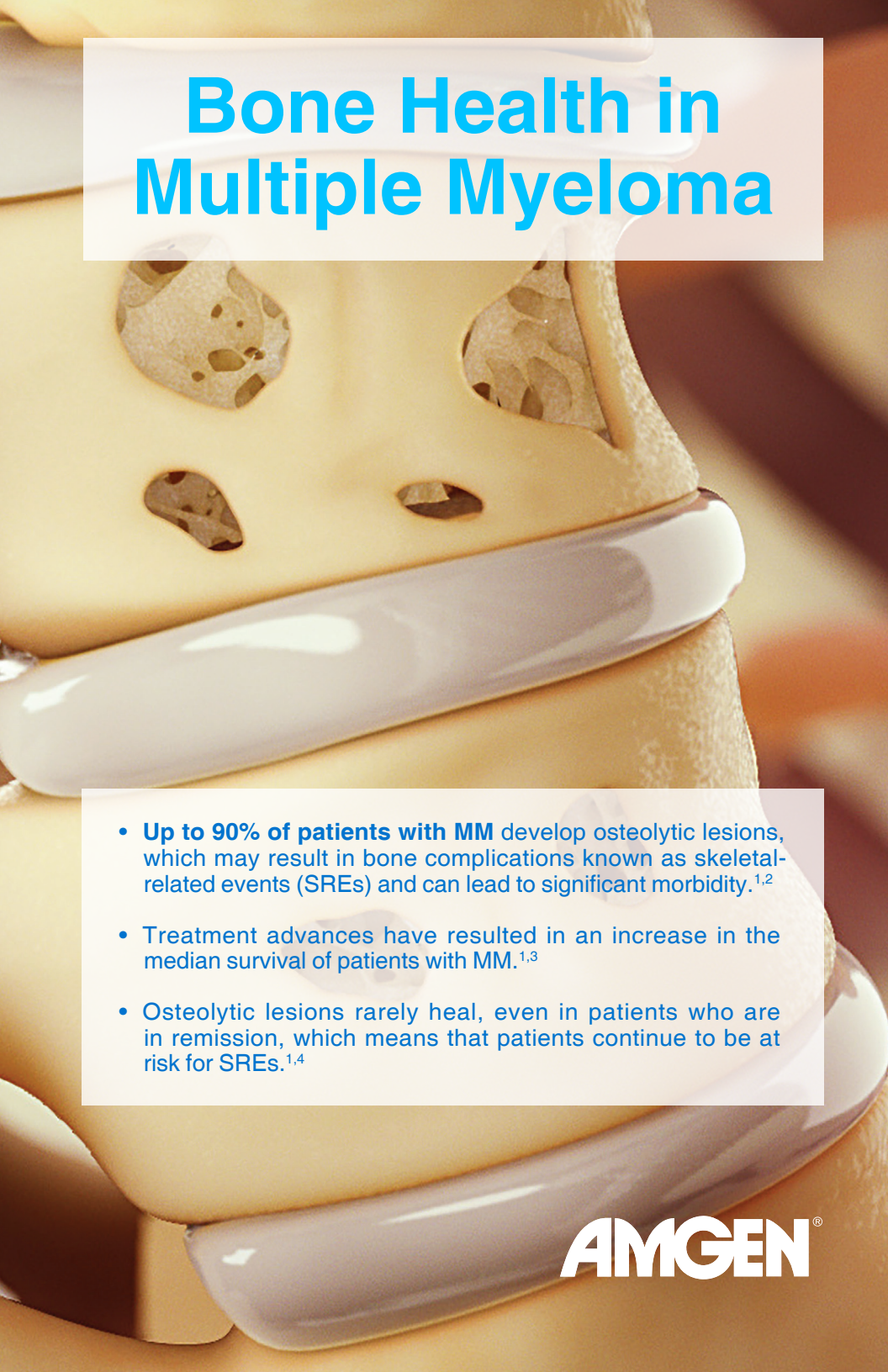
Bone Health in Multiple Myeloma



- **Up to 90% of patients with MM** develop osteolytic lesions, which may result in bone complications known as skeletal-related events (SREs) and can lead to significant morbidity.[1,2]
- Treatment advances have resulted in an increase in the median survival of patients with MM.[1,3]
- Osteolytic lesions rarely heal, even in patients who are in remission, which means that patients continue to be at risk for SREs.[1,4]

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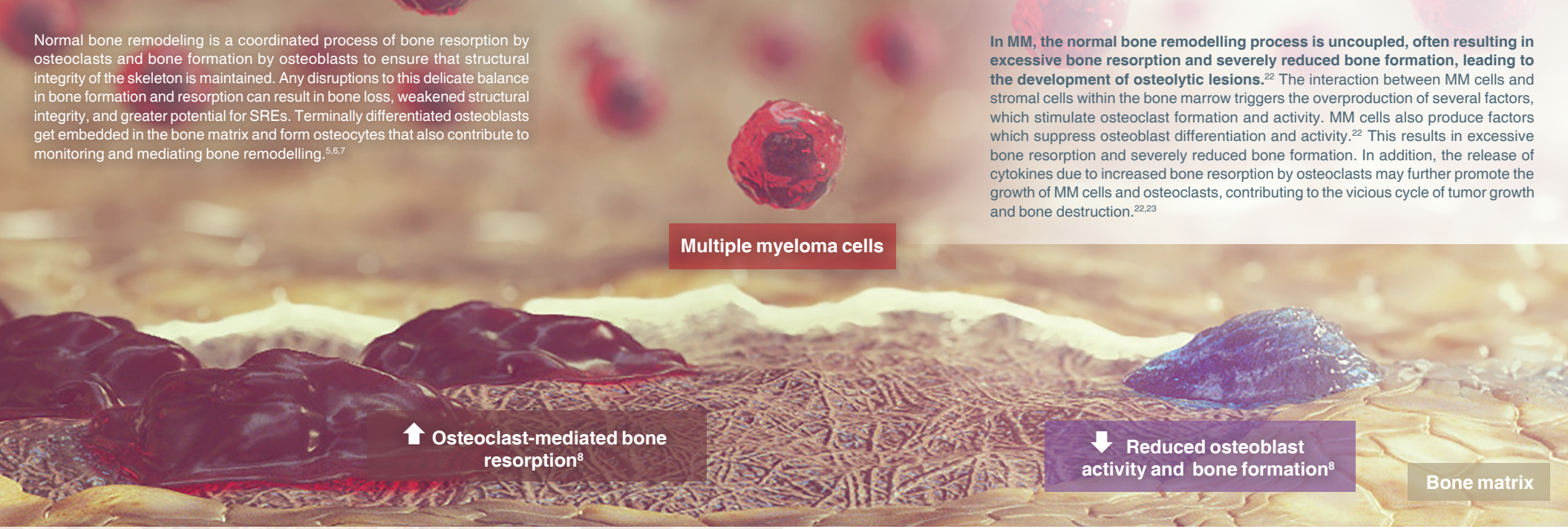
Normal bone remodeling is a coordinated process of bone resorption by osteoclasts and bone formation by osteoblasts to ensure that structural integrity of the skeleton is maintained. Any disruptions to this delicate balance in bone formation and resorption can result in bone loss, weakened structural integrity, and greater potential for SREs. Terminally differentiated osteoblasts get embedded in the bone matrix and form osteocytes that also contribute to monitoring and mediating bone remodelling.[5,6,7]

In MM, the normal bone remodelling process is uncoupled, often resulting in excessive bone resorption and severely reduced bone formation, leading to the development of osteolytic lesions.[22] The interaction between MM cells and stromal cells within the bone marrow triggers the overproduction of several factors, which stimulate osteoclast formation and activity. MM cells also produce factors which suppress osteoblast differentiation and activity.[22] This results in excessive bone resorption and severely reduced bone formation. In addition, the release of cytokines due to increased bone resorption by osteoclasts may further promote the growth of MM cells and osteoclasts, contributing to the vicious cycle of tumor growth and bone destruction.[22,23]



Multiple myeloma and bone disease

- Multiple myeloma (MM) is a plasma cell malignancy and the presence of bone lesions is one of the key criteria for a diagnosis of MM.[9,10,11]
  - At diagnosis, ~80% of patients show abnormalities in their bone radiographs[9]
  - ~90% develop osteolytic lesions during the course of their disease[1,12]
  - These osteolytic lesions mainly occur in the vertebrae, ribs, shoulders, skull, pelvis, and long bones[13]
- Ostelytic lesions can lead to bone complications, known as skeletal-related events (SREs).[6]
  - SREs are defined as pathological fracture, spinal cord compression, surgery to the bone and radiation to the bone,[14] and contribute to the potentially severe morbidity observed in patients with MM.[4]

SREs MAY RESULT IN:

1. **Significantly limited mobility**[8,15,16]
2. **Bone pain, including severe pain due to pathological fractures**[17]
3. **A decrease in health-related quality of life**[2,18]
4. **Increased treatment costs**[19,20]

Impact of SREs to patients and healthcare systems

- Approximately **40%** of patients have SREs at MM diagnosis.[11]
  - Patients who have already experienced an SRE have an increased risk of developing subsequent SREs.[21]
- The incidence of pathological fracture is higher in patients with MM compared to those with other types of cancer.[21]
  - Approximately 60% of all patients with MM experience a fracture during the course of the disease.[1]

Osteolytic lesions rarely heal even in patients who are in remission, which means patients continue to be at risk of SREs.[1,4]

Table 1. Factors responsible for uncoupled bone remodelling in MM affect both Osteoblast and/or Osteoclast activity

	Factor	Effects on Osteoclasts and Osteoblasts	Expression in MM	Cellular Source
Osteoclasts	MIP-1α[12,23]	Induces osteoclast formation	Increased	MM cells
Osteoclasts	IL-6[12,23,24]	Induces osteoclast formation and RANKL expression	Increased	BM stromal cells; endothelial cells; osteoclasts
Osteoclasts	RANKL[12,23,25]	Stimulates osteoclast formation and attachment to bone, activation, and survival	Increased	BM stromal cells, osteoblasts, osteocytes; MM cells
Osteoclasts	OPG[12,23,25]	Inhibits osteoclast formation and attachment to bone, activation, and survival	Decreased	BM stromal cells, osteoblasts
Osteoclasts / Osteoblasts	IL-3[12,23,26,27,28]	Supports osteoclast progenitor formation Inhibits osteoblast differentiation	Increased	MM cells; T cells
Osteoblasts	Sclerostin[5,29,30]	Wnt inhibitor; inhibits osteoblast development and stimulates mature osteoblast apoptosis	Increased	Osteocytes
Osteoblasts	DKK1[12,31]	Wnt inhibitor; inhibits osteoblast differentiation	Increased	MM cells; osteocytes
Osteoblasts	sFRP2[12]	Wnt inhibitor; inhibits osteoblast differentiation	Increased	MM cells

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