PFS: median 6.9 months | Negative |

Biomarkers : simulations

| | | | Bev | | |
|------------------------|------------|-----|--------------------|---|----------|
| Dowell, 2012 [266] | Phase II | 53 | CDDP-PEM-Bev | PFS rate at 6 months 56% | Negative |
| Kindler, 2012 [267] | Phase II R | 115 | CDP-GEM +/- Bev | PFS: median 6.9 months vs 6 months (p = 0.88) | Negative |

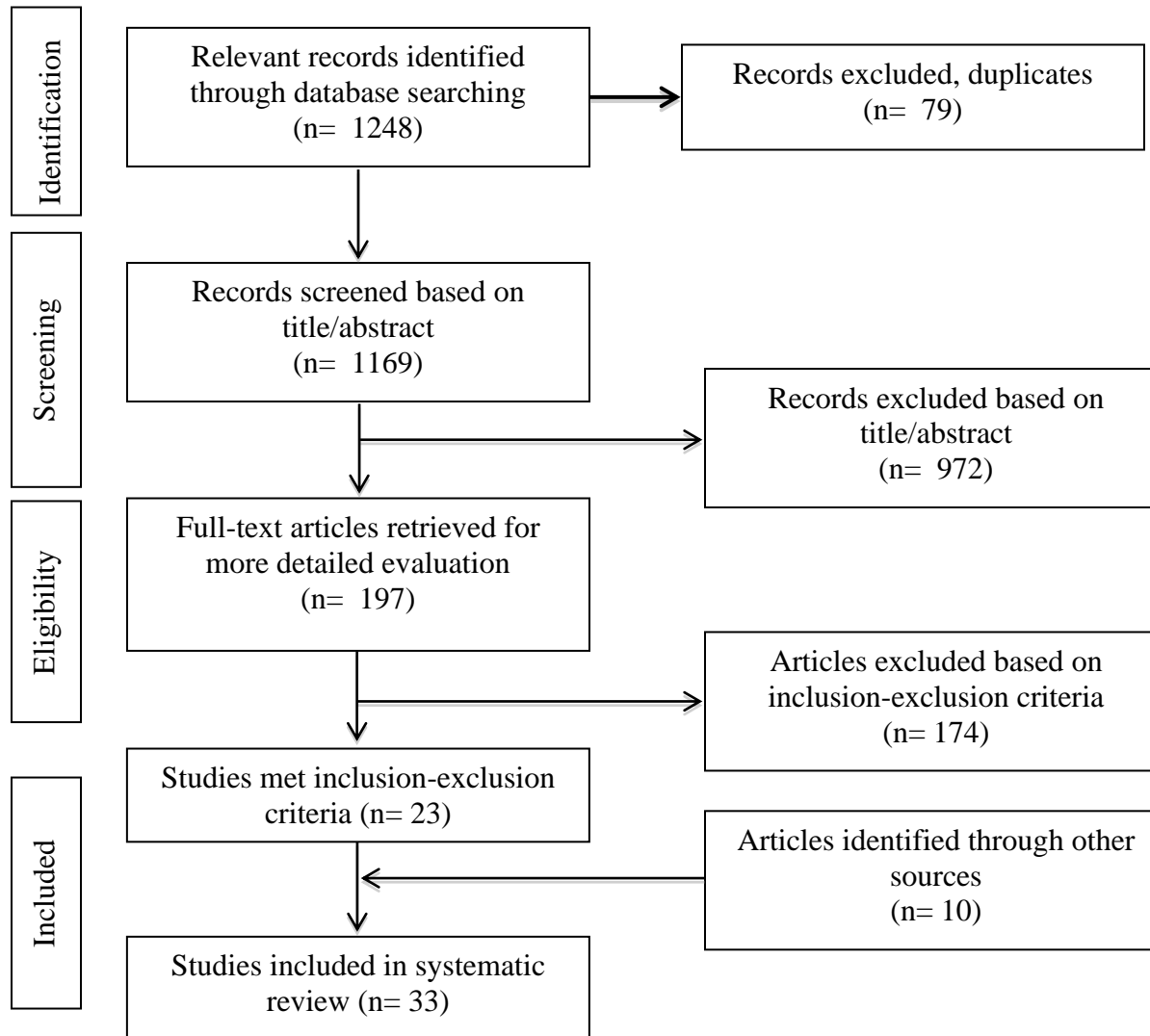
Pts : patients ; RR : response rate ; PFS : progression-free survival ; R : randomised ; CDDP : cisplatin ; PEM : pemetrexed ; GEM : gemcitabine ; DOC : docetaxel ; DOX : doxorubicin ; CBDCA : carboplatin ; MTX : methotrexate ; Bev : bevacizumab

Table S13. Studies assessing salvage therapy in malignant mesothelioma

| Reference | Design | N pts | Treatment | Results based on primary endpoint | Conclusion |
|----------------------------------|-----------|-------|-----------------------------|--|--------------|
| Targeted therapies | | | | | |
| Laurie, 2011 [249] | Phase II | 17 | Sunitinib | RR 0% | Negative |
| Dubey, 2010 [252] | Phase II | 30 | Sorafenib | RR 3.3% | Negative |
| Nowak, 2013 [268] | Phase II | 30 | BNC105P | RR 3% | Negative |
| Ou, 2015 [269] | Phase II | 59 | Everolimus | PFS rate at 4 months 29% | Negative |
| Papa, 2013 [270] | Phase II | 53 | Sorafenib | PFS rate at 6 months 36% | Positive |
| Wheatly-Price, 2016 [271] | Phase II | 17 | PF-03446962 | RR 0% | Negative |
| Fennell, 2012 [253] | Phase II | 23 | Bortezomib | RR 4.8% | Negative |
| Campbell, 2012 [272] | Phase II | 51 | Cediranib | RR 10% | Negative |
| Dudek, 2012 [273] | Phase II | 46 | Dasatinib | PFS rate at 6 months 23% | Negative |
| Garland, 2011 [274] | Phase II | 54 | Cediranib | RR 9% | Negative |
| Ramalingam, 2009 [275] | Phase II | 13 | Belinostat | RR 0% | Negative |
| Scherpereel, 2011 [276] | Phase II | 45 | DOX-VPA | RR 16% | Positive |
| Krug, 2015 [277] | Phase III | 661 | Vorinostat versus placebo | Survival: median 30.7 weeks vs 27.1 weeks (p = 0.86) | Negative |
| Conventional chemotherapy | | | | | |
| Stebbing, 2009 [278] | Phase II | 63 | Vinorelbine | ORR 16% | Positive |
| Tourkantonis, 2011 [279] | Phase II | 37 | DOX-GEM | No clear primary endpoint (RR 38.1%, median survival 19.4 months) | Positive (?) |
| Immunotherapy | | | | | |
| Calabro, 2013 [280] | Phase II | 29 | Tremelimumab | RR 7% | Negative |
| Calabro, 2015 [281] | Phase II | 29 | Tremelimumab | Immune related RR 13.8% | Negative |
| Maio, 2017 [282] | Phase III | 571 | Tremelimumab versus placebo | Survival: median 7.7 months vs 7.3 months (p = 0.41) | Negative |
| Gregorc, 2010 [283] | Phase II | 57 | NGR-hTNF | PFS rate at 12 weeks 38% | Negative |

Pts : patients ; RR : response rate ; PFS : progression-free survival ; GEM : gemcitabine ; DOX : doxorubicin ; VPA : valproic acid

Figure S1. Flow chart of the search of the literature.



Biomarkers : simulations
GRADE Evidence Profiles

Table S14: Should partial pleurectomy compared to talc pleurodesis be used as palliative surgery in patients with symptomatic malignant pleural mesothelioma?

Bibliography: Rintoul RC, Ritchie AJ, Edwards JG et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. Lancet 2014; 384: 1118-1127.

| Certainty assessment | | | | | | | Nº of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|--------------------------|------------------|-------------------|-------------------|-----------|------------|
| Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | VATS partial pleurectomy | talc pleurodesis | Relative (95% CI) | Absolute (95% CI) | | |

Quality of life at 6 months (assessed with: EQ-5D (MID 0.074); Scale from: 0 (dead) to 1 (full health))

| | | | | | | | | | | | | |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|----|----|--|--|-------------|----------|
| 1 | randomised trials | serious ^a | not serious | not serious | serious ^b | none | 56 | 56 | MD 0.08 higher (0.003 higher to 0.16 higher) | | ⊕⊕○○ LOW | CRITICAL |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|----|----|--|--|-------------|----------|

Quality of life at 1 year (assessed with: EQ-5D (MID 0.074); Scale from: 0 (dead) to 1 (full health))

| | | | | | | | | | | | | |
|---|-------------------|------------------------|-------------|-------------|----------------------|------|----|----|---|--|-------------|----------|
| 1 | randomised trials | serious ^{a,c} | not serious | not serious | serious ^b | none | 34 | 37 | MD 0.19 higher (0.05 higher to 0.32 higher) | | ⊕⊕○○ LOW | CRITICAL |
|---|-------------------|------------------------|-------------|-------------|----------------------|------|----|----|---|--|-------------|----------|

Overall survival

| | | | | | | | | | | | | |
|---|-------------------|-------------|-------------|-------------|----------------------|------|--|--|--|------------------|--|----------|
| 1 | randomised trials | not serious | not serious | not serious | serious ^d | none | There were no significant differences between VATS-PP and talc pleurodesis in the overall survival of patients up to 9 years of follow-up: HR: 1.04 (CI95% 0.76 to 1.42); p=0.81; N=175 patients. The Hazard Ratio, stratified by EORTC prognostic risk (high or low) was similar. Median survival was 13.1 month (IQR 7.3 to 20.3) in the VATS-PP and 13.5 (IQR 7.3 to 21.1) in the talc pleurodesis group. | | | ⊕⊕⊕○ MODERATE | | CRITICAL |
|---|-------------------|-------------|-------------|-------------|----------------------|------|--|--|--|------------------|--|----------|

Overall survival at 6 months

| | | | | | | | | | | | | |
|---|-------------------|-------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|------------------|----------|
| 1 | randomised trials | not serious | not serious | not serious | serious ^d | none | 68/87 (78.2%) | 70/88 (79.5%) | RR 0.98 (0.84 to 1.15) | 16 fewer per 1.000 (from 127 fewer to 119 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|---|-------------------|-------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|------------------|----------|

Overall survival at 1 year

| | | | | | | | | | | | | |
|---|-------------------|-------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|------------------|----------|
| 1 | randomised trials | not serious | not serious | not serious | serious ^d | none | 45/87 (51.7%) | 50/88 (56.8%) | RR 0.91 (0.69 to 1.20) | 51 fewer per 1.000 (from 176 fewer to 114 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|---|-------------------|-------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|------------------|----------|

Biomarkers : simulations

| Certainty assessment | | | | | | | Nº of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|--------------------------|------------------|-------------------|-------------------|-----------|------------|
| Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | VATS partial pleurectomy | talc pleurodesis | Relative (95% CI) | Absolute (95% CI) | | |

Post-operative morbidity (serious adverse events)

| | | | | | | | | | | | | |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|---------------|--------------|----------------------------------|---|-------------|----------|
| 1 | randomised trials | serious ^a | not serious | not serious | serious ^d | none | 13/78 (16.7%) | 8/73 (11.0%) | RR 1.52 (0.67 to 3.46) | 57 more per 1.000 (from 36 fewer to 270 more) | ⊕⊕○○ LOW | CRITICAL |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|---------------|--------------|----------------------------------|---|-------------|----------|

Number of patients with pleural effusion resolution at 1 year

| | | | | | | | | | | | | |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|-------------|----------|
| 1 | randomised trials | serious ^c | not serious | not serious | serious ^d | none | 23/33 (69.7%) | 27/35 (77.1%) | RR 0.90 (0.68 to 1.21) | 77 fewer per 1.000 (from 247 fewer to 162 more) | ⊕⊕○○ LOW | CRITICAL |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|-------------|----------|

Number of patients with pleural effusion resolution at 6 months

| | | | | | | | | | | | | |
|---|-------------------|-------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|------------------|-----------|
| 1 | randomised trials | not serious | not serious | not serious | serious ^e | none | 41/53 (77.4%) | 31/54 (57.4%) | RR 1.35 (1.03 to 1.77) | 201 more per 1.000 (from 17 more to 442 more) | ⊕⊕⊕○ MODERATE | IMPORTANT |
|---|-------------------|-------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|------------------|-----------|

Number of patients with pleural effusion resolution at 3 months

| | | | | | | | | | | | | |
|---|-------------------|-------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|------------------|-----------|
| 1 | randomised trials | not serious | not serious | not serious | serious ^d | none | 36/60 (60.0%) | 37/62 (59.7%) | RR 1.01 (0.75 to 1.34) | 6 more per 1.000 (from 149 fewer to 203 more) | ⊕⊕⊕○ MODERATE | IMPORTANT |
|---|-------------------|-------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|---|------------------|-----------|

Number of patients with pleural effusion resolution at 1 month

| | | | | | | | | | | | | |
|---|-------------------|-------------|-------------|----------------------|-------------|------|---------------|---------------|----------------------------------|---|------------------|-----------|
| 1 | randomised trials | not serious | not serious | serious ^f | not serious | none | 41/69 (59.4%) | 25/68 (36.8%) | RR 1.62 (1.12 to 2.33) | 228 more per 1.000 (from 44 more to 489 more) | ⊕⊕⊕○ MODERATE | IMPORTANT |
|---|-------------------|-------------|-------------|----------------------|-------------|------|---------------|---------------|----------------------------------|---|------------------|-----------|

Operative mortality

| | | | | | | | | | | | | |
|---|-------------------|-------------|-------------|-------------|---------------------------|------|---|--|--|--|-------------|-----------|
| 1 | randomised trials | not serious | not serious | not serious | very serious ^g | none | There were one death (at least possibly related to treatment) in the VAT-PP group and none in the talc pleurodesis group. | | | | ⊕⊕○○ LOW | IMPORTANT |
|---|-------------------|-------------|-------------|-------------|---------------------------|------|---|--|--|--|-------------|-----------|

Hospital length of stay

Biomarkers : simulations

| Certainty assessment | | | | | | | Nº of patients | | Effect | | Certainty | Importance |
|----------------------|-------------------|----------------------|---------------|----------------------|-------------|----------------------|--|------------------|-------------------|-------------------|-------------|------------|
| Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | VATS partial pleurectomy | talc pleurodesis | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | randomised trials | serious ^a | not serious | serious ^h | not serious | none | Median hospital stay after the procedure was 7 days (IQR 5 to 11) for the VAT-PP group and 3 days (IQR 2 to 5) for the talc pleurodesis group; p<0.0001) | | | | ⊕⊕○○ LOW | IMPORTANT |

Incidence of "seeding" tract metastases - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

Time to treatment failure - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

30 days mortality - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

90 days mortality - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

Time to disease progression - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

CI: Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

- a. Open trial design might have influenced the assessment of this outcome
- b. 95%CI crosses the MID threshold and ranges from non relevant effect to important benefit. Low number of patients - optimal information size not met
- c. Large number of patients lost of follow-up
- d. Limited number of events; 95%CI points to a substantial benefit or harm
- e. Limited number of events; 95%CI points to a substantial benefit or negligible effect

Biomarkers : simulations

f. Short follow-up. Results at one month does not seem to replicate at longer follow-up

g. One single event

h. Hospital length of stay is an administrative outcome much influenced by each institution policy and not directly related to patient important outcomes

EQ-5D MID from: Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005 Aug;14(6):1523-32.

Biomarkers : simulations

Table S15: Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used as in patients with symptomatic malignant pleural mesothelioma?

Bibliography: Treasure T, Lang-Lazdunski L, Waller D et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncology 2011; 12: 763-772

| Certainty assessment | | | | | | | No of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|--|-----------------------|-------------------|-------------------|-----------|------------|
| No of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | surgery (EPP: extra-pleural pneumectomy) | non surgical approach | Relative (95% CI) | Absolute (95% CI) | | |

Quality of life at 6 months (assessed with: EORTC, QLQ-C30 and QLQ-LC13)

| | | | | | | | | | | | | |
|---|-------------------|---------------------------|-------------|-------------|----------------------|------|--|--|------------------|--|----------|--|
| 1 | randomised trials | very serious ^a | not serious | not serious | serious ^b | none | Median quality-of-life scores seemed to be lower for the EPP group (58.3) than the no EPP group (66.7) | | ⊕○○○ VERY LOW | | CRITICAL | |
|---|-------------------|---------------------------|-------------|-------------|----------------------|------|--|--|------------------|--|----------|--|

Quality of life at 1 year (assessed with: EORTC, QLQ-C30 and QLQ-LC13)

| | | | | | | | | | | | | |
|---|-------------------|---------------------------|-------------|-------------|----------------------|------|--|--|------------------|--|----------|--|
| 1 | randomised trials | very serious ^a | not serious | not serious | serious ^b | none | Median quality-of-life scores seemed to be lower for the EPP group (41.7) than the no EPP group (70.8) | | ⊕○○○ VERY LOW | | CRITICAL | |
|---|-------------------|---------------------------|-------------|-------------|----------------------|------|--|--|------------------|--|----------|--|

Deaths at the end of follow-up (median 24.7 months)

| | | | | | | | | | | | | |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|--|-------------|----------|
| 1 | randomised trials | serious ^c | not serious | not serious | serious ^d | none | 17/24 (70.8%) | 13/26 (50.0%) | RR 1.42 (0.89 to 2.25) | 210 more per 1.000 (from 55 fewer to 625 more) | ⊕⊕○○ LOW | CRITICAL |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|---------------|---------------|----------------------------------|--|-------------|----------|

Overall survival

| | | | | | | | | | | | | |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|---|--|-------------|--|----------|--|
| 1 | randomised trials | serious ^c | not serious | not serious | serious ^e | none | The overall survival favored the non EPP group (non surgical approach): HR 2.75 (1.21 to 6.26) adjusted for sex, histological subtype, stage, and age at randomisation. | | ⊕⊕○○ LOW | | CRITICAL | |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|---|--|-------------|--|----------|--|

12-months survival

| | | | | | | | | | | | | |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|--|--|-------------|--|-----------|--|
| 1 | randomised trials | serious ^c | not serious | not serious | serious ^d | none | EPP (surgery) 52.2% (95% CI 30.5 to 70); no EPP (non surgical approach) 73.1% (51.7 to 86.2) (difference 18.0%, from -1.8 to 43.9) | | ⊕⊕○○ LOW | | IMPORTANT | |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|--|--|-------------|--|-----------|--|

Biomarkers : simulations

| Certainty assessment | | | | | | | Nº of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|--|-----------------------|-------------------|-------------------|-----------|------------|
| Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | surgery (EPP: extra-pleural pneumectomy) | non surgical approach | Relative (95% CI) | Absolute (95% CI) | | |

12-months recurrence-free survival

| | | | | | | | | | | | | |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|--|--|--|--|-------------|-----------|
| 1 | randomised trials | serious ^c | not serious | not serious | serious ^e | none | EPP (surgery) 34.8% (95% CI 16.6 to 53.7); no EPP (non surgical approach) 42.3% (23.5 to 60) | | | | ⊕⊕○○ LOW | IMPORTANT |
|---|-------------------|----------------------|-------------|-------------|----------------------|------|--|--|--|--|-------------|-----------|

Operative mortality

| | | | | | | | | | | | | |
|---|-------------------|----------------------|-------------|-------------|--------------------------|------|---|--|--|--|------------------|-----------|
| 1 | randomised trials | serious ^c | not serious | not serious | not serious ^f | none | There were 3 deaths among 19 patients receiving the EPP surgical approach. Non surgical approach is not linked to this adverse outcome. | | | | ⊕⊕⊕○ MODERATE | IMPORTANT |
|---|-------------------|----------------------|-------------|-------------|--------------------------|------|---|--|--|--|------------------|-----------|

Post-operative morbidity

| | | | | | | | | | | | | |
|---|-------------------|----------------------|-------------|-------------|--------------------------|------|---|--|--|--|------------------|-----------|
| 1 | randomised trials | serious ^c | not serious | not serious | not serious ^f | none | There were 11 post-operative complications among 16 patients completing the EPP surgical approach. Non surgical approach is not linked to this adverse outcome. | | | | ⊕⊕⊕○ MODERATE | IMPORTANT |
|---|-------------------|----------------------|-------------|-------------|--------------------------|------|---|--|--|--|------------------|-----------|

Location of recurrence - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

30 days mortality - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

90 days mortality - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

Hospital length of stay - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

Biomarkers : simulations

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio; **HR:** Hazard Ratio

Explanations

- a. Open trial design might have influenced the assessment of this outcome. Feasibility trial not reaching the pre-specified sample size. Significant number of patients did not complete the questionnaires
- b. 95%CI for differences only provided in figures, wide intervals
- c. Feasibility trial not reaching the pre-specified sample size
- d. Limited number of events; 95%CI points to a substantial benefit or harm
- e. Limited number of patients and events
- f. Although the number of patients and events is very limited, this adverse outcome is only related to surgical approach
- g. Hospital length of stay is an administrative outcome much influenced by each institution policy and not directly related to patient important outcomes

Biomarkers : simulations

Table S16: Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used as in patients with symptomatic malignant pleural mesothelioma?

Bibliography: Bovolato P, Casadio C, Bille A et al. Does surgery improve survival of patients with malignant pleural mesothelioma?: a multicenter retrospective analysis of 1365 consecutive patients. Journal of Thoracic Oncology 2014; 9: 390-396

| Certainty assessment | | | | | | | N° of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|---|-----------------------|-------------------|-------------------|-----------|------------|
| N° of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Surgery (EPP: extra-pleural pneumectomy or PD: pneumectomy/decortication) | non surgical approach | Relative (95% CI) | Absolute (95% CI) | | |

Survival

| | | | | | | | | | | | |
|---|-----------------------|----------------------|-------------|-------------|----------------------|------|--|--|------------------|--|----------|
| 1 | observational studies | serious ^a | not serious | not serious | serious ^b | none | Non-surgical approach: median 11.7 months (range 10.5 to 12.5); PD: median 20.5 months (95%CI 18.2 to 23.1); EPP median 18.8 months (95%CI 17.2 to 20.9) | | ⊕○○○ VERY LOW | | CRITICAL |
|---|-----------------------|----------------------|-------------|-------------|----------------------|------|--|--|------------------|--|----------|

Overall mortality

| | | | | | | | | | | | |
|---|-----------------------|--------------------------|-------------|-------------|-------------|------|---|--|-------------|--|----------|
| 1 | observational studies | not serious ^c | not serious | not serious | not serious | none | Against non-surgical approach the overall mortality in PD was HR 0.69 (95%CI 0.55 to 0.86) and in EPP was HR 0.77 (95%CI 0.64 to 0.93). | | ⊕⊕○○ LOW | | CRITICAL |
|---|-----------------------|--------------------------|-------------|-------------|-------------|------|---|--|-------------|--|----------|

Quality of life - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|----------|
| - | - | - | - | - | - | - | - | - | - | - | - | CRITICAL |
|---|---|---|---|---|---|---|---|---|---|---|---|----------|

30 days mortality

| | | | | | | | | | | | |
|---|-----------------------|----------------------|-------------|-------------|--------------------------|------|-------------------------------------|--|------------------|--|-----------|
| 1 | observational studies | serious ^a | not serious | not serious | not serious ^d | none | PD: 2.6% (5/202); EPP 4,1% (12/301) | | ⊕○○○ VERY LOW | | IMPORTANT |
|---|-----------------------|----------------------|-------------|-------------|--------------------------|------|-------------------------------------|--|------------------|--|-----------|

90 days mortality

| | | | | | | | | | | | |
|---|-----------------------|----------------------|-------------|-------------|--------------------------|------|------------------------------------|--|------------------|--|-----------|
| 1 | observational studies | serious ^a | not serious | not serious | not serious ^d | none | PD: 6% (12/202); EPP 6.9% (21/301) | | ⊕○○○ VERY LOW | | IMPORTANT |
|---|-----------------------|----------------------|-------------|-------------|--------------------------|------|------------------------------------|--|------------------|--|-----------|

Post-operative complications

Biomarkers : simulations

| Certainty assessment | | | | | | | Nº of patients | | Effect | | Certainty | Importance |
|----------------------|-----------------------|----------------------|---------------|--------------|--------------------------|----------------------|---|-----------------------|-------------------|-------------------|------------------|------------|
| Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Surgery (EPP: extra-pleural pneumectomy or PD: pneumectomy/decortication) | non surgical approach | Relative (95% CI) | Absolute (95% CI) | | |
| 1 | observational studies | serious ^a | not serious | not serious | not serious ^e | none | PD 10.4% (21/202); EPP: 21.6% (65/301) | | | | ⊕○○○ VERY LOW | IMPORTANT |

Length of hospital stay - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

Time to tumor progression - recurrence free survival - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

Location of recurrence - not reported

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|
| - | - | - | - | - | - | - | - | - | - | - | - | IMPORTANT |
|---|---|---|---|---|---|---|---|---|---|---|---|-----------|

CI: Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

- a. Retrospective cohort; not adjusted for this outcome
- b. Treatment group differences not provided, although results point to a benefit for surgical options individual estimates have a large 95%CI
- c. Retrospective cohort but Adjusted to key risk factors for this outcome
- d. Although the number of events is low, this short-term mortality is only linked to surgical approaches
- e. Although the number of events is low, this adverse outcome is only linked to surgical approaches

Biomarkers : simulations

Table S17: Should radiotherapy be used to prevent procedure-tract methastases (drain site parietal seeding) in patients with malignant pleural mesothelioma?

| Certainty assessment | | | | | | | Nº of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|---|----------------------------------|-------------------|-------------------|-----------|------------|
| Nº of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Radiotherapy for the prevention of procedure-tract metastases | control or deferred radiotherapy | Relative (95% CI) | Absolute (95% CI) | | |

Overall survival

| | | | | | | | | | | | |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|-----|-----|----------------------------------|------------------|-----------|
| 1 ¹ | randomised trials | not serious | not serious ^a | not serious | serious ^b | none | 102 | 101 | HR 1.00 (0.68 to 1.47) | ⊕⊕⊕○ MODERATE | IMPORTANT |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|-----|-----|----------------------------------|------------------|-----------|

Disease (metastasis) free survival

| | | | | | | | | | | | |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|----|----|----------------------------------|------------------|-----------|
| 1 ² | randomised trials | not serious | not serious ^a | not serious | Serious ^b | none | 31 | 30 | HR 1.28 (0.29 to 5.65) | ⊕⊕⊕○ MODERATE | IMPORTANT |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|----|----|----------------------------------|------------------|-----------|

Number of patients with tract-metastasis

| | | | | | | | | | | | | |
|------------------------|-------------------|-------------|----------------------|-------------|----------------------|------|---------------|----------------|----------------------------------|--|-------------|----------|
| 5 ^{1,2,3,4,5} | randomised trials | not serious | serious ^c | not serious | Serious ^b | none | 24/367 (9.9%) | 40/370 (16.6%) | OR 0.64 (0.27 to 1.51) | 4 fewer per 100 (from 8 fewer to 5 more) | ⊕⊕○○ LOW | CRITICAL |
|------------------------|-------------------|-------------|----------------------|-------------|----------------------|------|---------------|----------------|----------------------------------|--|-------------|----------|

Time to tract metastasis development

| | | | | | | | | | | | |
|------------------|-------------------|-------------|--------------------------|-------------|---------------------------|------|---|--|--|-------------|-----------|
| 2 ^{1,2} | randomised trials | not serious | not serious ^d | not serious | Very serious ^e | none | Clive 2016 does not show differences between groups in median time to tract metastasis (days) between immediate and delayed RT: 179 (IQR 126-221) vs. 224 (IQR 136-285), respectively. In O'Rourke 2007 the time from procedure until development of tract metastasis was 2.4 months in RT group and 6.4 months in control group (p=0.8). | | | ⊕⊕○○ LOW | IMPORTANT |
|------------------|-------------------|-------------|--------------------------|-------------|---------------------------|------|---|--|--|-------------|-----------|

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio

Explanations

Biomarkers : simulations

- a. Single study
- b. Wide 95%CI that includes the possibility of a large benefit or harm
- c. Large variability among individual studies effects estimates
- d. Both effect estimates seem to point a benefit of RT or immediate RT
- e. The effect estimates cannot be pooled and the range of potential real effect (95%CI) is unknown.

References

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3. Bydder S, Phillips M,Joseph DJ,Cameron F,Spry NA,DeMelker Y,Musk AW. A randomised trial of single-dose radiotherapy to prevent procedure tract metastasis by malignant mesothelioma. British Journal of Cancer; 2004.
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Biomarkers : simulations

Table S18: Should adjuvant post-operative radiotherapy be used in patients with malignant pleural mesothelioma?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|-------------------|-------|-------------------|-------------------|-----------|------------|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Post-operative RT | no RT | Relative (95% CI) | Absolute (95% CI) | | |

Overall survival time from treatment initiation

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|--------------------------|--------------------------|----------------------|------|----|----|--|--|------------------|----------|
| 1 ¹ | randomised trials | not serious | not serious ^a | not serious ^b | serious ^c | None | 27 | 27 | 19.3 months (11.5–21.8) in the radiotherapy group 20.8 months (95% CI 14.4–27.8) in the no radiotherapy group | MD 1.5 months fewer (11.12 fewer to 8.12 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|--------------------------|--------------------------|----------------------|------|----|----|--|--|------------------|----------|

Locoregional relapse free survival time from treatment initiation

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|----|----|--|---|------------------|----------|
| 1 ¹ | randomised trials | not serious | not serious ^a | not serious | serious ^c | None | 27 | 27 | 12.2 months (9.5–14.8) in the radiotherapy group 11 months (95% CI 7.5–13.5) in the no radiotherapy group | MD 1.2 months fewer (5.41 fewer to 3.01 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|----|----|--|---|------------------|----------|

Locoregional relapse free survival time from surgery

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|----|----|--|--|------------------|----------|
| 1 ¹ | randomised trials | not serious | not serious ^a | not serious | serious ^c | None | 27 | 27 | 9.4 months (6.5–11.9) in the radiotherapy group 7.6 months (95% CI 4.5–10.7) in the no radiotherapy group | MD 1.8 months more (2.25 fewer to 5.85 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|----|----|--|--|------------------|----------|

Biomarkers : simulations

Quality of life

| | | | | | | | | | | | |
|----------------|-------------------|-------------|--------------------------|-------------|---------------------------|------|----|----|--|-------------|----------|
| 1 ¹ | randomised trials | not serious | not serious ^a | not serious | very serious ^d | None | 27 | 27 | <p>Quality of life, psychological and physical symptom distress and activity level impairment improved over time in patients not receiving radiotherapy.</p> <p>Patients receiving radiotherapy reported rather stable scores in these domains, except for their activity level, which worsened up to 4 weeks after randomisation, but recovered to baseline scores thereafter. No changes in the scores for the overall evaluation of quality life in both groups up to week 14 after randomisation</p> | ⊕⊕○○ LOW | CRITICAL |
|----------------|-------------------|-------------|--------------------------|-------------|---------------------------|------|----|----|--|-------------|----------|

Adverse events

| | | | | | | | | | | | |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|----|----|---|-------------|----------|
| 1 ¹ | randomised trials | not serious | not serious ^a | not serious | serious ^e | None | 27 | 27 | <p>Grade 3 toxic effects induced by radiotherapy were nausea or vomiting, oesophagitis, fatigue, weight loss, dyspnoea, diarrhoea, and increased alkaline phosphatase concentration. One patient had grade 4 radiation pneumonitis of the contralateral lung and one patient died of a complicated pneumonia during radiotherapy.</p> | ⊕⊕○○ LOW | CRITICAL |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|----|----|---|-------------|----------|

CI: Confidence interval; HR: Hazard Ratio; OR: Odds ratio

Explanations

- Single study
- The overall median survival of 20 months in part 2 was less than expected when compared with—often retrospective—clinical reports. This result might partly be explained by the inclusion of patients with worse prognosis in this study.
- Wide 95%CI that includes appreciable harm or benefit
- No comparative numerical results given.
- Low number of patients. Although the results refers only to radiotherapy group, in those patients not receiving radiotherapy these adverse events are not expected.

References

- Stahel RA, Riesterer O, Xyrafas A, Opitz I, Beyeler M, Ochsenbein A, et al. Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomised, international, multicentre phase 2 trial. Lancet Oncol. 2015

Biomarkers : simulations

Table S19: Should first line chemotherapy consisting of platinum alone or in combination with pemetrexed be used in patients with malignant pleural mesothelioma?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|-------------------|----------------------|--------------------------|--------------|---------------------------|----------------------|--|----------------------------|---------------------------|--|-------------|------------|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | FIRST LINE Conventional chemotherapy with Cisplatin and Carboplatin | Carboplatin and pemetrexed | Relative (95% CI) | Absolute (95% CI) | | |
| Response rate (complete and partial response) | | | | | | | | | | | | |
| 1 ¹ | randomised trials | serious ^a | not serious ^b | not serious | serious ^c | none | 15/19 (78.9%) | 10/21 (47.6%) | RR 1.66 (1.00 to 2.75) | 314 more per 1.000 (from 0 fewer to 833 more) | ⊕⊕○○ LOW | CRITICAL |
| Overall survival | | | | | | | | | | | | |
| 1 ¹ | randomised trials | Not serious | not serious ^b | not serious | Very serious ^d | none | 11/19 (57.9%) | 9/21 (42.9%) | RR 1.35 (0.72 to 2.52) | 150 more per 1.000 (from 120 fewer to 651 more) | ⊕⊕○○ LOW | CRITICAL |

CI: Confidence interval; **RR:** Risk ratio

Explanations

- a. Not blinded assessment for a data adjudication (subjective) outcome.
- b. Single study
- c. Low number of events; wide 95%CI includes no effect or large benefit
- d. Very low number of events from underpowered study; 95%CI includes either large benefit or harm

References

1. Habib EE, Fahmy ES. Chemotherapy management of malignant pleural mesothelioma: a phase II study comparing two popular chemotherapy regimens. Clin Transl Oncol. 2013;15(11):965-8.

Biomarkers : simulations

Table S20: Should bevacizumab be added to first line standard chemotherapy in patients with malignant pleural mesothelioma?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|--|-------------------------------------|-------------------|-------------------|-----------|------------|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | FIRST LINE with bevacizumab added to standard CT | standard CT (alone or with placebo) | Relative (95% CI) | Absolute (95% CI) | | |

Median time to progression

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|-------------|-------------|----------------------|------|-----|-----|---|---|------------------|----------|
| 1 ¹ | randomised trials | not serious | not serious | not serious | serious ^a | none | 223 | 225 | - | MD 1.9 months more (0.71 more to 3.09 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|-------------|-------------|----------------------|------|-----|-----|---|---|------------------|----------|

Time to progression survival

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|-------|-------|------------------------|--|------------------|----------|
| 1 ¹ | randomised trials | not serious | not serious ^b | not serious | serious ^c | none | -/223 | -/225 | HR 0.61 (0.50 to 0.74) | | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|--------------------------|-------------|----------------------|------|-------|-------|------------------------|--|------------------|----------|

Median overall survival

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|-------------|-------------|----------------------|------|-----|-----|---|--|------------------|----------|
| 1 ¹ | randomised trials | not serious | not serious | not serious | serious ^c | none | 223 | 225 | - | MD 2.7 months more (1.18 fewer to 6.58 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|-------------|-------------|----------------------|------|-----|-----|---|--|------------------|----------|

Overall survival

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|-------------|-------------|----------------------|------|-------|-------|------------------------|--|------------------|----------|
| 1 ¹ | randomised trials | not serious | not serious | not serious | serious ^c | none | -/223 | -/225 | HR 0.77 (0.62 to 0.96) | | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|-------------|-------------|----------------------|------|-------|-------|------------------------|--|------------------|----------|

Number of patients discontinued due to adverse events

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|--------------------------|-------------|-------------|------|----------------|---------------|------------------------|---|--------------|-----------|
| 1 ¹ | randomised trials | not serious | not serious ^e | not serious | not serious | none | 53/222 (23.9%) | 13/224 (5.8%) | RR 4.11 (2.31 to 7.33) | 180 more per 1.000 (from 76 more to 367 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
|----------------|-------------------|-------------|--------------------------|-------------|-------------|------|----------------|---------------|------------------------|---|--------------|-----------|

Number of patients discontinued due to progression

Biomarkers : simulations

| Certainty assessment | | | | | | | N° of patients | | Effect | | Certainty | Importance |
|----------------------|-------------------|--------------|--------------------------|--------------|-------------|----------------------|--|-------------------------------------|----------------------------------|---|--------------|------------|
| N° of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | FIRST LINE with bevacizumab added to standard CT | standard CT (alone or with placebo) | Relative (95% CI) | Absolute (95% CI) | | |
| 1 ¹ | randomised trials | not serious | not serious ^d | not serious | not serious | none | 137/222 (61.7%) | 189/224 (84.4%) | RR 0.73 (0.65 to 0.82) | 228 fewer per 1.000 (from 295 fewer to 152 fewer) | ⊕⊕⊕⊕ HIGH | IMPORTANT |

Number of patients with grade 3-4 adverse events

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|-------------|-------------|----------------------|------|-----------------|-----------------|----------------------------------|--|------------------|----------|
| 1 ¹ | randomised trials | not serious | not serious | not serious | serious ^c | none | 158/222 (71.2%) | 139/224 (62.1%) | RR 1.15 (1.00 to 1.31) | 93 more per 1.000 (from 0 fewer to 192 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|-------------|-------------|----------------------|------|-----------------|-----------------|----------------------------------|--|------------------|----------|

Number of patients with neutropenia

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|-------------|-------------|-------------|------|-----------------|-----------------|----------------------------------|--|--------------|-----------|
| 1 ¹ | randomised trials | not serious | not serious | not serious | not serious | none | 173/222 (77.9%) | 177/224 (79.0%) | RR 0.99 (0.89 to 1.09) | 8 fewer per 1.000 (from 87 fewer to 71 more) | ⊕⊕⊕⊕ HIGH | IMPORTANT |
|----------------|-------------------|-------------|-------------|-------------|-------------|------|-----------------|-----------------|----------------------------------|--|--------------|-----------|

CI: Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

- a. Wide 95%CI does not exclude no effect or benefit
- b. Large heterogeneity mostly due to the small study. Both studies show a beneficial effect but larger study points to significant reduction in time to progression.
- c. Wide 95%CI does not exclude harm or benefit
- e. Single study

References

1. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, Molinier O, Corre R, Monnet I, Gounant V, Rivière F, Janicot H, Gervais R, Locher C, Milleron B, Tran Q, Lebitasy MP, Morin F, Creveuil C, Parienti JJ, Scherpereel A, (IFCT)., French Cooperative Thoracic Intergroup. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet; 2016.

Biomarkers : simulations

Table S21: Should targeted therapies (including axitinib, nintedanib, defactinib, thalidomide, CBP501) be added to first line standard chemotherapy in patients with malignant pleural mesothelioma?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|-------------------------------|---------|-------------------|-------------------|-----------|------------|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | FIRST LINE Targeted therapies | placebo | Relative (95% CI) | Absolute (95% CI) | | |

Median time to progression - First line

| | | | | | | | | | | | | |
|--------------------|-------------------|-------------|-------------|------------------------------|------------------------|------|----|----|---|---|------------------|----------|
| 2 ^{1,2,3} | randomised trials | not serious | not serious | not serious ^{a,b,c} | serious ^{d,e} | none | 54 | 34 | - | MD 1.55 months more (0.75 fewer to 3.86 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|--------------------|-------------------|-------------|-------------|------------------------------|------------------------|------|----|----|---|---|------------------|----------|

Median time to progression - Maintenance

| | | | | | | | | | | | | |
|------------------|-------------------|-------------|-------------|----------------------------|-------------|------|-----|-----|---|--|--------------|----------|
| 2 ^{4,5} | randomised trials | not serious | not serious | not serious ^{f,g} | not serious | none | 284 | 281 | - | MD 0.1 months more (0.93 fewer to 1.13 more) | ⊕⊕⊕⊕ HIGH | CRITICAL |
|------------------|-------------------|-------------|-------------|----------------------------|-------------|------|-----|-----|---|--|--------------|----------|

Time to progression survival - First line

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|-------------|--------------------------|------------------------|------|------|------|--|------------------------|------------------|----------|
| 1 ² | randomised trials | not serious | not serious | not serious ^b | serious ^{d,e} | none | -/44 | -/43 | | HR 0.56 (0.34 to 0.92) | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|-------------|--------------------------|------------------------|------|------|------|--|------------------------|------------------|----------|

Time to progression survival - Maintenance

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|-------------|--------------------------|----------------------|------|-------|-------|--|------------------------|------------------|----------|
| 1 ⁴ | randomised trials | not serious | not serious | not serious ^f | Serious ⁱ | none | -/111 | -/110 | | HR 0.95 (0.73 to 1.24) | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|-------------|--------------------------|----------------------|------|-------|-------|--|------------------------|------------------|----------|

Median overall survival - First line

| | | | | | | | | | | | | |
|------------------|-------------------|-------------|----------------------|----------------------------|------------------------|------|----|----|---|---|-------------|----------|
| 2 ^{1,3} | randomised trials | not serious | serious ^h | not serious ^{a,c} | serious ^{e,i} | none | 54 | 34 | - | MD 0.49 months more (4.99 fewer to 5.98 more) | ⊕⊕○○ LOW | CRITICAL |
|------------------|-------------------|-------------|----------------------|----------------------------|------------------------|------|----|----|---|---|-------------|----------|

Median overall survival - Maintenance

| | | | | | | | | | | | | |
|------------------|-------------------|-------------|----------------------|----------------------------|----------------------|------|-----|-----|---|--|-------------|----------|
| 2 ^{4,5} | randomised trials | not serious | serious ^h | not serious ^{f,g} | serious ^j | none | 284 | 281 | - | MD 1.79 months fewer (5.02 fewer to 1.45 more) | ⊕⊕○○ LOW | CRITICAL |
|------------------|-------------------|-------------|----------------------|----------------------------|----------------------|------|-----|-----|---|--|-------------|----------|

Biomarkers : simulations

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|----------------------|--------------|--------------|---------------|--------------|-------------|----------------------|-------------------------------|---------|-------------------|-------------------|-----------|------------|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | FIRST LINE Targeted therapies | placebo | Relative (95% CI) | Absolute (95% CI) | | |

Overall survival - First line

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|----------------------|--------------------------|------------------------|------|------|------|----------------------------------|--|-------------|----------|
| 1 ² | randomised trials | not serious | serious ^h | not serious ^b | serious ^{e,i} | none | -/54 | -/34 | HR 0.77 (0.46 to 1.29) | | ⊕⊕○○ LOW | CRITICAL |
|----------------|-------------------|-------------|----------------------|--------------------------|------------------------|------|------|------|----------------------------------|--|-------------|----------|

Overall survival - Maintenance

| | | | | | | | | | | | | |
|------------------|-------------------|-------------|----------------------|----------------------------|----------------------|------|-------|-------|----------------------------------|--|-------------|----------|
| 2 ^{4,5} | randomised trials | not serious | serious ^h | not serious ^{f,g} | serious ⁱ | none | -/284 | -/281 | HR 1.12 (0.89 to 1.40) | | ⊕⊕○○ LOW | CRITICAL |
|------------------|-------------------|-------------|----------------------|----------------------------|----------------------|------|-------|-------|----------------------------------|--|-------------|----------|

Number of patients with partial response

| | | | | | | | | | | | | |
|--------------------|-------------------|-------------|-------------|------------------------------|------------------------|------|---------------|---------------|----------------------------------|--|------------------|-----------|
| 3 ^{1,2,3} | randomised trials | not serious | not serious | not serious ^{a,b,c} | serious ^{e,i} | none | 42/97 (43.3%) | 23/74 (31.1%) | RR 1.42 (0.96 to 2.10) | 131 more per 1.000 (from 12 fewer to 342 more) | ⊕⊕⊕○ MODERATE | IMPORTANT |
|--------------------|-------------------|-------------|-------------|------------------------------|------------------------|------|---------------|---------------|----------------------------------|--|------------------|-----------|

Number of patients with stable disease

| | | | | | | | | | | | | |
|------------------|-------------------|-------------|-------------|----------------------------|------------------------|------|---------------|---------------|----------------------------------|---|------------------|-----------|
| 2 ^{1,3} | randomised trials | not serious | not serious | not serious ^{a,c} | serious ^{e,i} | none | 21/53 (39.6%) | 18/31 (58.1%) | RR 0.69 (0.44 to 1.08) | 180 fewer per 1.000 (from 325 fewer to 46 more) | ⊕⊕⊕○ MODERATE | IMPORTANT |
|------------------|-------------------|-------------|-------------|----------------------------|------------------------|------|---------------|---------------|----------------------------------|---|------------------|-----------|

Number of patients with grade 3-4 adverse events - First line

| | | | | | | | | | | | | |
|------------------|-------------------|-------------|----------------------|----------------------------|------------------------|------|---------------|---------------|----------------------------------|---|-------------|----------|
| 2 ^{2,3} | randomised trials | not serious | serious ^k | not serious ^{b,c} | serious ^{e,i} | none | 56/84 (66.7%) | 35/66 (53.0%) | RR 1.23 (0.75 to 2.04) | 122 more per 1.000 (from 133 fewer to 552 more) | ⊕⊕○○ LOW | CRITICAL |
|------------------|-------------------|-------------|----------------------|----------------------------|------------------------|------|---------------|---------------|----------------------------------|---|-------------|----------|

Number of patients with grade 3-4 adverse events - Maintenance

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|-------------|--------------------------|----------------------|------|----------------|----------------|----------------------------------|--|------------------|----------|
| 1 ⁴ | randomised trials | not serious | not serious | not serious ^f | serious ⁱ | none | 43/111 (38.7%) | 31/110 (28.2%) | RR 1.37 (0.94 to 2.01) | 104 more per 1.000 (from 17 fewer to 285 more) | ⊕⊕⊕○ MODERATE | CRITICAL |
|----------------|-------------------|-------------|-------------|--------------------------|----------------------|------|----------------|----------------|----------------------------------|--|------------------|----------|

Number of patients with any adverse event

Biomarkers : simulations

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|----------------------|-------------------|--------------|---------------|--------------------------|----------------------|----------------------|-------------------------------|----------------|----------------------------------|---|------------------|------------|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | FIRST LINE Targeted therapies | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| 1 ⁴ | randomised trials | not serious | not serious | not serious ^f | serious ⁱ | none | 106/111 (95.5%) | 89/110 (80.9%) | RR 1.18 (1.07 to 1.30) | 146 more per 1.000 (from 57 more to 243 more) | ⊕⊕⊕○ MODERATE | CRITICAL |

Number of patients with neutropenia - First line

| | | | | | | | | | | | | |
|------------------|-------------------|-------------|-------------|----------------------------|------------------------|------|---------------|---------------|----------------------------------|--|------------------|-----------|
| 2 ^{1,2} | randomised trials | not serious | not serious | not serious ^{a,b} | serious ^{e,i} | none | 38/64 (59.4%) | 13/52 (25.0%) | RR 2.38 (1.44 to 3.93) | 345 more per 1.000 (from 110 more to 733 more) | ⊕⊕⊕○ MODERATE | IMPORTANT |
|------------------|-------------------|-------------|-------------|----------------------------|------------------------|------|---------------|---------------|----------------------------------|--|------------------|-----------|

Number of patients with neutropenia - Maintenance

| | | | | | | | | | | | | |
|----------------|-------------------|-------------|-------------|--------------------------|------------------------|------|----------------|---------------|----------------------------------|---|------------------|-----------|
| 1 ⁴ | randomised trials | not serious | not serious | not serious ^f | serious ^{e,i} | none | 14/111 (12.6%) | 10/110 (9.1%) | RR 1.39 (0.64 to 2.99) | 35 more per 1.000 (from 33 fewer to 181 more) | ⊕⊕⊕○ MODERATE | IMPORTANT |
|----------------|-------------------|-------------|-------------|--------------------------|------------------------|------|----------------|---------------|----------------------------------|---|------------------|-----------|

CI: Confidence interval; MD: Mean difference; HR: Hazard Ratio; RR: Risk ratio

Explanations

- a. Axitinib
- b. Nintedanib
- c. CBP501
- d. 95%CI includes either a substantial benefit or no effect.
- e. Limited number of patients included
- f. Thalidomide
- g. Defactinib
- h. Median overall survival values have not a normal distribution and are not consistent with time-to-event data
- i. 95%CI includes a substantial benefit or harm.
- j. 95%CI includes a substantial harm or no effect
- k. Large variability among individual studies effect estimates

References

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Biomarkers : simulations

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5. Fennell DA, Baas P, Taylor P et al.. Maintenance Defactinib Versus Placebo After First-Line Chemotherapy in Patients With Merlin-Stratified Pleural Mesothelioma: COMMAND-A Double-Blind, Randomized, Phase II Study. *Journal of Clinical Oncology*; 2019.

Table S22: Should immunotherapies (including immune checkpoint inhibitor tremelimumab and vorinostat) be used as salvage therapy in patients with malignant pleural mesothelioma who failed to first-line standard chemotherapy?

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|--|-------------------|--------------|--------------------------|--------------|----------------------|----------------------|---|--------------------|----------------------------|--|------------------|------------|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | SALVAGE therapies | placebo | Relative (95% CI) | Absolute (95% CI) | | |
| Overall survival | | | | | | | | | | | | |
| 2 ^{1,2} | randomised trials | not serious | not serious | not serious | serious ^a | none | 711 | 521 | HR 0.95 (0.84 to 1.08) | | ⊕⊕⊕○ MODERATE | CRITICAL |
| Overall mortality (at data cutoff) | | | | | | | | | | | | |
| 1 ¹ | randomised trials | not serious | not serious ^b | not serious | serious ^a | none | 307/382 (80.4%) | 154/189 (81.5%) | RR 0.99 (0.91 to 1.07) | 8 fewer per 1.000 (from 57 more to 73 fewer) | ⊕⊕⊕○ MODERATE | CRITICAL |
| Median overall survival | | | | | | | | | | | | |
| 2 ^{1,2} | randomised trials | not serious | not serious | not serious | serious ^c | none | Tremelimumab: 7.7 months (95%CI 6.8-8.9); Placebo: 7.3 months (95%CI 5.9-8.7) (571 patients). Vorinostat 30.7 weeks (95%CI 26.7-36.1); placebo: 27.1 weeks (95%CI 23.1-31.9) (661 patients) | | | ⊕⊕⊕○ MODERATE | CRITICAL | |
| Number of patients with partial response | | | | | | | | | | | | |
| 1 ¹ | randomised trials | not serious | not serious ^b | not serious | serious ^d | none | 17/382 (4.5%) | 2/189 (1.1%) | RR 4.21 (0.98 to 18.01) | 34 more per 1.000 (from 0 fewer to 180 more) | ⊕⊕⊕○ MODERATE | IMPORTANT |
| Number of patients with stable disease | | | | | | | | | | | | |
| 1 ¹ | randomised trials | not serious | not serious ^b | not serious | serious ^a | | 104/382 (27.2%) | 41/189 (21.7%) | RR 1.26 (0.91 to 1.72) | 56 more per 1.000 (from 20 fewer to 156 more) | - | IMPORTANT |

Biomarkers : simulations

1. Maio M, Scherpereel A, Calabrò L, Aerts J, Perez SC, Bearz A, Nackaerts K, Fennell DA, Kowalski D, Tsao AS, Taylor P, Grosso F, Antonia SJ, Nowak AK, Taboada M, Puglisi M, Stockman PK, Kindler HL.. Tremelimumab as second-line or third-line treatment in relapsed malignant mesothelioma (DETERMINE): a multicentre, international, randomised, double-blind, placebo-controlled phase 2b trial.. *Lancet Oncol*; 2017.
2. Krug LM, Kindler HL, Calvert H, Manegold C, Tsao AS, Fennell D, Öhman R, Plummer R, Eberhardt WE, Fukuoka K, Gaafar RM, Lafitte JJ, Hillerdal G, Chu Q, Buikhuisen WA, Lubiniecki GM, Sun X, Smith M, Baas P.. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial.. *Lancet Oncol*; 2015.

Detailed PICO questions

| | Should partial pleurectomy compared to talc pleurodesis be used as palliative surgery in patients with symptomatic malignant pleural mesothelioma? |
|------------------------|--|
| Patients | Patients with symptomatic (short of breath) malignant pleural mesothelioma patients |
| Intervention | Partial pleurectomy |
| Comparison | Talc pleurodesis |
| Outcomes | Overall survival Postoperative morbidity Time to progression Time to treatment failure (effusion control) Health-related quality of life (QOL) Hospital length of stay Operative mortality 30 day mortality 90 day mortality "Seeding" – tract metastases |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials |

| | Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used as in patients with symptomatic malignant pleural mesothelioma? |
|------------------------|--|
| Patients | Patients with symptomatic (short of breath) malignant pleural mesothelioma patients |
| Intervention | Radical surgery including extrapleural pneumonectomy or pneumonectomy/decortication |
| Comparison | Treatment approach NOT including radical surgery |
| Outcomes | Overall survival Postoperative morbidity Time to progression Time to treatment failure (effusion control) Health-related quality of life (QOL) Hospital length of stay Operative mortality 30 day mortality 90 day mortality "Seeding" – tract metastases |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials |

| | Should radiotherapy be used for pain relief in patients with malignant pleural mesothelioma? |
|------------------------|--|
| Patients | Patients with malignant pleural mesothelioma with persistent pain (regardless of adequate management of pain with analgesia) |
| Intervention | Radiotherapy of the painful area |
| Comparison | NO radiotherapy |
| Outcomes | Response rate (measured as pain reduction) Health-related quality of life (QOL) Adverse events |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials |

| | Should radiotherapy be used to prevent procedure-tract methastases (drain site parietal seeding) in patients with malignant pleural mesothelioma? |
|------------------------|---|
| Patients | Patients with malignant pleural mesothelioma after pleural intervention (thoracic surgery, large bore chest drain, indwelling pleural catheter or local anaesthetic thoracoscopy) |
| Intervention | Radiotherapy |
| Comparison | NO adjuvant radiotherapy |
| Outcomes | Overall survival Progression-free survival Number of patients with tract metastasis Health-related quality of life (QOL) Adverse events |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials |

| | Should adjuvant post-operative radiotherapy be used in patients with malignant pleural mesothelioma? |
|------------------------|---|
| Patients | Patients with resected malignant pleural mesothelioma, after pleurectomy, or EPP or any type of surgery except diagnostic thoracoscopy |
| Intervention | Postoperative Radiotherapy |
| Comparison | NO adjuvant radiotherapy |
| Outcomes | Overall survival Progression-free survival Time to progression Time to treatment failure Health-related quality of life (QOL) Adverse events |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials Non randomized prospective trials |

| | Should first line chemotherapy consisting of platinum alone or in combination with pemetrexed be used in patients with malignant pleural mesothelioma? |
|------------------------|--|
| Patients | Patients with malignant pleural mesothelioma |
| Intervention | First line chemotherapy consisting of platinum alone (cisplatin or carboplatin) |
| Comparison | Carboplatin and pemetrexed |
| Outcomes | Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials |

| | Should bevacizumab be added to first line standard chemotherapy in patients with malignant pleural mesothelioma? |
|------------------------|--|
| Patients | Patients with malignant pleural mesothelioma: - Not previously treated with chemotherapy. - Fit for chemotherapy |
| Intervention | Bevacizumab be added to first line standard chemotherapy |
| Comparison | standard chemotherapy |
| Outcomes | Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials |

| | Should targeted therapies (including axitinib, nintedanib, defactinib, thalidomeide,CBP501) be added to first line standard chemotherapy in patients with malignant pleural mesothelioma? |
|------------------------|--|
| Patients | Patients with malignant pleural mesothelioma: - Not previously treated with chemotherapy. - Fit for chemotherapy |
| Intervention | Targeted therapies added to first line standard chemotherapy: Axitinib, nintedanib, defactinib, thalidomeide,CBP501 |
| Comparison | standard chemotherapy |
| Outcomes | Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials |

| | Should immunotherapies (including immune checkpoint inhibitor tremelimumab and vorinostat) be used as salvage therapy in patients with malignant pleural mesothelioma who failed to first-line standard chemotherapy? |
|------------------------|--|
| Patients | Patients with malignant pleural mesothelioma who previously failed to first line chemotherapy . |
| Intervention | Immunotherapies: - Including immune checkpoint inhibitor tremelimumab and vorinostat |
| Comparison | Placebo |
| Outcomes | Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials |

| | |
|------------------------|--|
| | Should multimodal therapy approach (combining more than one method of cancer treatment: surgery, chemotherapy, radiation therapy) compared to chemotherapy alone be used in patients with malignant pleural mesothelioma? |
| Patients | Patients with resectable malignant pleural mesothelioma who are eligible for neoadjuvant therapy and or adjuvant treatment (good performance status, low tumor burden and early stage disease) |
| Intervention | Multimodal therapy approach: - Combining more than one method of cancer treatment: surgery, chemotherapy, radiation therapy) |
| Comparison | No treatment combination (surgery, chemotherapy or radiation therapy alone) |
| Outcomes | Overall survival Progression-free survival Response rate Time to progression/ treatment failure Health-related quality of life (QOL) Adverse events |
| Type of studies | Systematic reviews of randomized controlled trials Randomized controlled trials |

| Implications of strong and weak recommendations for different users of guidelines | | |
|--|--|---|
| | Strong Recommendation | Weak Recommendation |
| For patients | Most individuals in this situation would want the recommended course of action and only a small proportion would not. | The majority of individuals in this situation would want the suggested course of action, but many would not. |
| For clinicians | Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. | Recognize that different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision. |
| For policy makers | The recommendation can be adapted as policy in most situations including for the use as performance indicators. | Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place. |

| QUESTIONS (*PICO) | RECOMMENDATIONS |
|---|--|
| EPIDEMIOLOGY | |
| MPM screening | Research priority: The relationship between PP and MPM should be ascertained in large international epidemiological studies. The effectiveness of CT scan screening in the population exposed to asbestos should be determined in well-designed clinical trials. |
| Biomarkers for MPM | Research priority: Routine determination of previously proposed biomarkers in MPM have currently no validated role for diagnosis, prognosis or clinical follow up (disease monitoring) . Thus further research into the role of biomarkers in these goals is required and highly encouraged. |
| STAGING | |
| Clinical staging | Research priority: Prospective data collection about the measurement of tumour thickness or volume is to be encouraged. |
| Pre-treatment staging investigations | Research priority: The prospective use of volumetric assessment software should be encouraged. |
| Which other prognostic factors are of importance? | Research priority: The use of the Brims score is encouraged in routine, and other scores as part of clinical trials |
| SURGERY* | |
| Should partial pleurectomy compared to talc pleurodesis be used as a palliative procedure in patients with symptomatic MPM? | <p>We recommend talc poudrage via thoracoscopy to control a recurrent MPM effusion as the first choice to achieve pleurodesis in patients with expanded lungs (strong recommendation, low quality of evidence).</p> <p>We suggest palliative VATS partial pleurectomy for selected patients fit enough to undergo surgery to obtain pleural effusion control in symptomatic patients who cannot benefit from (or after failure of) chemical pleurodesis or indwelling catheter (weak recommendation, low quality of evidence).</p> |
| Should radical surgery (including extrapleural pneumonectomy or pneumonectomy/decortication) be used in patients with MPM? | <p>Research priority: patients considered for radical surgery should be either included in prospective, randomized, controlled clinical trials or in national/international surgical registries.</p> <p><i>Remark:</i> Surgery may be appropriate for carefully and highly</p> |

| | |
|--|---|
| | <i>selected MPM patients. This would usually be eP/D rather than EPP because of its lower comparative respiratory postoperative morbidity and preservation of quality of life, performed in centres of excellence and as part of multimodality treatment. Patients with sarcomatoid or sarcomatoid predominant histology, N2 disease (8th edition TNM staging system) and/or stage IV should not be considered for radical surgery unless in the context of research. However, as no single prognostic factor influences treatment allocation then prognostic scores encompassing several prognostic factors should be preferred (see Staging/allocation chapter).</i> |
| RADIOTHERAPY* | |
| Should radiotherapy be used for pain relief in patients with MPM? | <i>We suggest that palliative radiotherapy for pain relief should be considered in cases of painful sites of disease caused by local infiltration of normal structures (weak recommendation, low quality evidence).</i> |
| Should radiotherapy be used to prevent procedure-tract methastases (drain site parietal seeding) in patients with MPM? | <i>We do not recommend prophylactic drain site radiotherapy in routine clinical care (strong recommendation, moderate quality evidence).</i> |
| Should adjuvant post-operative radiotherapy be used in patients with MPM? | Research priority: <i>Radiotherapy after pleurectomy ± decortication or after EPP should be only considered within the context of clinical trials and/or included in national/international surgical registries.</i> |
| MEDICAL TREATMENT* | |
| Should first line chemotherapy consisting of platinum in combination with pemetrexed be used in patients with MPM? | <p><i>we recommend first line combination chemotherapy consisting of platinum and pemetrexed (with folic acid and vitamin B12 supplementation) in patients fit for chemotherapy (good performance status, PS ECOG 0-2, no contra-indications) (strong recommendation, low quality evidence)</i></p> <p>Research priority: <i>Patients demonstrating prolonged symptomatic and objective response with first line pemetrexed-based chemotherapy may be treated again with the same regimen in the event of recurrence. In the other cases, inclusion of the patients in clinical trials is highly encouraged.</i></p> |
| Should targeted therapies be added to first line standard chemotherapy in patients with MPM? | <i>We suggest bevacizumab may be proposed in combination with cisplatin/pemetrexed as first line treatment in patients fit for bevacizumab and cisplatin but not for macroscopic complete resection (weak recommendation, moderate quality of evidence).</i> |
| Should bevacizumab be added to first line standard chemotherapy in patients with MPM? | |

| | |
|--|--|
| | |
| Should immunotherapy be used as salvage therapy in patients with MPM who failed first-line standard chemotherapy? | Research priority: <i>Novel insights in immunotherapy are promising but need further development and results from ongoing or planned phase III trials before to draw any clear recommendation for their use in routine. Inclusion of patients in these trials is highly recommended.</i> |
| MULTIMODAL TREATMENT* | |
| Should a multimodal therapy approach (combining more than one method of cancer treatment: surgery, chemotherapy, radiation therapy) compared to chemotherapy alone be used in patients with MPM? | Research priority: <i>We still recommend that patients who are considered candidates for a multimodal approach should be adequately informed of its challenges and referred to expert centers in order to be included in a prospective (randomized) clinical trial or registered in a large institutional database.</i> |
| TREATMENT ALLOCATION of MPM | |
| | Research priority: <i>Current and future scores suggested for patients treatment allocation, always decided by MPM expert multidisciplinary board, would require prospective validation by multicenter studies.</i> |
| FOLLOW-UP of MPM PATIENTS | |
| What should be the follow-up of a patient after active treatment of MPM? | <p>Research priority: <i>The role of a periodic follow-up with imaging (chest-abdominal CT scan, MRI or PET) should be assessed in clinical trials.</i></p> <p>Remarks: <i>Monitoring of disease progression should be guided by signs and symptoms occurring during clinical follow up. However, in addition to clinical follow-up, and waiting for further evidence from clinical trials, the TF group suggest a chest-abdominal CT scan every 3 to 6 months after active treatment of MPM patients.</i></p> |