Emerging Anti-Angiogenesis Therapies in Pleural Mesothelioma

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Educational Objectives

Following this activity, the participants will be able to:

1. Summarize clinical trials with angiokinase inhibitors
2. Review the value of novel angiokinase inhibitors for the treatment of patients with MPM
3. Outline the advantages of combining an angiokinase inhibitor with chemotherapy or immunotherapy for treatment of patients with MPM
4. Reflect on the future of MPM treatment

MPM, malignant pleural mesothelioma.

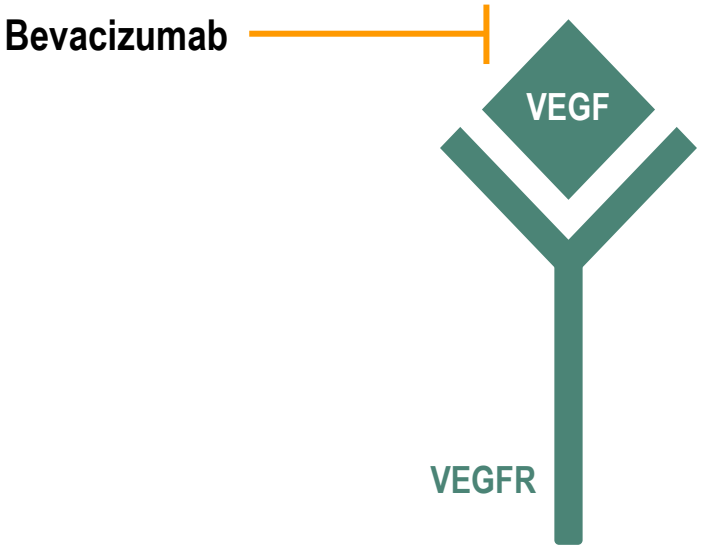
Background

- The VEGF pathway is a target for treatment of MPM[1]
- The study of anti-angiogenesis as a treatment strategy was pioneered by Dr Judah Folkman in the 1970s[2]
- Angiostatin and endostatin are angiogenesis-inhibiting agents that occur naturally in patients with primary malignancies[3]
- New, more effective, angiokinase inhibitors are now emerging[4]
- Combination therapies in which anti-angiogenic agents are combined with other treatment strategies are being explored[1]

1. Manusco MR, Neal JW. Transl Lung Cancer Res. 2017;6:295-314.
2. Folkman J. Ann Surg. 1972;175:409-16.
3. O'Reilly MS, et al. Cell. 1997;88:277-85.
4. Zhao Y, Adjei AA. Oncologist. 2015;20:660-73.

VEGF, vascular endothelial growth factor.

MAPS: Randomized, Controlled, Open-Label Phase 3 Trial

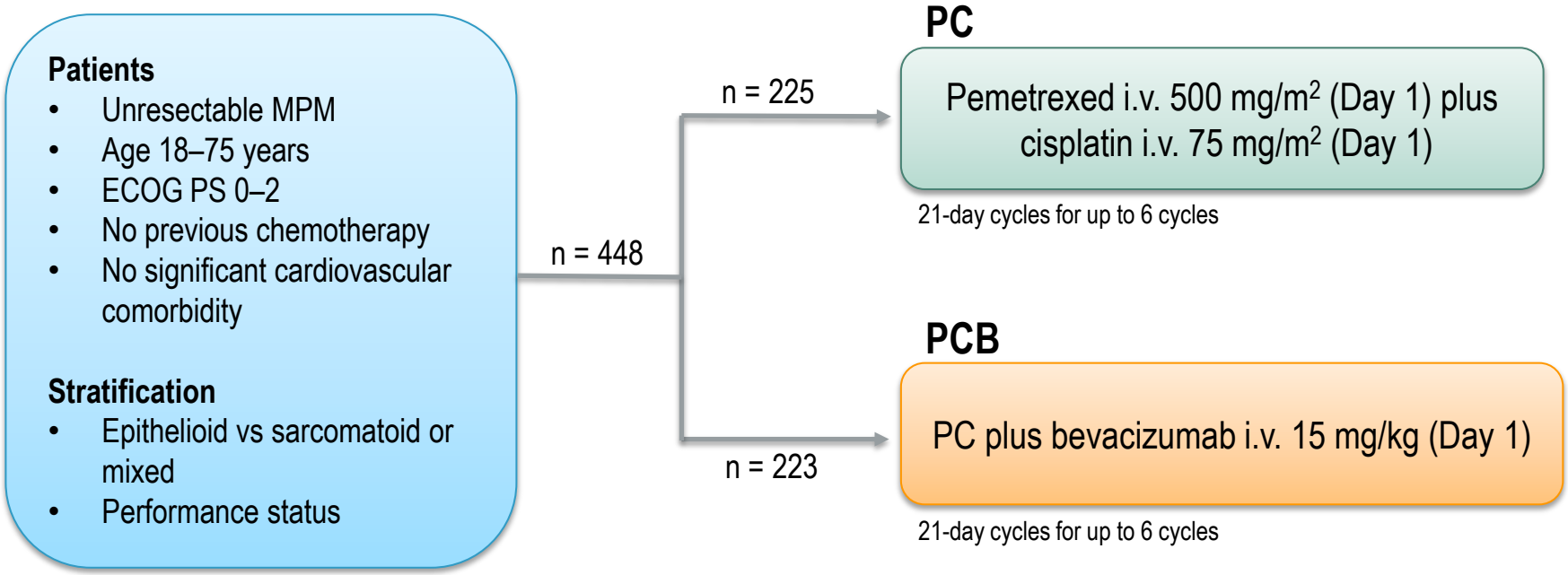


- Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS)

VEGFR, VEGF receptor.

Zalcman G, et al. Lancet. 2016;387:1405-14.

MAPS Phase 3 Trial



ECOG PS, Eastern Cooperative Oncology Group performance status; i.v., intravenous; PC, pemetrexed plus cisplatin; PCB, PC plus bevacizumab.

Zalcman G, et al. Lancet. 2016;387:1405-14.

MAPS Phase 3 Trial

	PC	PCB
Primary Outcome Median OS	16.1 months	18.8 months
	Adjusted HR 0.77; p = 0.0167	

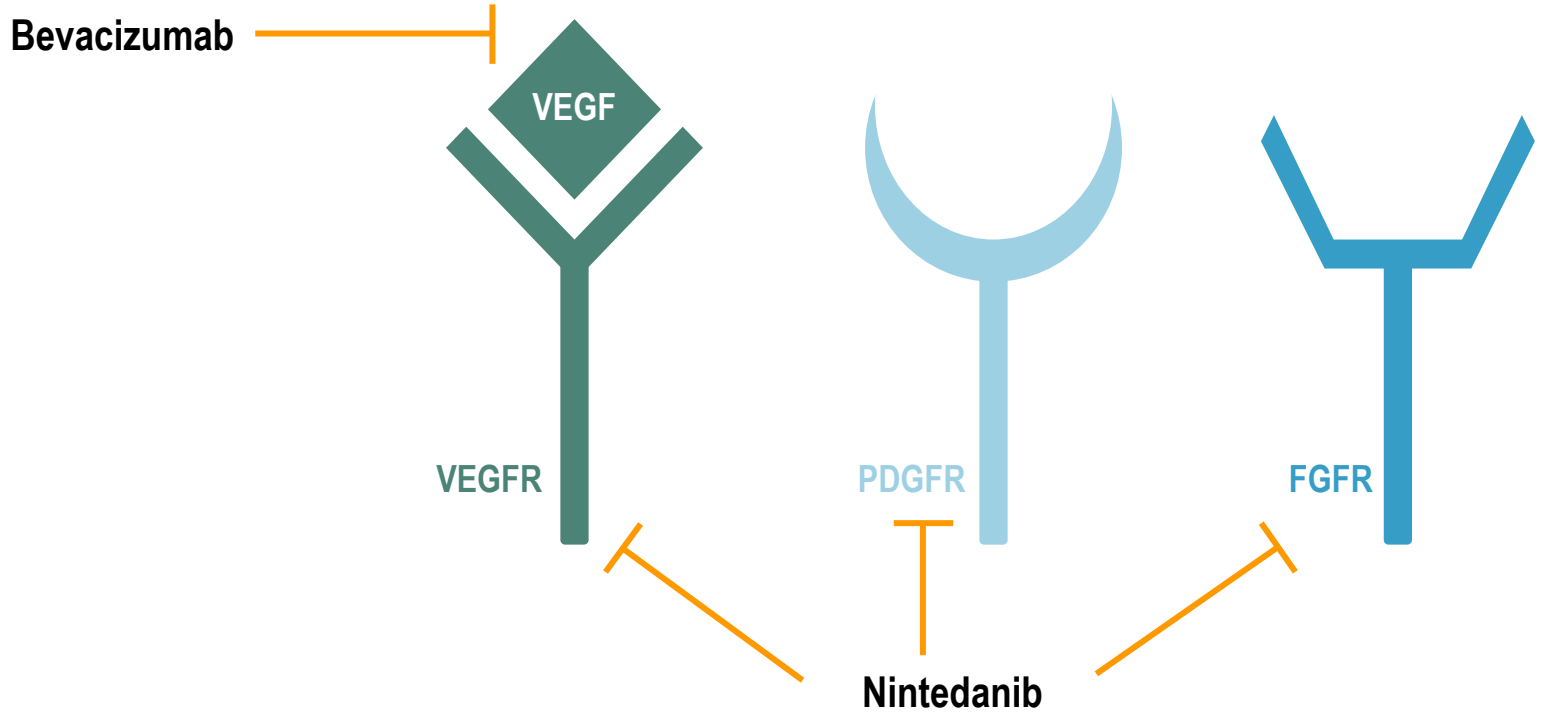
	PC	PCB
Secondary Outcome Median PFS	7.3 months	9.2 months
	Adjusted HR 0.61; p < 0.0001	

- AE frequencies generally similar; increase in cardiovascular AEs as expected
- Benefits seen in all patient groups

AE, adverse event; HR, hazard ratio;
OS, overall survival; PFS, progression-free survival.

Zalcman G, et al. Lancet. 2016;387:1405-14.

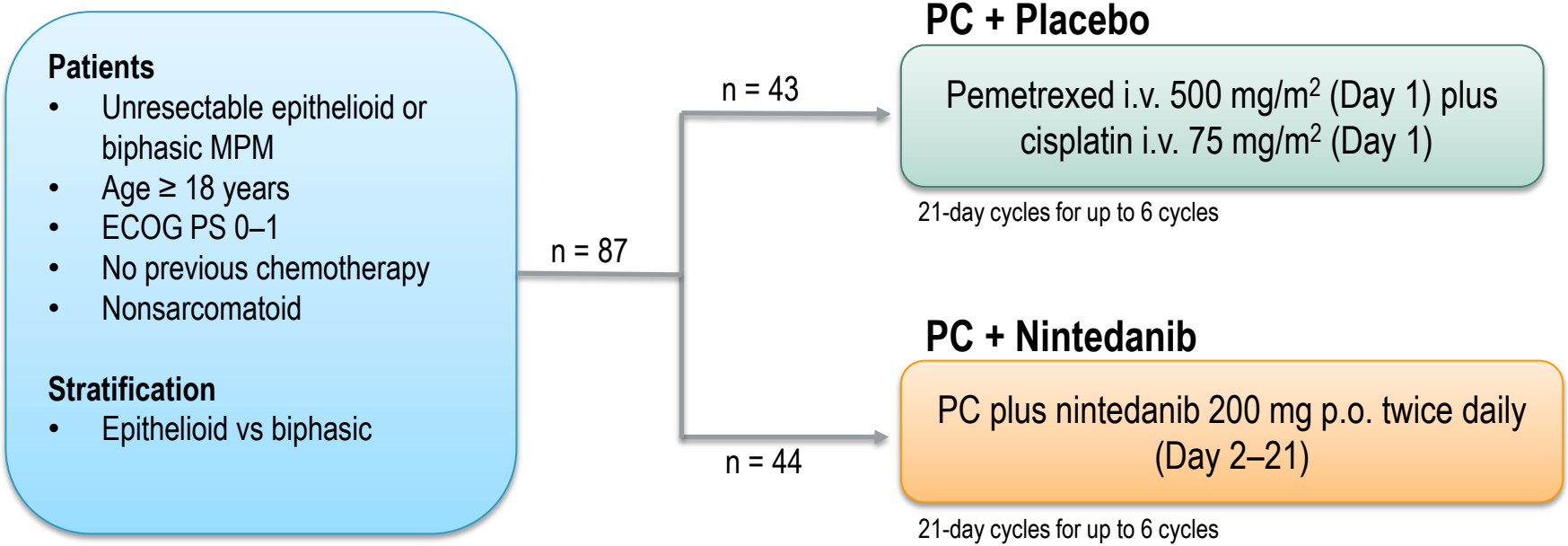
Nintedanib



FGFR, fibroblast growth factor receptor;
PDGFR, platelet-derived growth factor receptor.

Based on: Awasthi N, Schwarz RE. Onco Targets Ther. 2015;8:3691-701.

LUME-Meso: Randomized, Double-Blind, Phase 2 Trial



p.o., orally.

Grosso F, et al. J Clin Oncol. 2017;35:3591-600.

LUME-Meso Phase 2 Trial

		PC + Placebo	PC + Nintedanib
Primary Outcome Median PFS	All patients	**5.7 months**	**9.4 months**
		Adjusted HR 0.54; p = 0.010	
	Epithelioid patients	**5.7 months**	**9.7 months**
		Adjusted HR 0.49; p = 0.006	

		PC + Placebo	PC + Nintedanib
Secondary Outcome Median OS	All patients	**14.2 months**	**18.3 months**
		Adjusted HR 0.77; p = 0.319	
	Epithelioid patients	**15.2 months**	**20.6 months**
		Adjusted HR 0.70; p = 0.197	

Grosso F, et al. J Clin Oncol. 2017;35:3591-600.

LUME-Meso Phase 2 Trial[1]

Safety

- Manageable toxicities; increased incidence of diarrhea and neutropenia

Summary

- Statistically significant increase in PFS
- No significant increase in toxicities

LUME-Meso phase 3 trial ongoing[2]

- Epithelioid patients only

1. Grosso F, et al. J Clin Oncol. 2017;35:3591-600.
2. Scagliotti GV, et al. Clin Lung Cancer. 2017;18:589-93.

Discussion: Histological Subtypes

What approach would you suggest for patients with sarcomatoid and mixed-histology MPM using an anti-angiogenic treatment strategy along with cytoreductive surgery?
Would this be in the neoadjuvant or adjuvant setting?

- Potential toxicities are a concern with anti-angiogenics in the neoadjuvant setting
- Anti-angiogenics seem safe in the adjuvant setting

Personal communication: Sugarbaker DJ, Tsao AS.

Discussion: Combination Therapies

Do you think that use of these anti-angiogenic agents in combination either with traditional chemotherapy or with agents such as gemcitabine and other standard approaches in mesothelioma will have a positive impact on OS?

- A phase 2 trial testing the combination gemcitabine + bevacizumab showed negative results[1]
- There are positive data for the combination of anti-angiogenics with pemetrexed/cisplatin[2,3]
- In future, the combination of anti-angiogenics with immunotherapy will probably become important[4]

1. Kindler HL, et al. J Clin Oncol. 2012;30:2509-15.
2. Grosso F, et al. J Clin Oncol. 2017;35:3591-600.
3. Zalcman G, et al. Lancet. 2016;387:1405-14.
4. Personal communication: Sugarbaker DJ, Zhang J, Tsao AS.

Discussion: Clinical Practice

How do the emerging data on anti-angiogenics relate to clinical practice?

- The NCCN guidelines already include pemetrexed/cisplatin + bevacizumab[1]
- The MAPS trial had positive results; however, bevacizumab has not been filed for registration with FDA/EMA because the trial was not run as a registration trial[2]
- The LUME-Meso phase 3 trial of nintedanib is being conducted as a registration trial[3]

EMA, European Medicines Agency; FDA, US Food and Drug Administration; NCCN, National Comprehensive Cancer Network.

1. NCCN Clinical Practice Guidelines for Malignant Pleural Mesothelioma Version 2.2017. Available from: https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf. Accessed December 2017.
2. Zalcman G, et al. Lancet. 2016;387:1405-14.
3. Grosso F, et al. J Clin Oncol. 2017;35:3591-600.

Discussion: Strategies for Nonresponders

Given the fact that the response rate is still low, if these agents are approved in combination with chemotherapy, what should the strategy be for those patients with no response to chemotherapy?

- Combinations of immunotherapy with chemotherapy and anti-angiogenics will play a role
- There are promising data for other tumor types using combination strategies including immunotherapy

Personal communication: Sugarbaker DJ, Zhang J, Tsao AS.

Discussion: Biomarkers

Is there a reliable genetic marker for the response to bevacizumab or nintedanib?

- We do not yet have predictive biomarkers for anti-angiogenics
- There are some developments for populations with poor prognosis

Personal communication: Sugarbaker DJ, Zhang J, Tsao AS.

Discussion: Outlook

- Personalized medicine and a better understanding of the genetics involved will be important
- Anti-angiogenics are expected to have a place in the frontline setting
- The role of immunotherapy with chemotherapy still has to be defined, either in combination with anti-angiogenics or in the frontline setting for patients who are not candidates for anti-angiogenics
- Complete macroscopic resection, in patients where this can be achieved, allows for systemic therapy to start with a relatively low count of malignant mesothelial cells; this leads to higher expected response rates

Personal communication: Sugarbaker DJ, Zhang J, Tsao AS.