Chugai Oncology Media Seminar

September 2, 2008

Progress in the Treatment of Metastatic Colorectal Cancer

One Year After the Launch of Avastin®

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Contents

- Treatment of metastatic colorectal cancer and Avastin®
- Data on efficacy and safety of Avastin® in Japan
- Correlation between Avastin® and biomarkers

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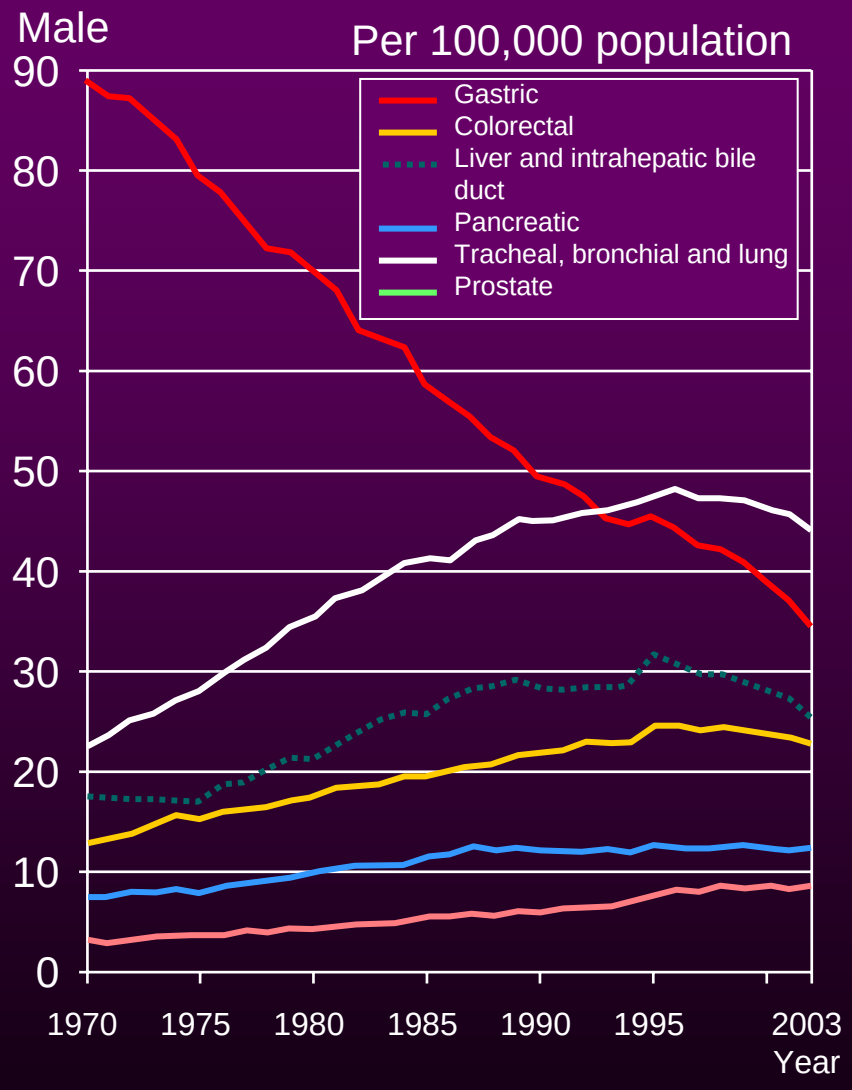
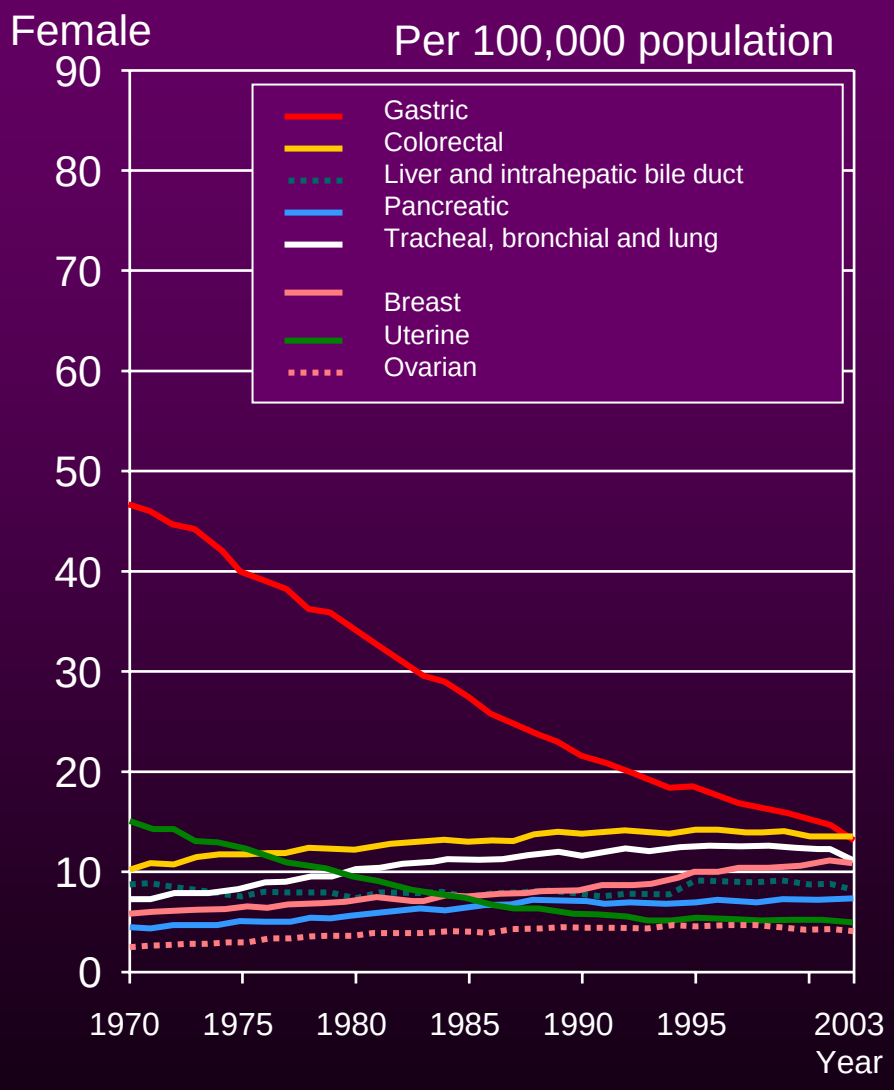
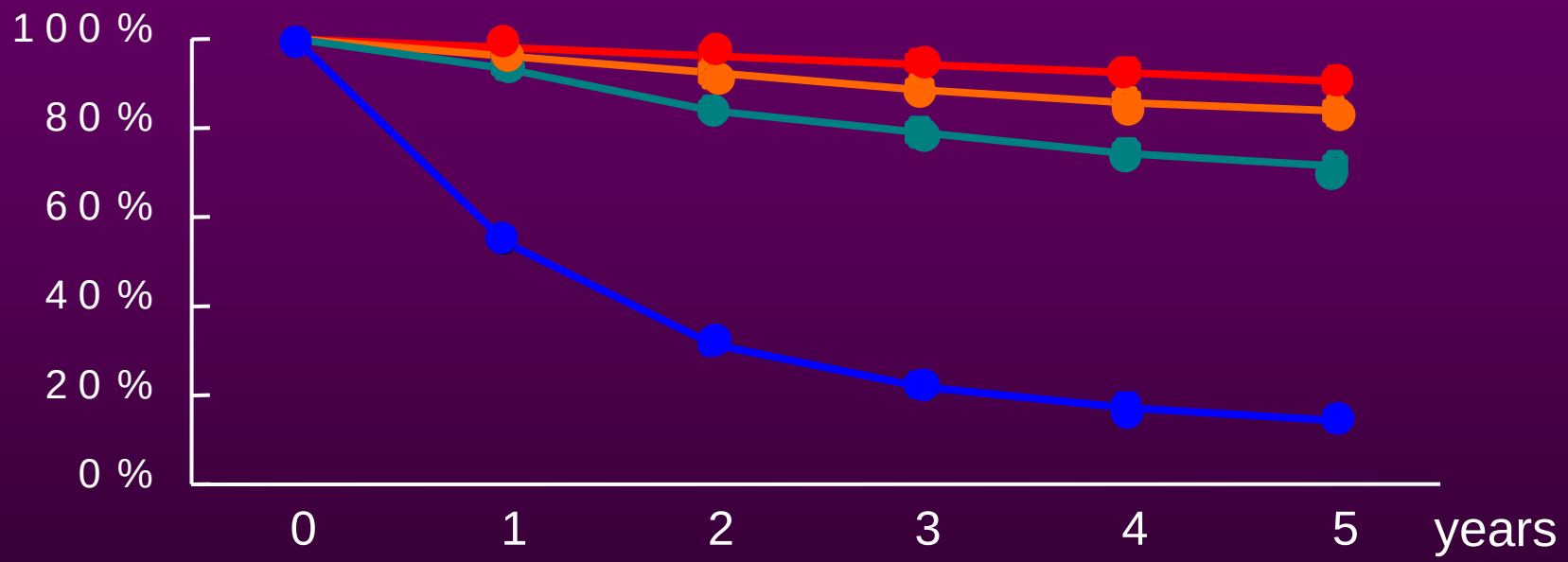
Age-adjusted death Rates





Cancer Statistics in Japan—2005

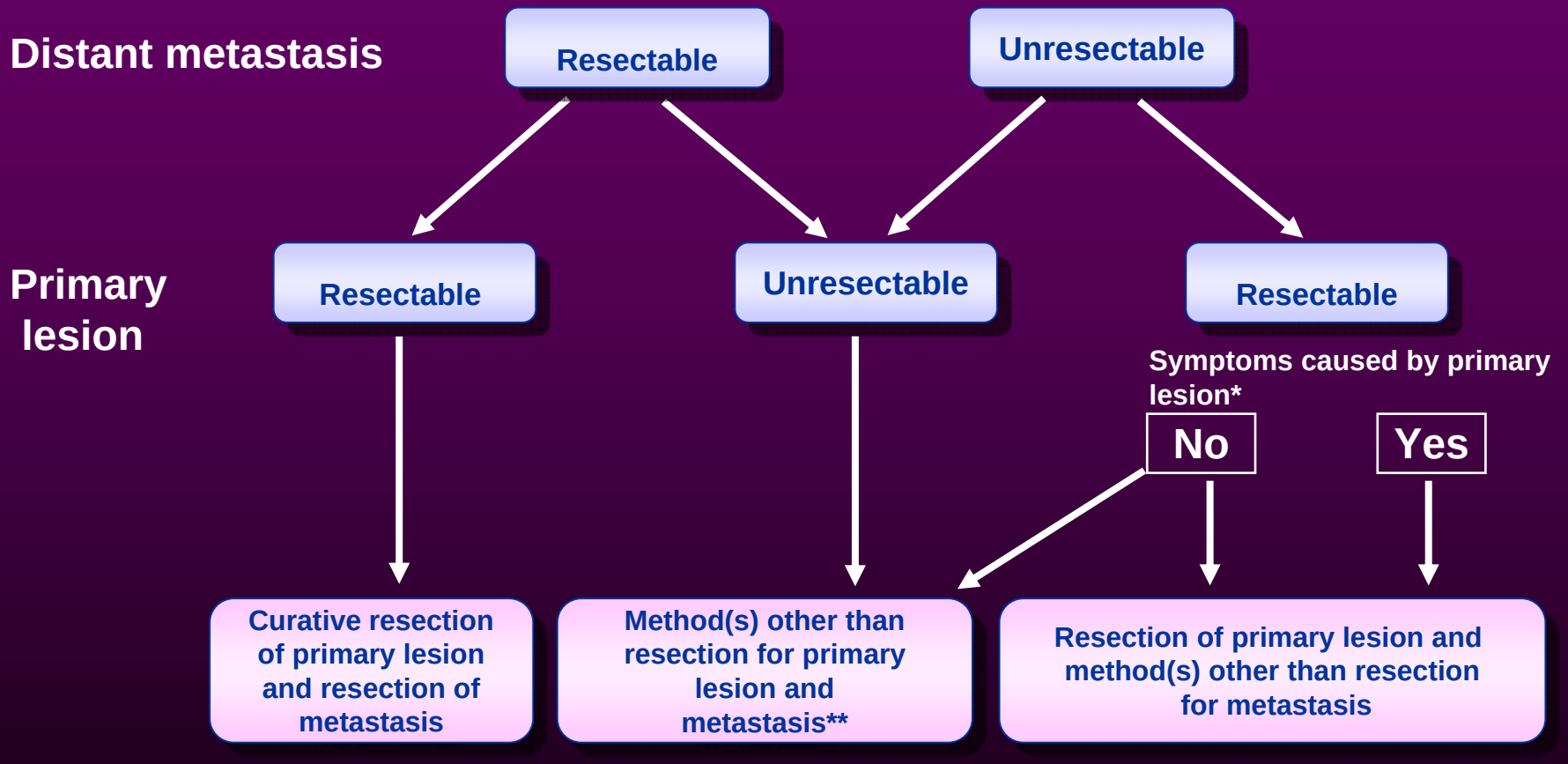
Survival Rates for Colon Cancer by Clinical Stage (1991-1994)



Stage I	100%	98%	96%	95%	93%	91%
Stage II	100%	96%	93%	89%	86%	84%
Stage III	100%	94%	84%	79%	75%	71%
Stage IV	100%	55%	32%	22%	17%	14%

Colorectal Cancer Treatment Guidelines (2005 edition)

Treatment Guidelines for Stage IV Colorectal Cancer



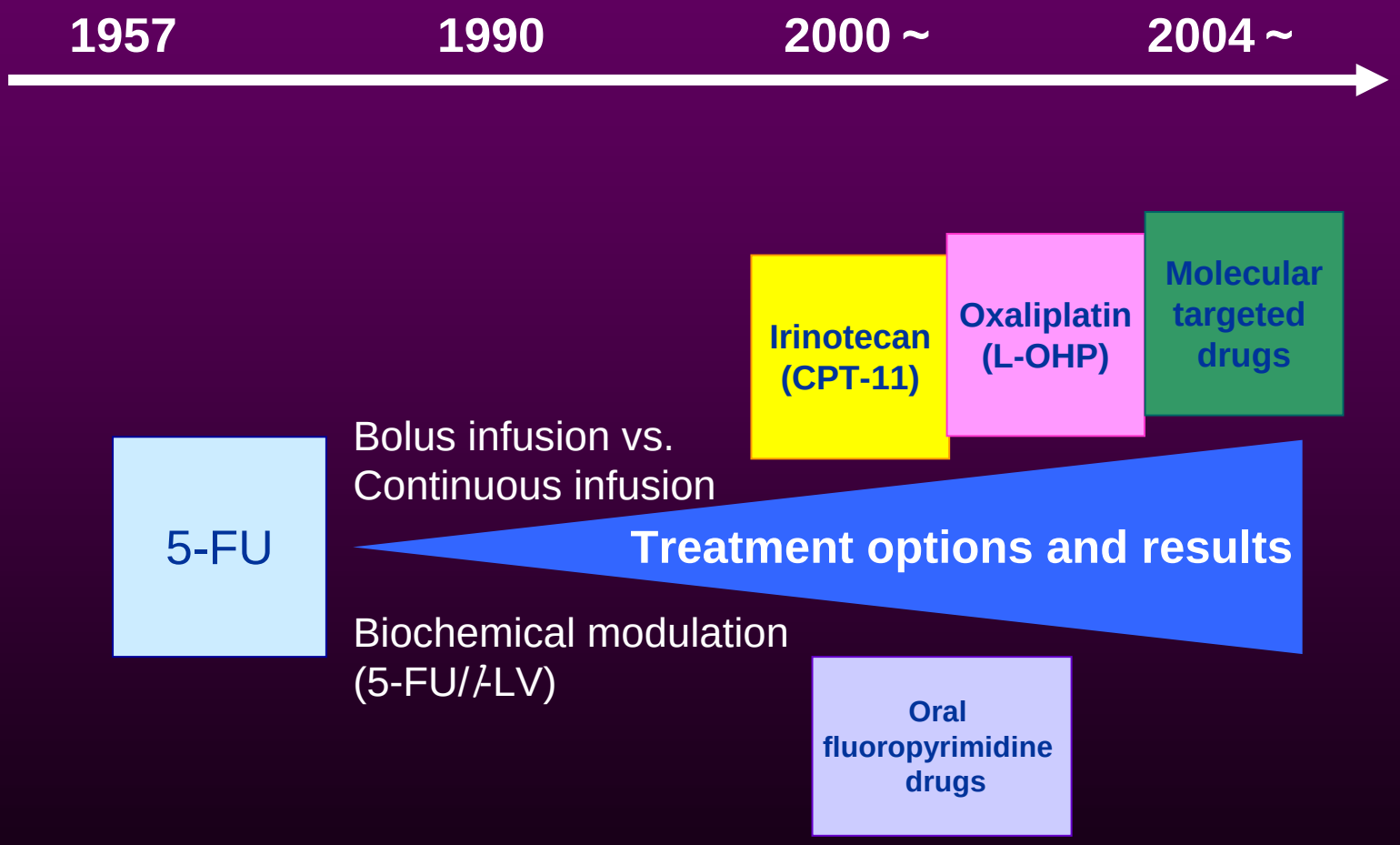
* Symptoms caused by primary lesion: hemorrhage, severe anemia, penetration, perforation, stenosis, etc.

** Method(s) other than resection: See also treatment guidelines for palliative surgery for primary lesion, chemotherapy, radiotherapy and hematogenous metastasis

Colorectal Cancer Treatment Guidelines (2005 edition)

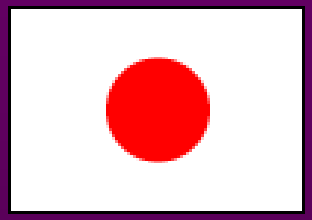
Standard Therapy for Metastatic Colorectal Cancer

Development of Chemotherapy for Metastatic Colorectal Cancer



Adapted from Clinical Tumor Practice (Satoshi Saito): 1 (2), 172, 2005

Chemotherapy for Metastatic Colorectal Cancer



June 2007

5-FU/ℓ-LV with Avastin®

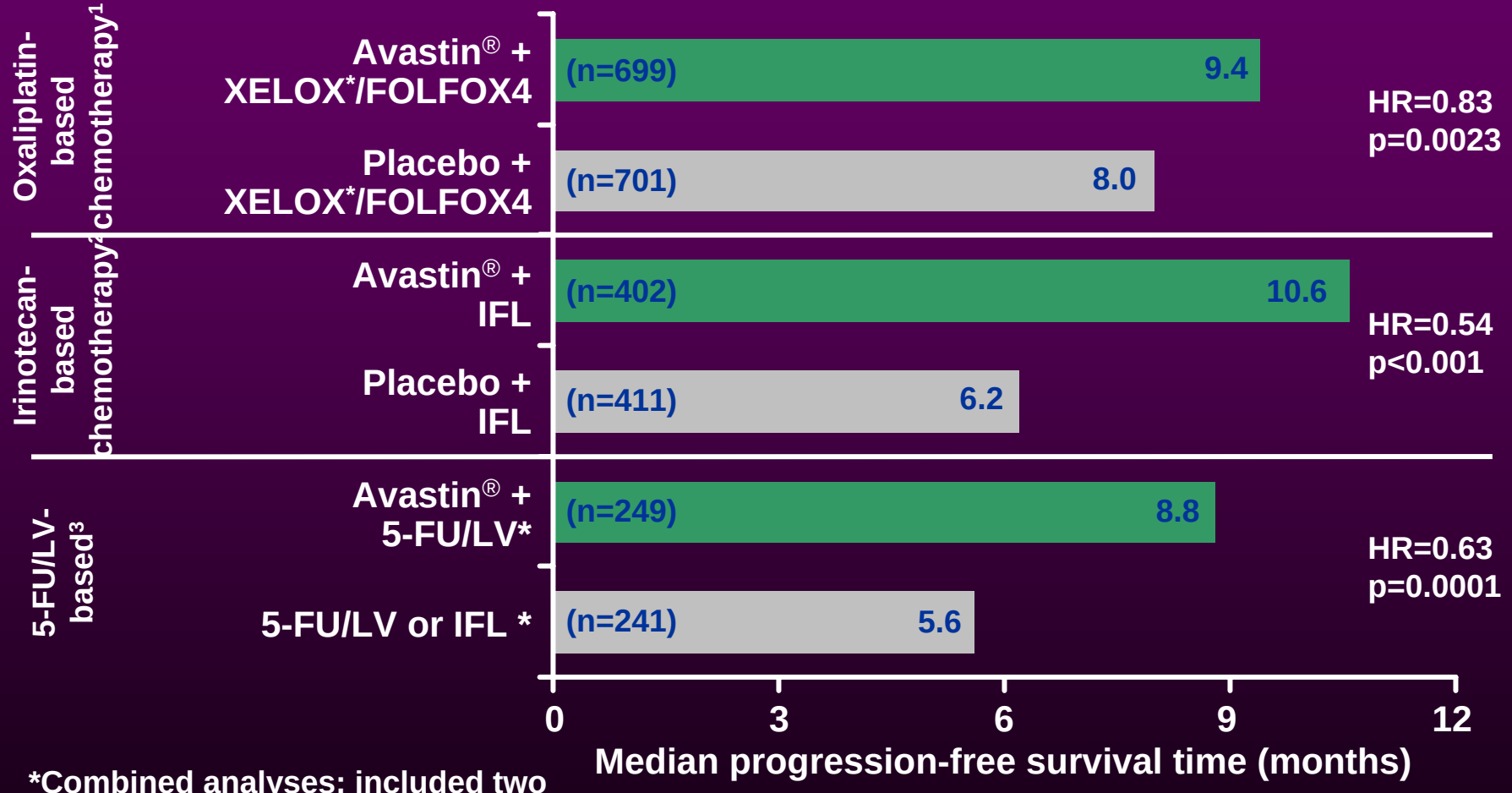
IFL with Avastin®
FOLFIRI with Avastin®

FOLFOX with Avastin®

Effects of Anti-VEGF Therapy

Initial effects	Expected therapeutic effects
1. Regression of existing microvasculature	Enhanced and sustained tumor shrinkage
2. Normalization of tumor vasculature	Improved delivery of anticancer drugs to tumor tissue
	Reduced interstitial pressure
	The rationale for effectiveness when used in combination with anticancer drugs
Sustained effects	**Expected therapeutic effects**
3. Inhibition of newly formed vessels and revascularization	Sustained tumor reduction
	Prolonged progression-free survival and overall survival times
	Possibly effective as postoperative adjuvant chemotherapy

Additive Effect of Avastin®: PFS

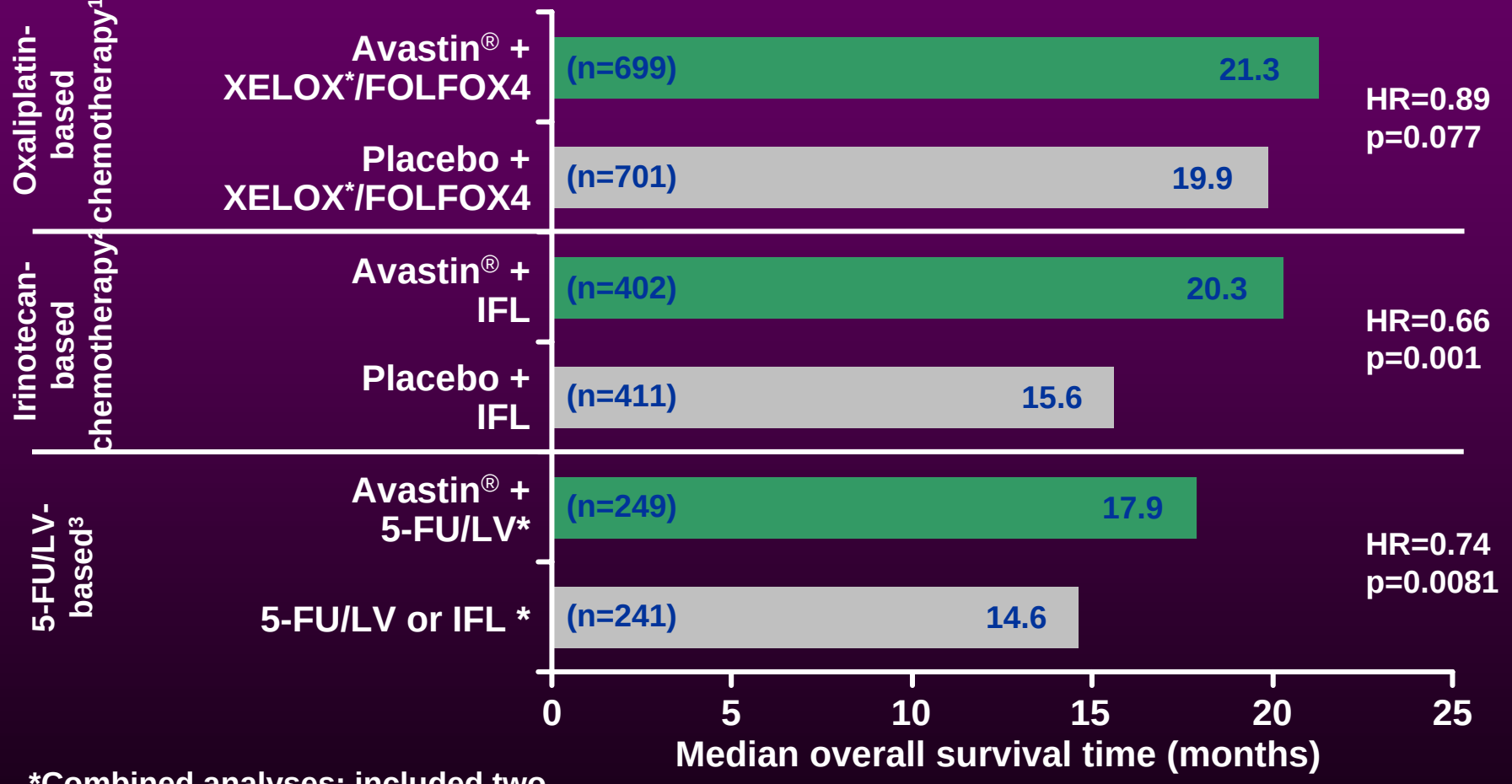


***Combined analyses: included two phase II trials and one phase III study**
HR = hazard ratio

* Neither the XELOX regimen nor 7.5 mg/kg Avastin® administered at intervals of 21 days has yet been approved in Japan

1. Saltz, et al. JCO 2008
2. Hurwitz, et al. NEJM 2004
3. Kabbinavar, et al. JCO 2005

Additive Effect of Avastin®: OS



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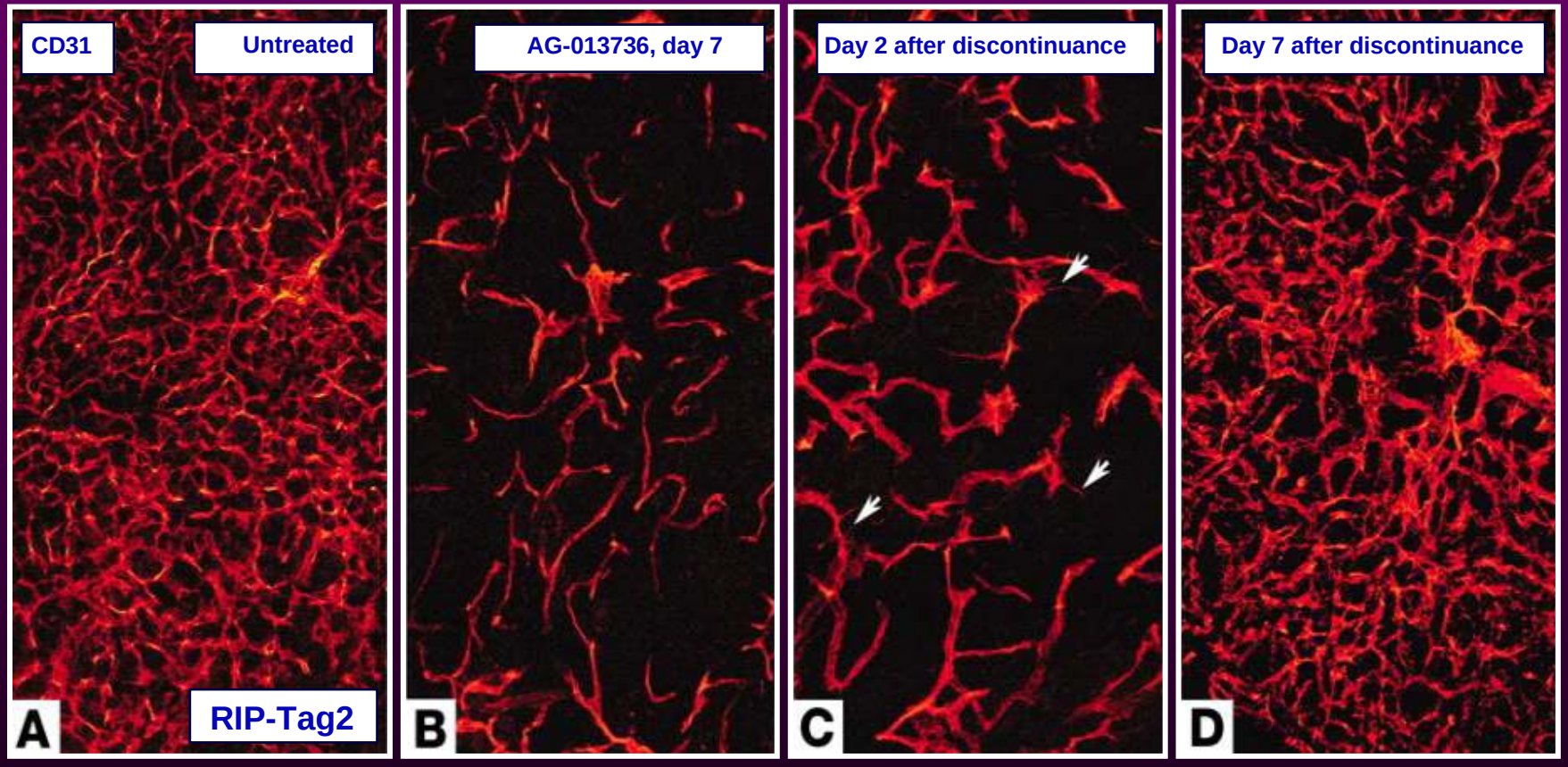
Administration Period of Avastin and PFS

47% of the placebo group continued treatment until PD, compared to 29% of the Avastin® group.

Patients for whom administration of oxaliplatin was discontinued as a result of neuropathy or allergic reactions should be given 5-FU and Avastin® until PD.

[1]Hurwitz, *NEJM* 2004; [2]Saltz, *ASCO GI* 2007

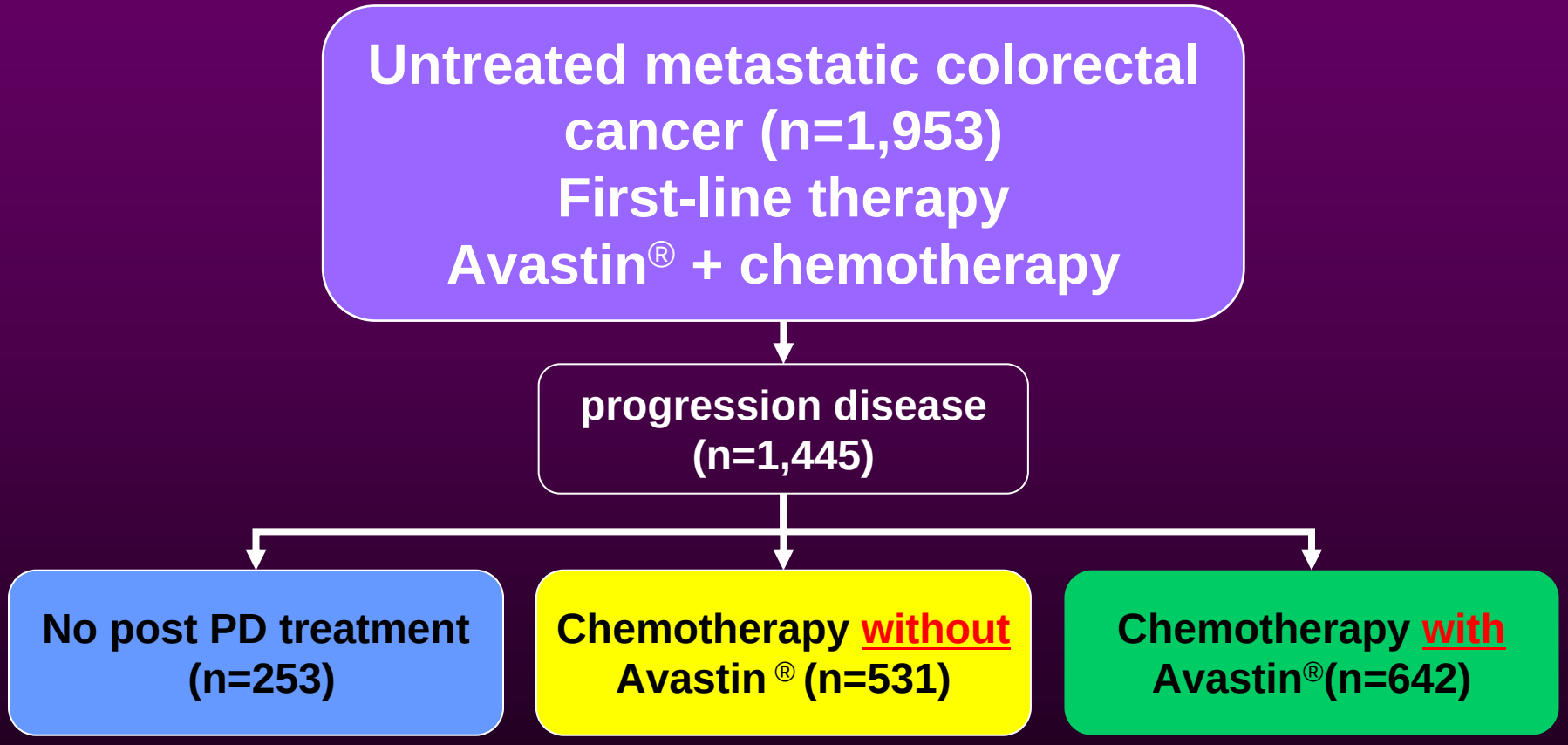
Discontinuance of Anti-angiogenesis Therapy and Renewed Vascular Proliferation



In basic research, it is important to continue anti-angiogenesis therapy to avoid renewed vascular proliferation.

Mancuso, et al. J Clin Invest 2006

Administration Period of Avastin®—BRiTE Trial

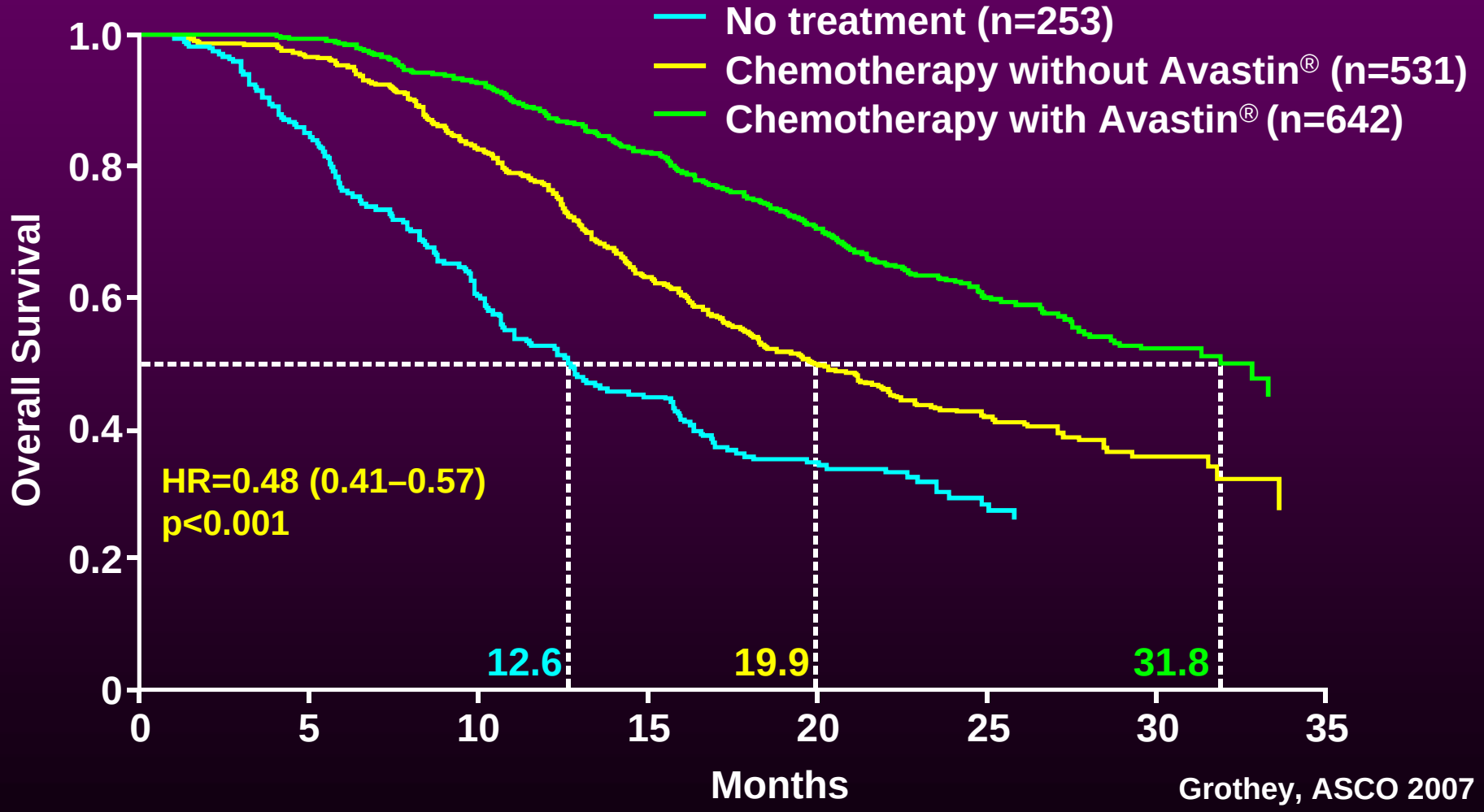


Deaths: 932
Median follow-up time: 19:6 months

Grothey, ASCO 2007

BRiTE Trial: Avastin®

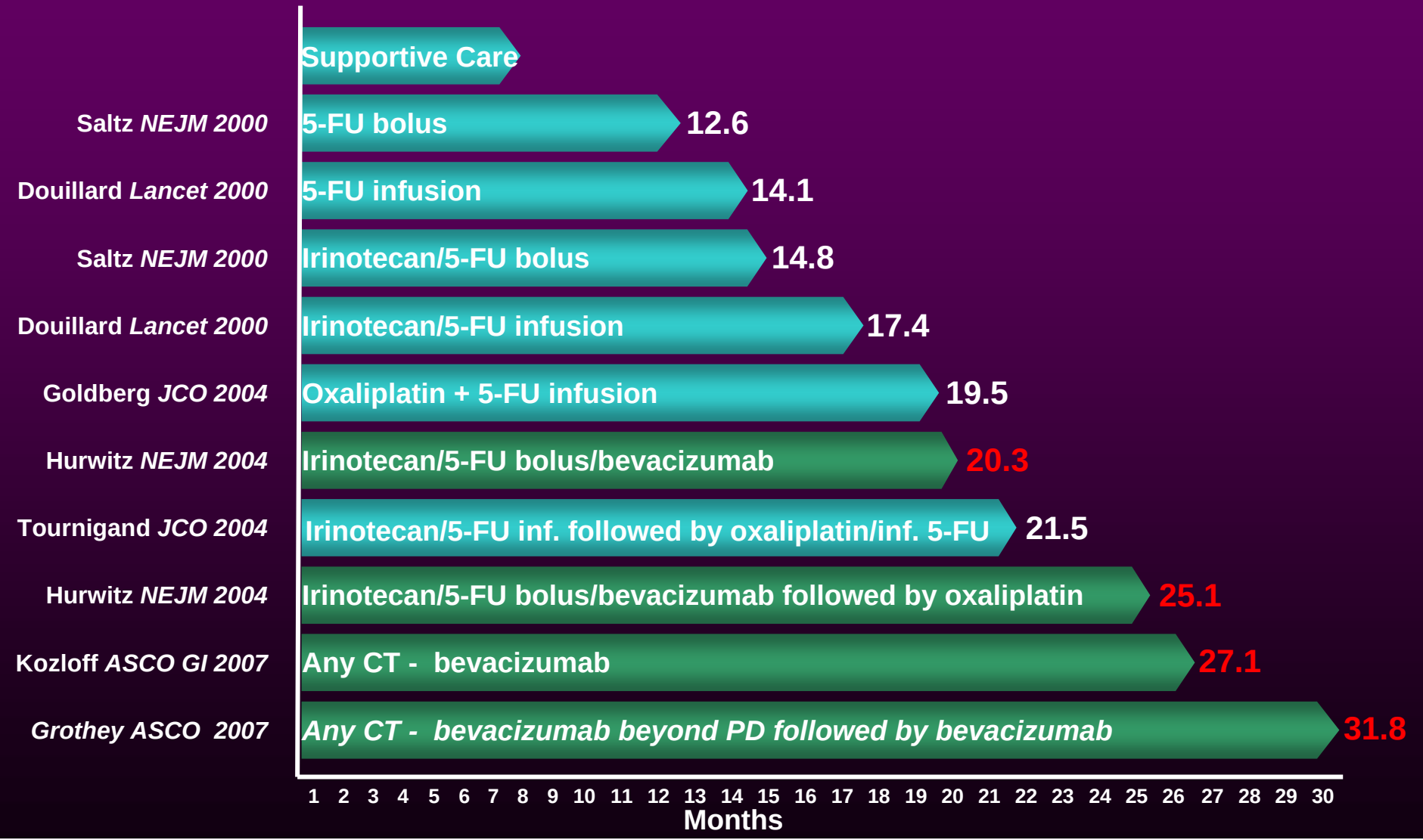
Use Avastin® with different chemotherapy even after progression, while using Avastin® in first line therapy (!?)



Grothey, ASCO 2007

Progress in Chemotherapy for Metastatic Colorectal Cancer

Median time (overall survival)



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Safety Confirmation Study in Japan (JO18158)

Objective: evaluate the safety of BV and FOLFOX4 combination therapy for advanced or refractory colorectal cancer

Inclusion criteria: performance status (PS) 0-1, aged 20-74

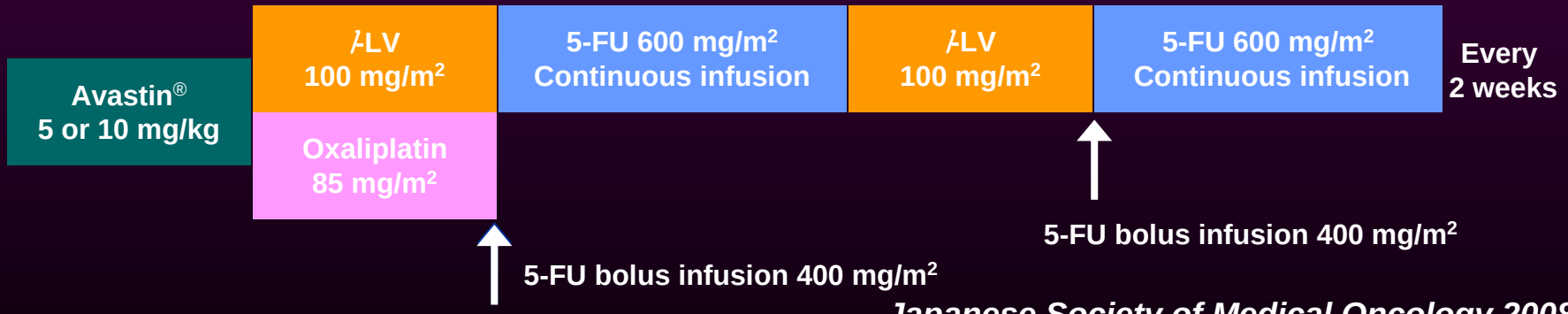
Exclusion criteria: cancerous body cavity fluid, cerebral metastasis, operation within 28 days, hemorrhagic tendency, coagulation abnormality (INR≧1.5), port inserted within 7 days, uncontrollable hypertension, cardiac disease of G2 or greater, peripheral neuropathy of G1 or greater

BV dosage: 1st-line therapy 5 mg/kg/2 weeks, second-line therapy 10 mg/kg/2 weeks

Primary endpoint: safety

Secondary endpoints: Serum concentration of BV and biomarkers (VEGF, anti-BV antibody)

Efficacy (Response rate)



Japanese Society of Medical Oncology 2008

Safety Confirmation Study in Japan (JO18158)

	Avastin® 5 mg/kg group (n = 34)* (First-line patients)	Avastin® 10 mg/kg group (n = 23)* (Second-line and beyond patients)
CR	-	-
PR	27 （79.4%）	11 （47.8%）
SD	7 （20.6%）	12 （52.2%）
PD	-	-
Response rate (%)	79.4	47.8
95%CI	62.1 – 91.3	26.8 – 69.4
	n = 38	n = 25
PFS	13.6 months (414 days)	9.7 months (294 days)
95% CI	252 – 458 days	216 - . days
Median follow-up time	252.5 days	170.0 days

*Patients with target lesions according to RECIST

Japanese Society of Medical Oncology 2008

JO18158: Adverse Events Typically Associated With Avastin® (grade 3 and higher)

	5 mg/kg group	10 mg/kg group
Hypertension	2/38*1)	6/26*1)
Hemorrhage	0/38	0/26
Proteinuria	0/38	1/26
Gastrointestinal perforations	3/38*2,3)	0/26
Arterial thrombosis	1/38*3)	0/26
Venous thrombosis	1/38*3)	0/26

*1) Controllable with medication, did not require withdrawal from study
*2) including appendiceal perforation in one patient
*3) Two out of the three cases of Gastrointestinal perforations, the one case of arterial thrombosis and one case of venous thrombosis developed post study. Although the grade of these adverse events was not determined, they are included in the totals as they were deemed to be serious.

Japanese Society of Medical Oncology 2008

Overview of Post Marketing Surveillance Study

- Subjects: all cancer patients prescribed with Avastin®
- Objectives:
  - ① Confirm that the incidences of Gastrointestinal perforation and tumor-related hemorrhage are similar to those found in overseas clinical trials
  - ② Evaluate the dose response for patients given 5mg/kg/2 weeks and 10mg/kg/2 weeks
  - ③ Investigate incidence of adverse drug reactions
  - ④ Confirm efficacy (overall survival time and response rate)
- Target number of cases: 2500
- Enrollment period: June 11 to November 9, 2007
- Follow-up period: six months from start of administration
- Since few patients have been prescribed to this drug at the approval in Japan, information about adverse drug reactions will be collected and made available as soon as possible
- All results temporarily collected 1, 3 and 6 months after launch

Overview of Interim Results

- Total number of cases included: 1,018
  - Survey data on patients for whom follow-up period completed and results collected by March 7, 2008 (includes patients for whom review not completed)

- Interim results
  - Patient backgrounds
  - Previous treatment
  - Laboratory test values before start of administration
  - Exposure to Avastin® and combination chemotherapy
  - Effects and outcomes
  - Assessment of proper use
  - Incidence of adverse drug reactions

Post Marketing Surveillance Study Interim Results (1)

Patient Backgrounds

Sex	Male / Female	608 / 410
Age	Mean: 59.9 ±10.9, median: 60 Range: 18-86 (368 patients aged 65 or over)	
Cancer type	Colon cancer / rectal cancer / colorectal cancer	598 / 413 / 7
Stage of therapy	First-line / Second-line / Third-line	419 / 577 / 22
P.S	0 / 1 / 2 / 3≦	800 / 202 / 16 / 0
Primary lesion	with / without	169 / 837
Distant metastasis	with / without →Local / lung / liver / peritoneum / lymph node / bone / Other	1009 / 4 121 / 398 / 582 / 167 / 257* / 59 / 60 *excluding lymph nodes in the pelvis

Total number of cases included: 1018 (cases for whom follow-up period completed and results collected by March 7, 2008)

Post Marketing Surveillance Study Interim Results (2)

ADR incidence by patient background

		Cases enrolled	Total number of patients with ADR (severe/non-severe)		ADR incidence rate*
Sex	Male	608	367	(105/327)	60.36%
	Female	410	259	(73/232)	63.17%
Age	< 20	1	1	(1/0)	100.00%
	20-64	649	393	(113/355)	60.55%
	65 ≤	368	232	(65/204)	63.04%
Stage of therapy	First-line	419	249	(76/221)	59.43%
	Second-line	577	362	(99/324)	62.74%
	Third-line and beyond	22	15	(3/14)	68.18%
Dose of Avastin® (induction)	5mg/kg	910	556	(151/501)	61.10%
	10mg/kg	87	60	(24/50)	68.97%

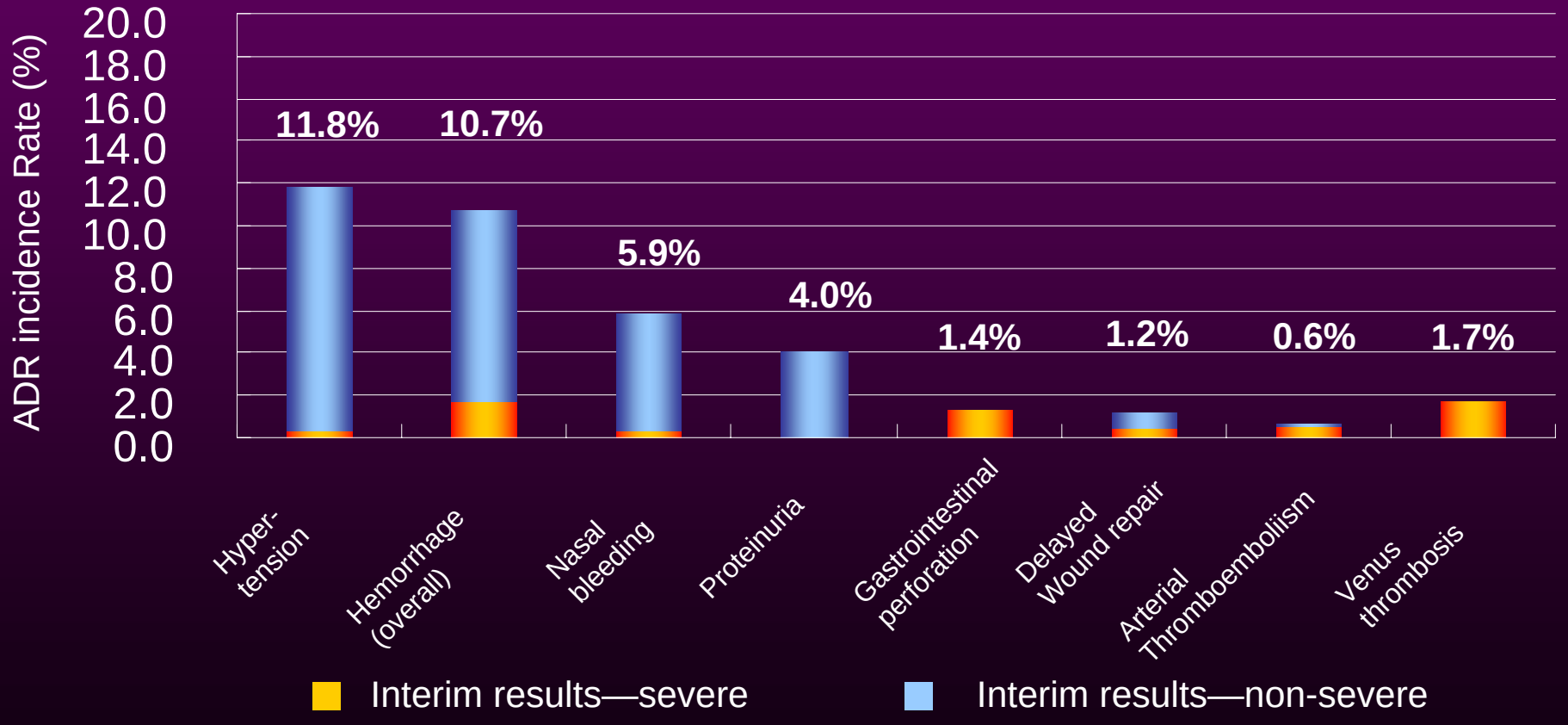
* ADR incidence rate for each group according to background

Post Marketing Surveillance Study Interim Results (3)

Main ADR

Total number of cases included: 1018

Total ADR: 626 cases, 2271 reports (61.5%); serious ADR: 178 cases, 303 reports (17.5%)



Comparison of Serious Adverse Events in Japan and Overseas

	PMS study (Japan)		Safety confirmation study (Japan)		Overseas clinical trials※1					Overseas PMS studies*1	
	Interim results	All patients	FOLFOX4		5mg/kg			10mg/kg		First-BEAT	BRiTE
	All regimens	All regimens	Avastin 5mg/kg n=38	Avastin 10mg/kg n=26	NO16966	AVF2107g	AVF2192g	E3200		All regimens	All regimens
	All doses n=1018	All doses n=2712			FOLFOX +Avastin n=341	IFL +Avastin n=392	5FU/LV ＋Avastin n=100	FOLFOX +Avastin n=287	Avastin single agent therapy*3 n=234	All doses n=1295	All doses n=1968
Hypertension	0.29	0.26	5.3	23.1	3.2	12.5	15.0	6.2	7.3	0.5	16.4※2
Hemorrhage (overall)	1.67	1.22	0.0	0.0	2.1	3.4	5.0	3.7	3.0	0.8	1.9
Proteinuria	0.00	0.07	0.0	3.8	0.9	0.8	1.0	0.7	0.0		
Gastrointestinal perforation	1.38	0.77	2.6	0.0	0.3	2.0	2.0	1.7	1.7	0.7	1.7
Delayed wound repair	0.39	0.29	0.0	0.0	0.0	8.3	33.3	0.0	0.0	0.3	1.2
Arterial thromboembolism	0.49	0.29	0.0	0.0	0.9	3.4	9.0	1.0	0.8	0.6	2.1
Venous thrombosis	1.67	1.07	2.6	0.0	9.4	15.3	8.0	3.4	0.4	1.0	

*1: Incidence rate of severe adverse events for overseas clinical trials and PMS studies
*2: Hypertension requiring treatment (including grade 2) (all severe ADR: 12.0%)
*3: Avastin single agent therapy not approved in Japan

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USA TODAY, June 2, 2008
(during American Society of Clinical Oncology Annual Meeting, 2008)

Is the *K-ras* gene
a predictive factor
for molecular-targeted drugs?
Or is it
a negative predictive factor
for anti-EGFR antibodies?

Health

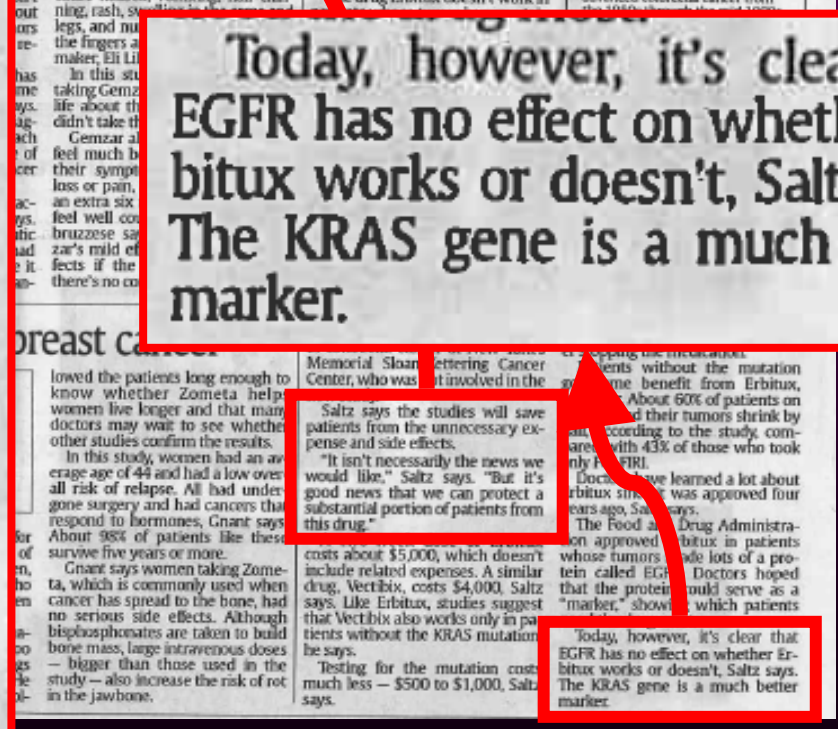
There's good news from th

That finding — along with similar results in three other recent studies — will change the way Erbitux is used, says Leonard Saltz, an expert in colorectal cancer at New York's Memorial Sloan-Kettering Cancer Center, who was not involved in the new study.

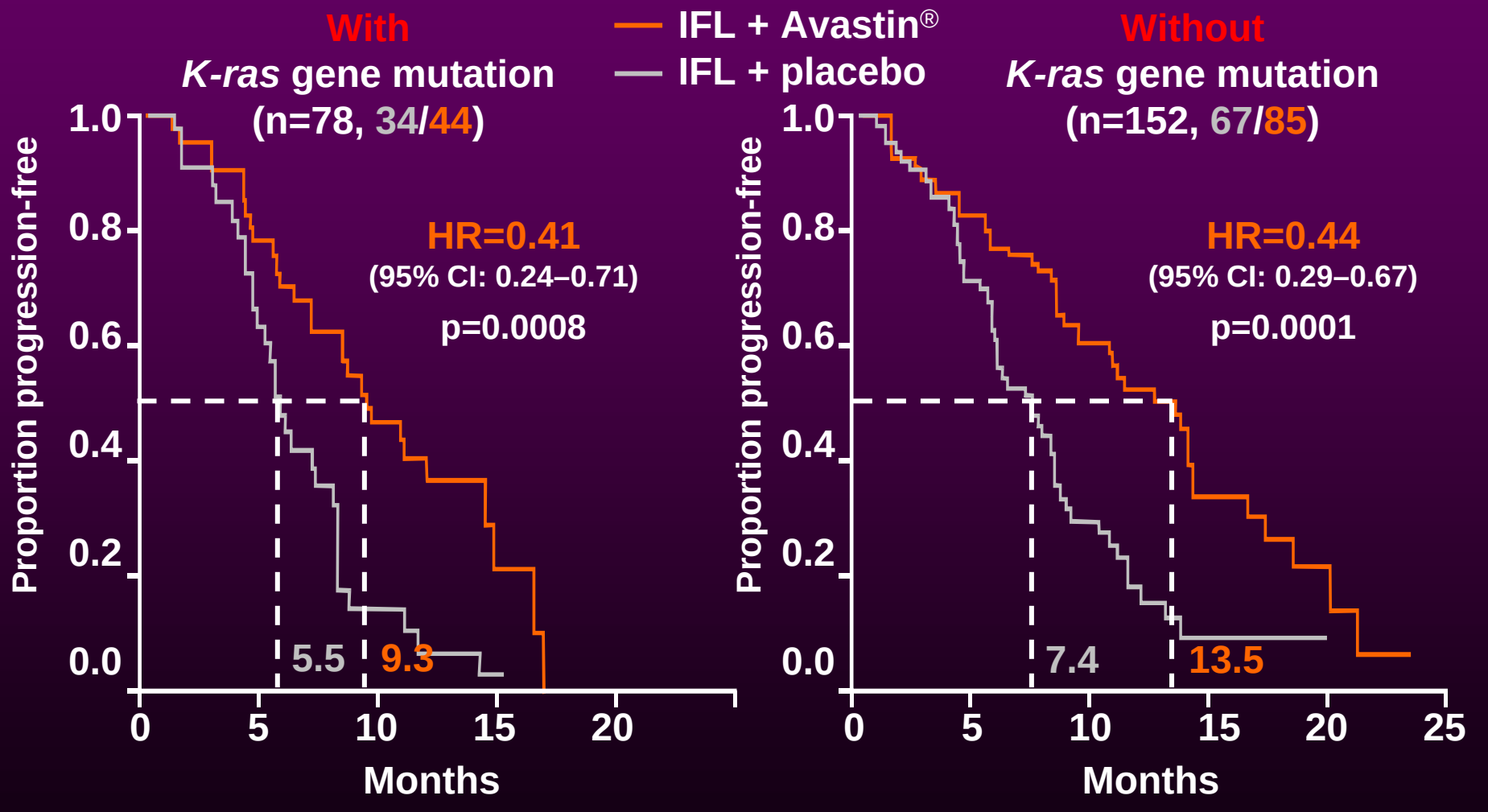
Saltz says the studies will save patients from the unnecessary expense and side effects.

"It isn't necessarily the news we would like," Saltz says. "But it's good news that we can protect a substantial portion of patients from this drug."

Today, however, it's clear that EGFR has no effect on whether Erbitux works or doesn't, Saltz says. The KRAS gene is a much better marker.

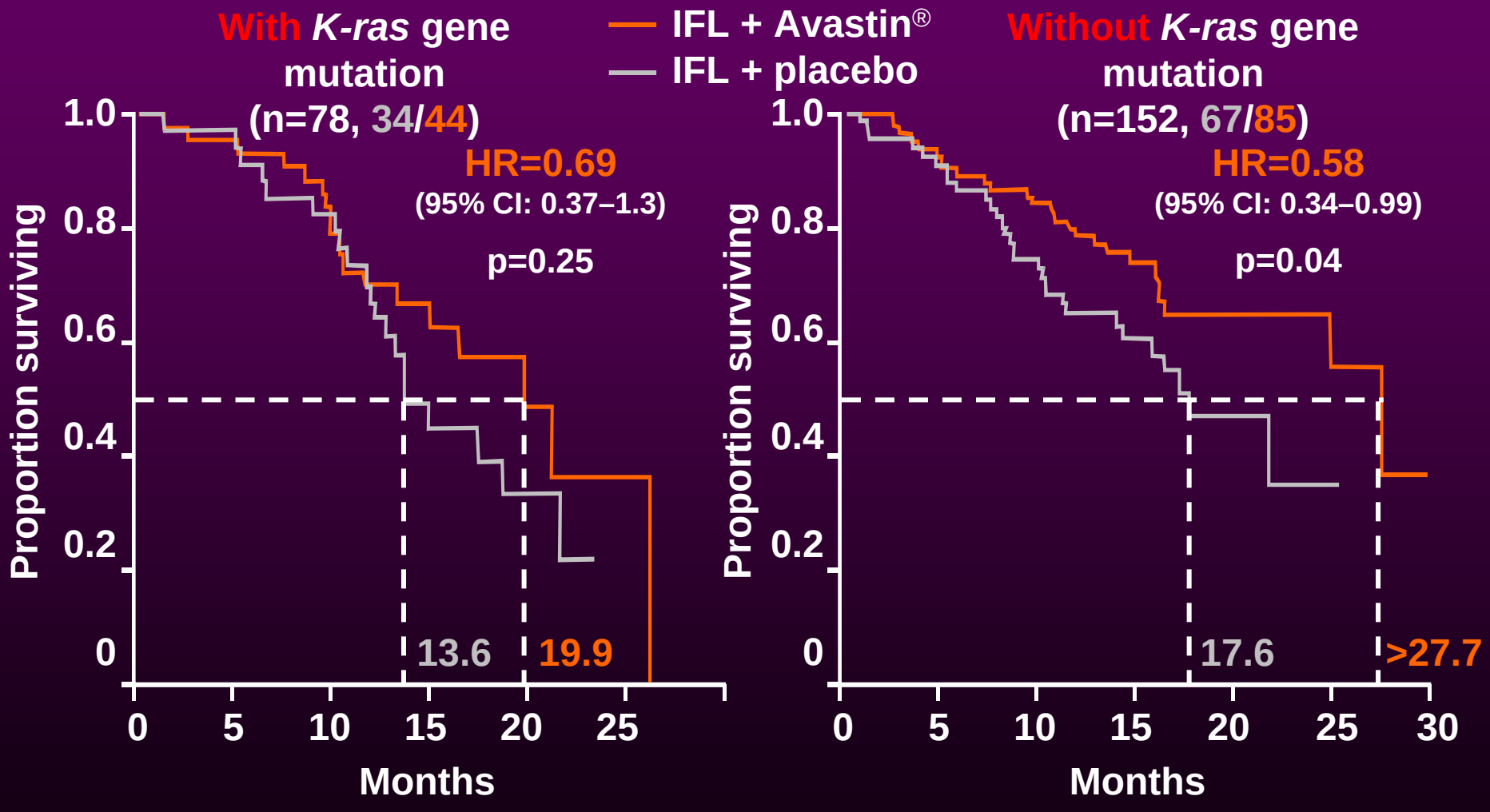


Additive Effect of Avastin®: PFS According to *K-ras* Gene Mutation Status



Hurwitz, WCGIC 2008

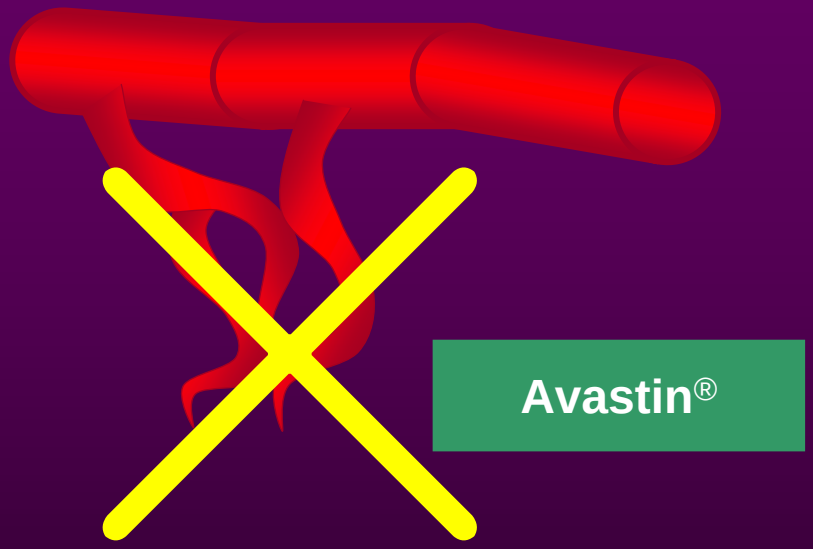
Additive Effect of Avastin®: OS According to *K-ras* Gene Mutation Status



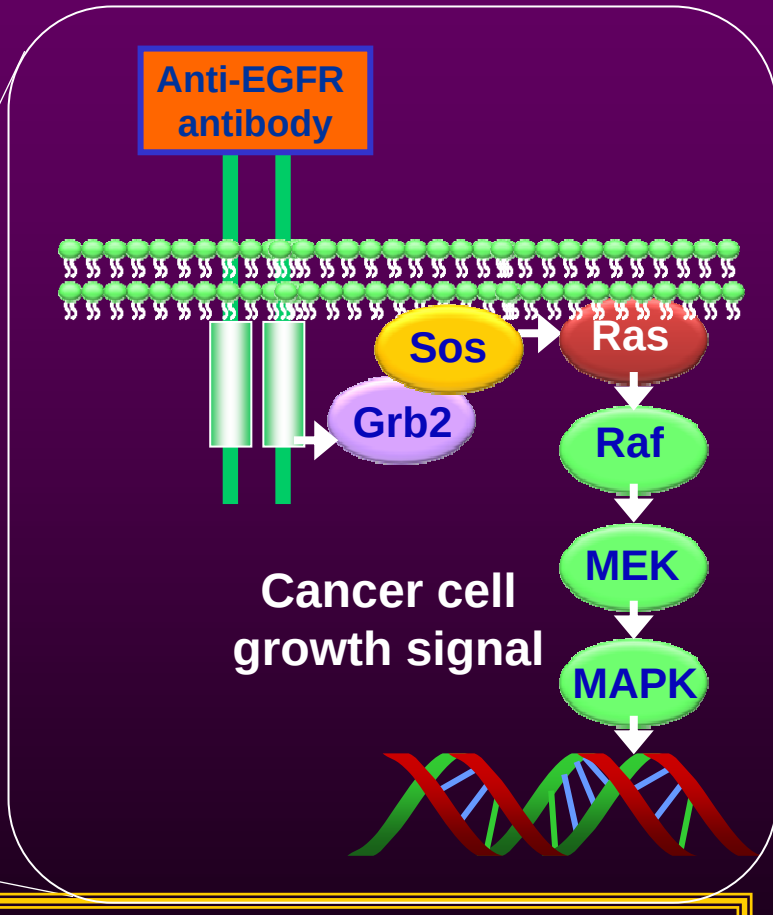
Hurwitz, WCGIC 2008

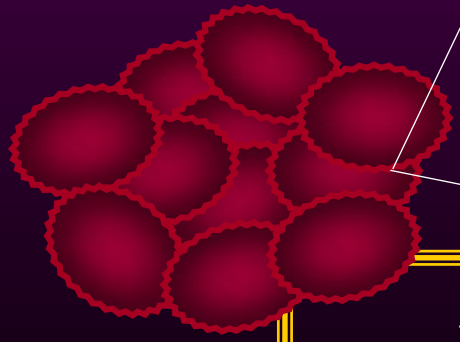
Avastin® and Anti-EGFR Antibodies

Outside tumor cell



Inside tumor cell



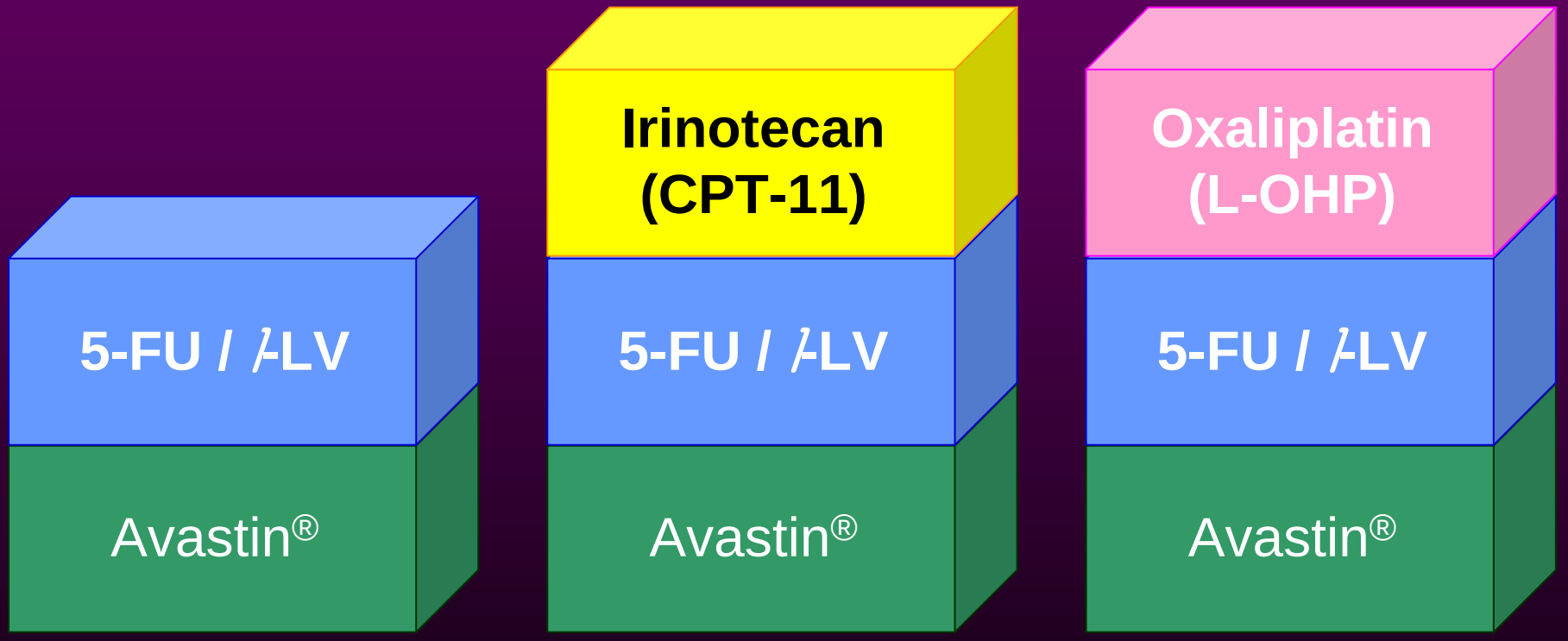


Cancer tumor cell

Avastin® and anti-EGFR antibodies have completely different mechanisms of action!

Standard Therapy for Metastatic Colorectal Cancer

Avastin® is the base drug for treatment of metastatic colorectal cancer!



Avastin® with 5-FU/ℒ-LV

Avastin® with IFL
Avastin® with FOLFIRI

Avastin® with FOLFOX

Summary

- The anti-VEGF antibody Avastin® is an effective base drug for treatment of metastatic colorectal cancer.

- Avastin® prolongs survival when used as a first- or second-line therapy with effective chemotherapy, thus fulfilling the role of base drug for treatment of metastatic colorectal cancer.

- The tolerability of Avastin® in Japanese patients was confirmed in the large-scale trial (interim results).

- Although anti-EGFR antibodies are not usually effective for treating colorectal cancer patients with *K-ras* gene mutations, Avastin® is equally effective for patients regardless *K-ras* gene mutations status.