CNS TUMORS/SARCOMA

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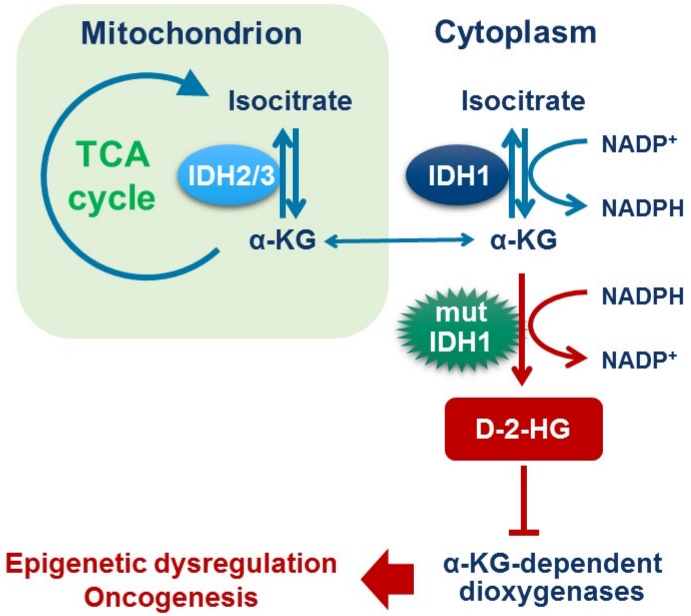
Molecular Markers in Gliomas

1. **Mutations of isocitrate dehydrogenase (IDH) 1 and 2**
2. **1p/19q Chromosomal codeletions**
3. **O^6–Methylguanine-DNA methyltransferase (MGMT)**

1p/19q: short arm of chromosome 1/long arm of chromosome 19

Isocitrate Dehydrogenase (IDH) 1 Mutations in Gliomas

- Approximately 70–80% of WHO grade II/III gliomas harbor *IDH1* mutations[1]
- Mutant IDH1 produces the oncometabolite D-2-HG, accumulation of which leads to oncogenesis and subsequent clonal expansion[2]
- In gliomas, the *IDH1* mutation is a "trunk mutation" and is considered as a promising therapeutic target
  - It occurs early in gliomagenesis[1]
  - It is ubiquitous within the tumor mass and persists throughout progression[1]



2-HG = 2-hydroxyglutarate; α-KG = alpha-ketoglutarate, IDH = isocitrate dehydrogenase; $NADP^+$/NADPH = nicotinamide adenine dinucleotide phosphate; TCA = tricarboxylic acid.

1. Suzuki H, et al. *Nat Genet*. 2015;47:458-68.
2. Cairns RA, et al. *Cancer Discov*. 2013;3:730-41.

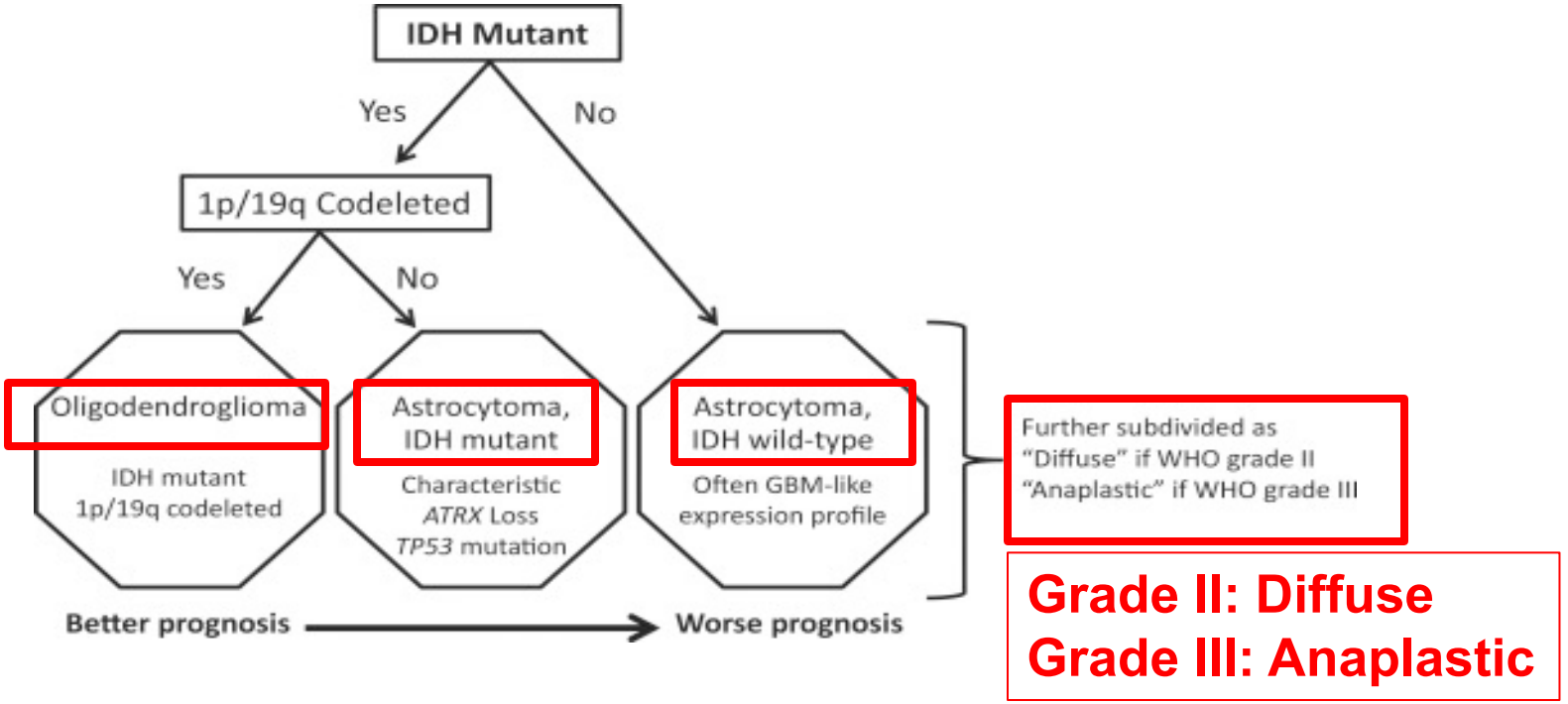


Figure 2. Diagnostic schema for WHO World Health Organization grades II and III infiltrating gliomas in adults.

Low grade gliomas are now divided into 3 molecular categories

1. IDH-wild type
2. IDH-mutant/1p/19q codeleted
3. IDH-mutant/1p/19q non-codeleted

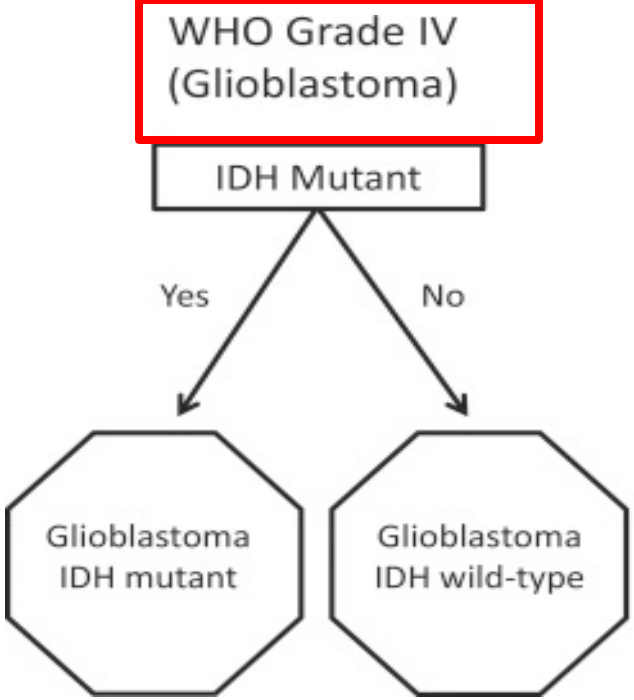
ATRX gene: Chromatin remodeler

Treatment of Patients With Gliomas: An Outline

	Grade I	Grade II	Grade III	Grade IV
Astrocytomas	Pilocytic	Diffuse	Anaplastic	Glioblastoma multiforme
	No trials	RTOG 9802 IDH inhibitors	CATNON	TMZ/XRT then maintenance TMZ TMZ/XRT then maintenance TMZ/Bevacizumab(AVAglio and RTOG 0825) TTF (EF-14) Bevacizumab (BRAIN) Bevacizumab/Lomustine TTF (EF-11) Checkmate 143
Oligodendrogiomas	Not Applicable	Diffuse	Anaplastic	Not Applicable
		RTOG 9802	EORTC 26951 RTOG 9402 CODEL	

TTF: Tumor Treating Felds: Disrupts the growth of cancer cells via alternating positive and negative electric fields
TMZ: Temozolomide
XRT: Radiation therapy
RTOG: Radiation Therapy Oncology Group
EORTC: European Organization for Research and Treatment of Cancer

Glioblastoma Multiforme
(Grade IV Astrocytomas)



Glioblastoma, IDH mutant

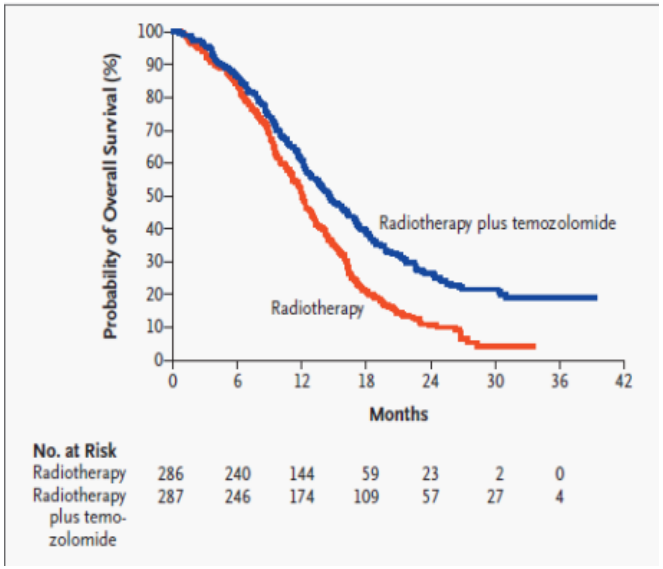
- ~10% of GBMs
- Younger median age at diagnosis
- Better prognosis
- More likely to be *MGMT* methylated
- Most "secondary" GBMs
- IDH mutation is possible target for therapeutic agents (trials ongoing)

Glioblastoma, IDH wild-type

- ~90% of GBMs
- Older median age at diagnosis
- Poorer prognosis
- Most "primary" GBMs

Figure 3. Diagnostic schema for GBM glioblastoma (WHO World Health Organization grade IV astrocytoma), with key features of primary and secondary tumors.

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma



Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

Median Follow-up: 28 months

	Overall Survival	Progression-Free Survival
RT	12.1 months	5 months
RT/Temozolomide	14.5 months	6.9 months
HR	0.63	0.54
95% Confidence Interval	0.52-0.75	0.45 – 0.64
P value	< 0.001	< 0.001

Stupp R, N Engl J Med 352: 987, 2005.

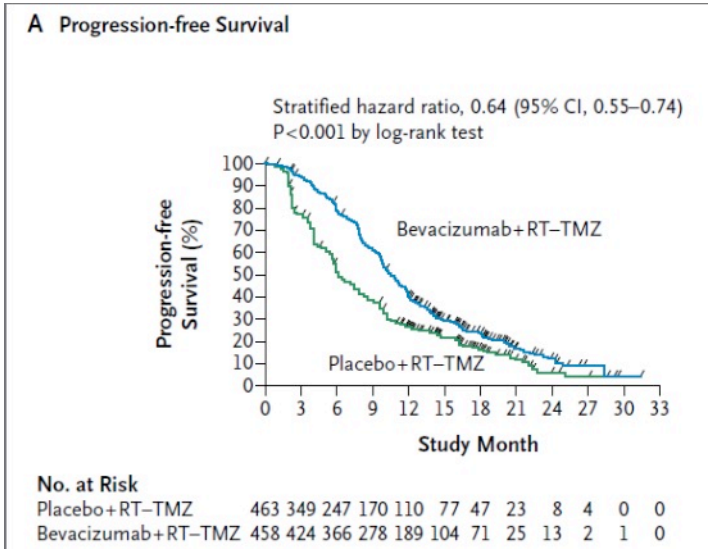
Bevacizumab plus Radiotherapy–Temozolomide for Newly Diagnosed Glioblastoma (AVAglio Trial)

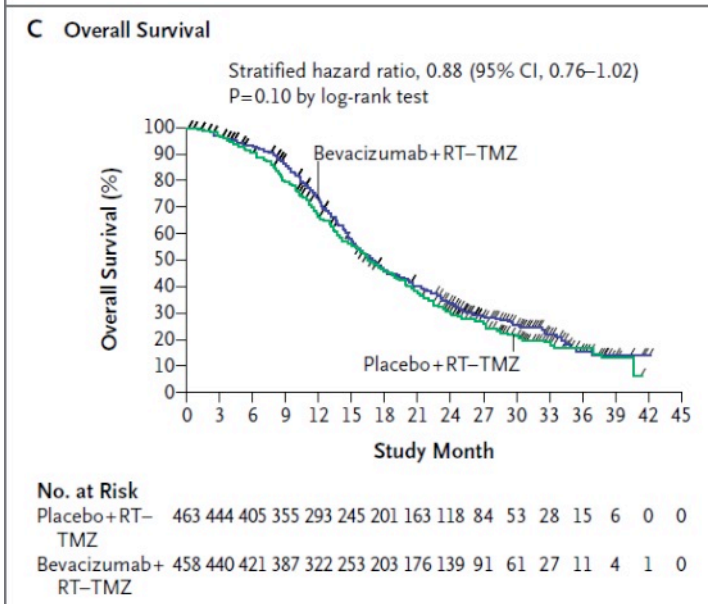
Progression-free Survival (PFS)

	TMZ/Placebo	TMZ/Bevavizumab
PFS	6.2 months	10.6 months
HR	0.64	
95% confidence interval	0.55 – 0.74	
P value	< 0.001	

Overall Survival (OS)

	TMZ/Placebo	TMZ/Bevavizumab
OS	16.7 months	16.8 months
HR	0.68	
95% confidence interval	0.76 – 1.02	
P value	0.10	





Chinot OL et al. N Engl J Med 370: 709, 2014

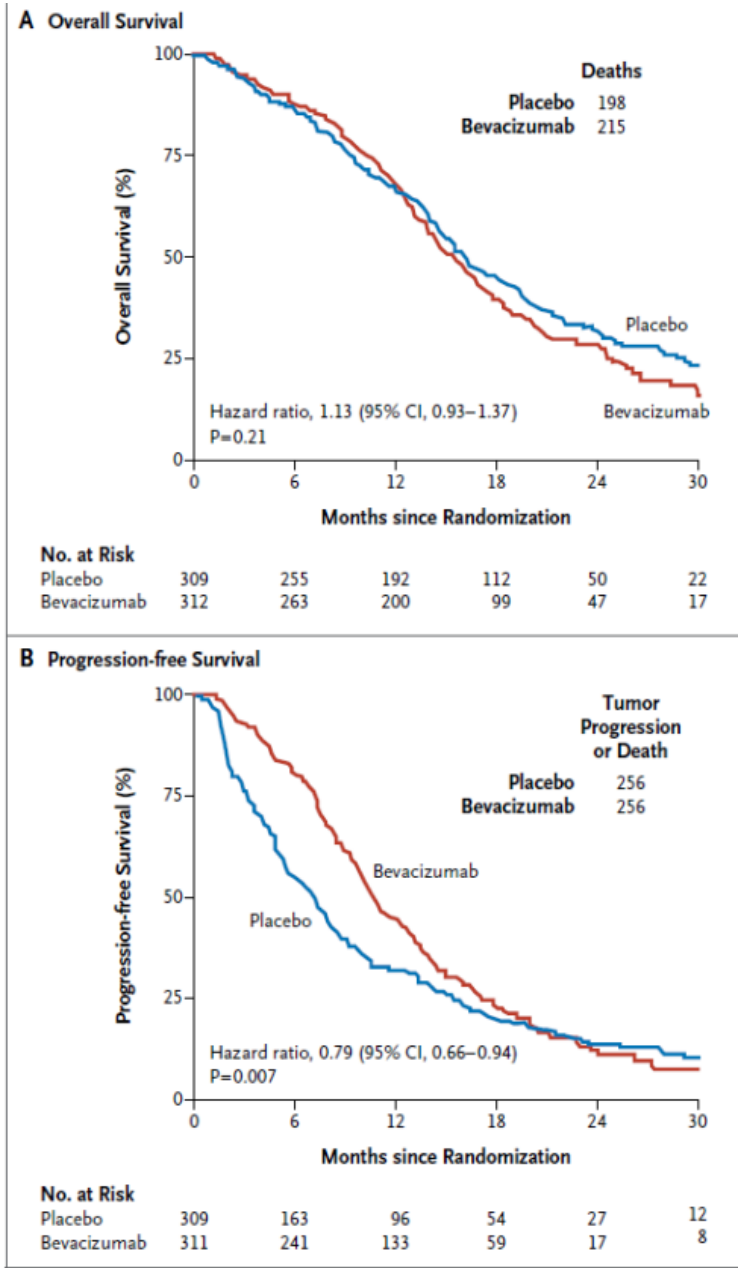
A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma (RTOG 0825)

Progression-free Survival (PFS)

	TMZ/Placebo	TMZ/Bevavizumab
PFS	7.3 months	10.7 months
HR	0.79	
95% confidence interval	0.66 – 0.79	
P value	0.007	

Overall Survival (OS)

	TMZ/Placebo	TMZ/Bevavizumab
OS	16.1 months	15.7 months
HR	1.13	
95% confidence interval	0.93 – 1.13	
P value	0.21	



Gilbert MR et al. N Engl J Med 370: 699, 2014

Lomustine and Bevacizumab in Progressive Glioblastoma

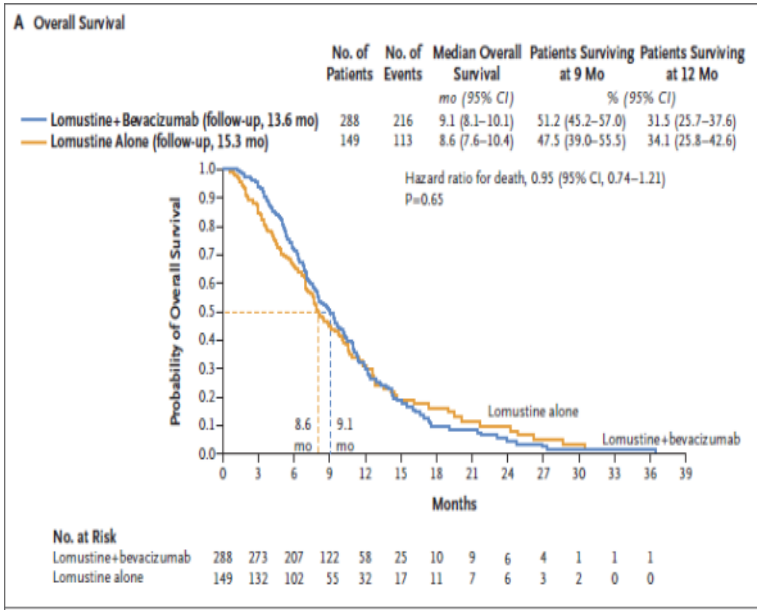
Primary end-point: Overall Survival

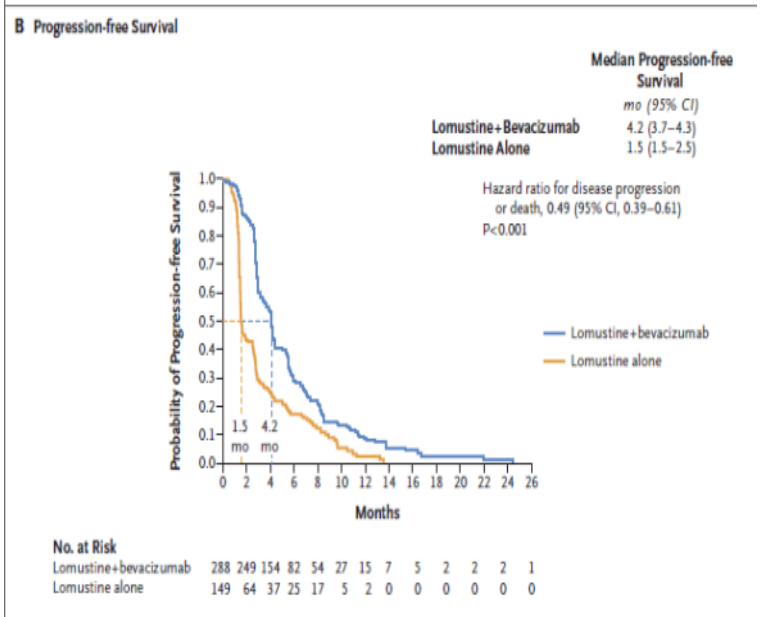
Progression-free Survival (PFS)

	Lomustine alone	Lomustine/Bevacizumab
PFS	1.5 months	4.2 months
HR	0.49	
95% confidence interval	0.39 – 0.61	
P value	< 0.001	

Overall Survival (OS)

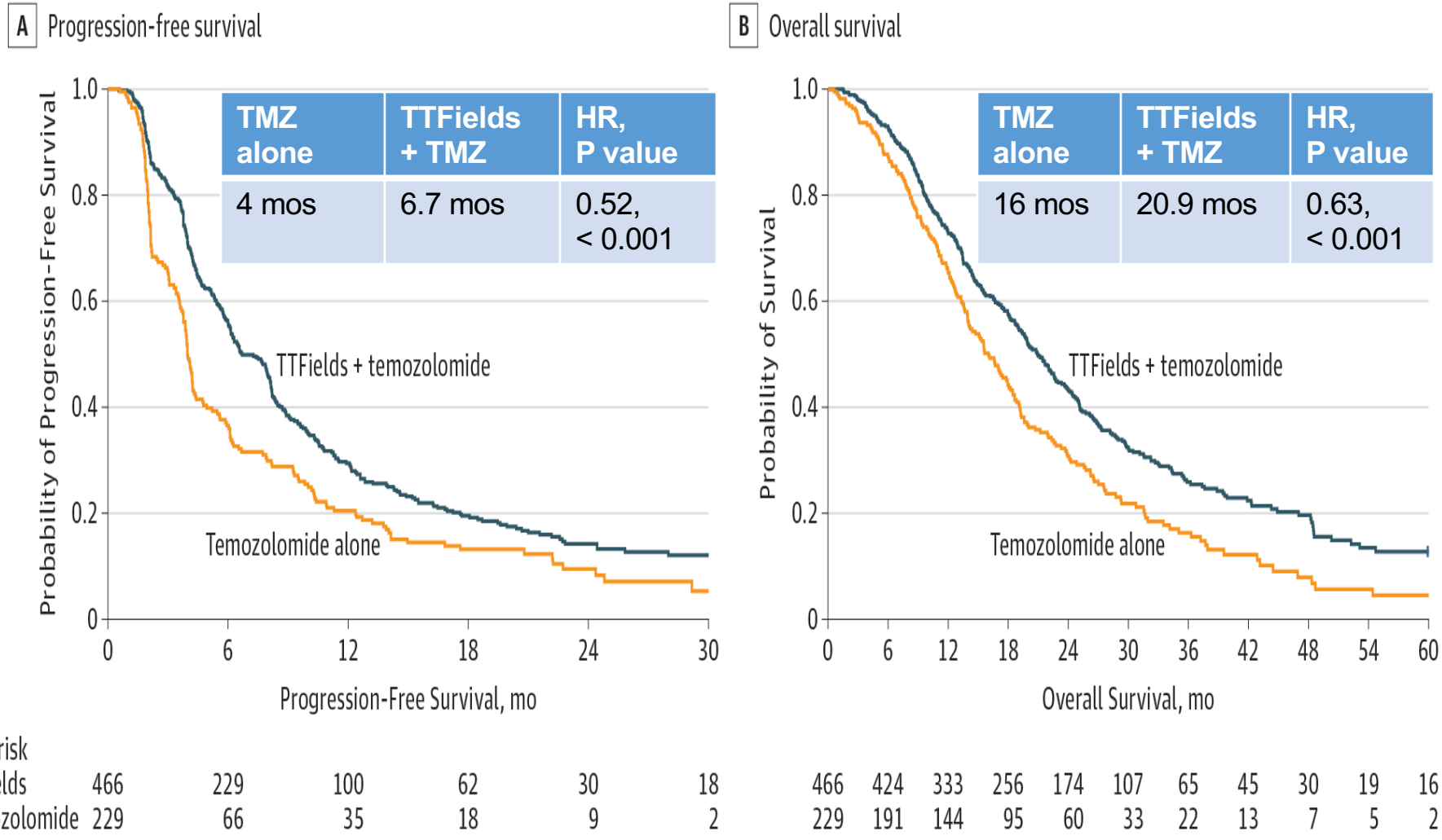
	Lomustine alone	Lomustine/Bevacizumab
OS	9.1 months	8.6 months
HR	0.95	
95% confidence interval	0.74 – 1.21	
P value	0.65	





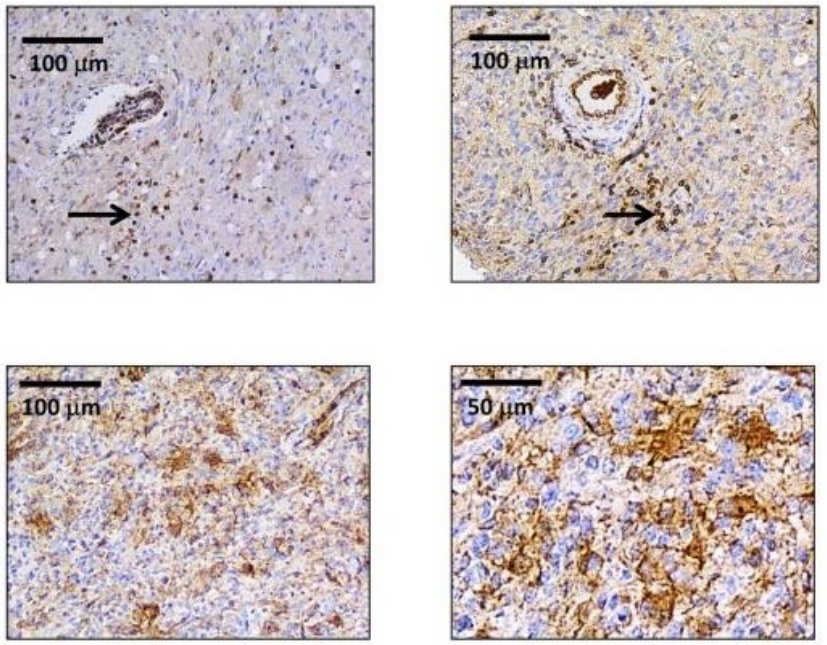
Wolfgang E et al. N Engl J Med 377: 1954, 2017

Progression-Free and Overall survival with Tumor Treating (TT) Fields + Temozolomide (TMZ) versus TMZ alone was significantly higher at the 2-year landmark analysis and remained higher at 5 years (EF-14 Trial) Median followup 44 months



PD-L1 expression in GBM: common, but weak

- 60% of GBMs are tumor cell PD-L1+
- However, median % of PD-L1+ tumor cells in GBM by cell surface staining is only 2.8%
  - ~40% have ≥ 5% expression
  - ~20% have ≥ 25% expression
  - ~5% have ≥ 50% expression



Nduom et al, *Neuro Oncol* 2016

Randomized Phase 3 Study: Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma (CheckMate 143)

- **N=369** patients with no prior VEGF therapy
- **Randomized 1:1: nivolumab 3 mg/kg every 2 weeks** or **bevacizumab 10 mg/kg every 2 weeks**
  - At baseline in both arms, ~80% of patients had measurable disease and ~40% of patients required corticosteroids
- **Grade 3–4 treatment-related adverse events:**
  - 18% (nivolumab)
  - 15% (bevacizumab)
- **Primary endpoint was overall survival (OS) – no difference in median OS or OS rate at 12 months**
  - Also no difference in multiple subgroup analyses (e.g. PD-L1 expression at cut-off of 1%)

Reardon DA et al, World Federation of Neuro-Oncology Societies Quadrennial Meeting Zurich, Switzerland 2017

Bevacizumab in recurrent Glioblastoma Multiforme

FDA approval in recurrent disease in 2009 based on 2 phase II studies:
BRAIN Trial: J Clin Oncol 2009
Phase II
167 patients with recurrent disease: Bevacizumab alone or with irinotecan

	6 months PFE	RR
Bevacizumab	43%	28%
Bevacizumab/Irinotecan	50%	38%

Bevacizumab decreases the need to escalate the corticosteroid dosage.
Intracranial hemorrhage 4% with bevacizumab + Irinotecan
Grade 3 or greater: Hypertension 8%, convulsions 6% and fatigue 90%

Low Grade (Grade 2) Gliomas

Radiation plus Procarbazine, CCNU, and Vincristine (PCV) in Grade 2 Glioma (RTOG 9802)

- Patients with **grade 2** astrocytoma, oligoastrocytoma, or oligodendroglioma who were younger than 40 years of age and had undergone subtotal resection or biopsy or who were 40 years of age or older and had undergone biopsy or resection of any of the tumor.

- Patients were stratified according to age, histologic findings, Karnofsky performance-status score, and presence or absence of contrast enhancement on preoperative images. Patients were randomly assigned to **radiation therapy alone (XRT alone)** or to **radiation therapy followed by six cycles of combination chemotherapy (XRT/PCV)**.

- 251 eligible patients: 125 patients XRT/PCV and 126 patients XRT alone

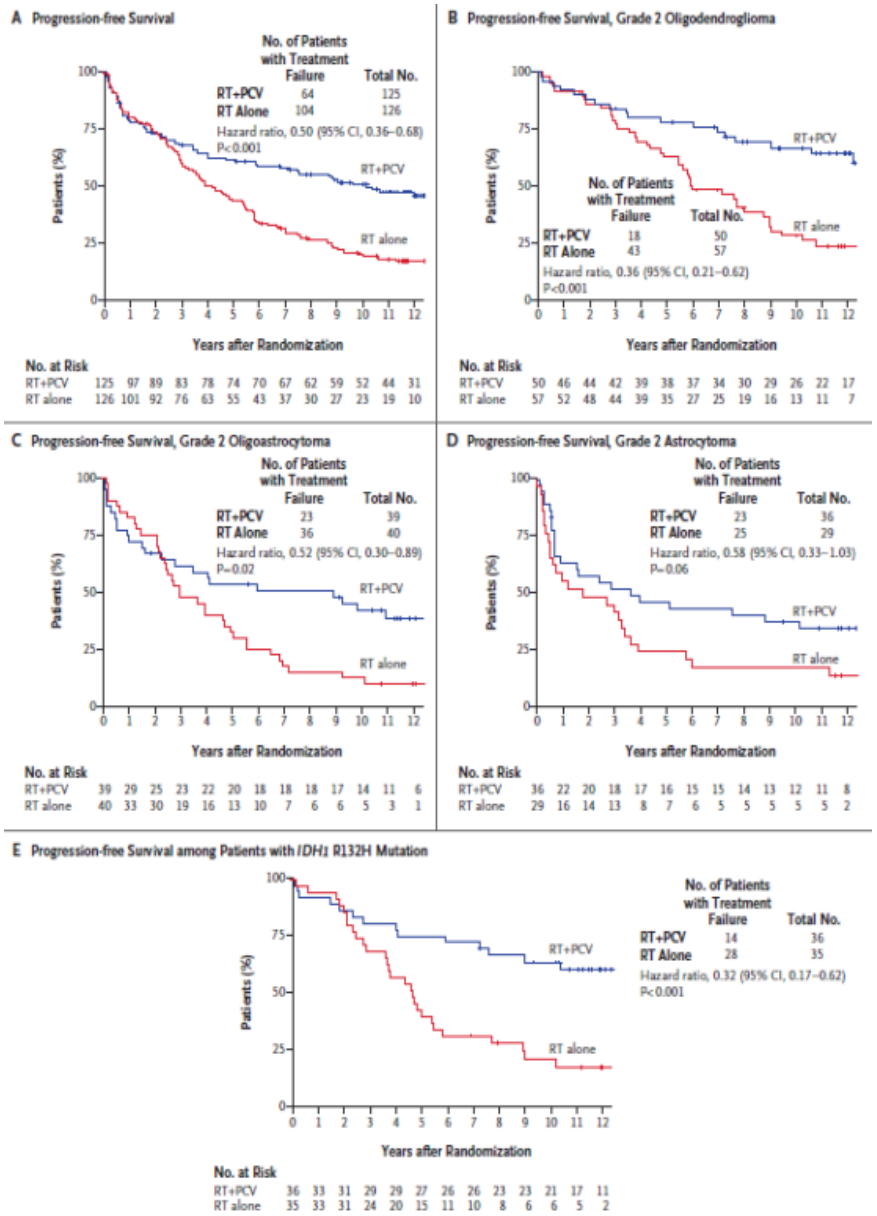
- Enrolled: 1998 through 2002. Median follow up 11.9 years

Buckner JC et al. N Engl J Med 374: 1344, 2016

Progression-free Survival According to Treatment Group

XRT/PCV versus XRT alone

	HR	P value
All patients	0.50	< 0.001
Grade 2 oligodendroglioma	0.36	< 0.001
Grade 2 oligoastrocytoma	0.52	0.02
Grade 2 astrocytoma	0.56	0.06
IDH1 R132H mutation	0.32	< 0.001



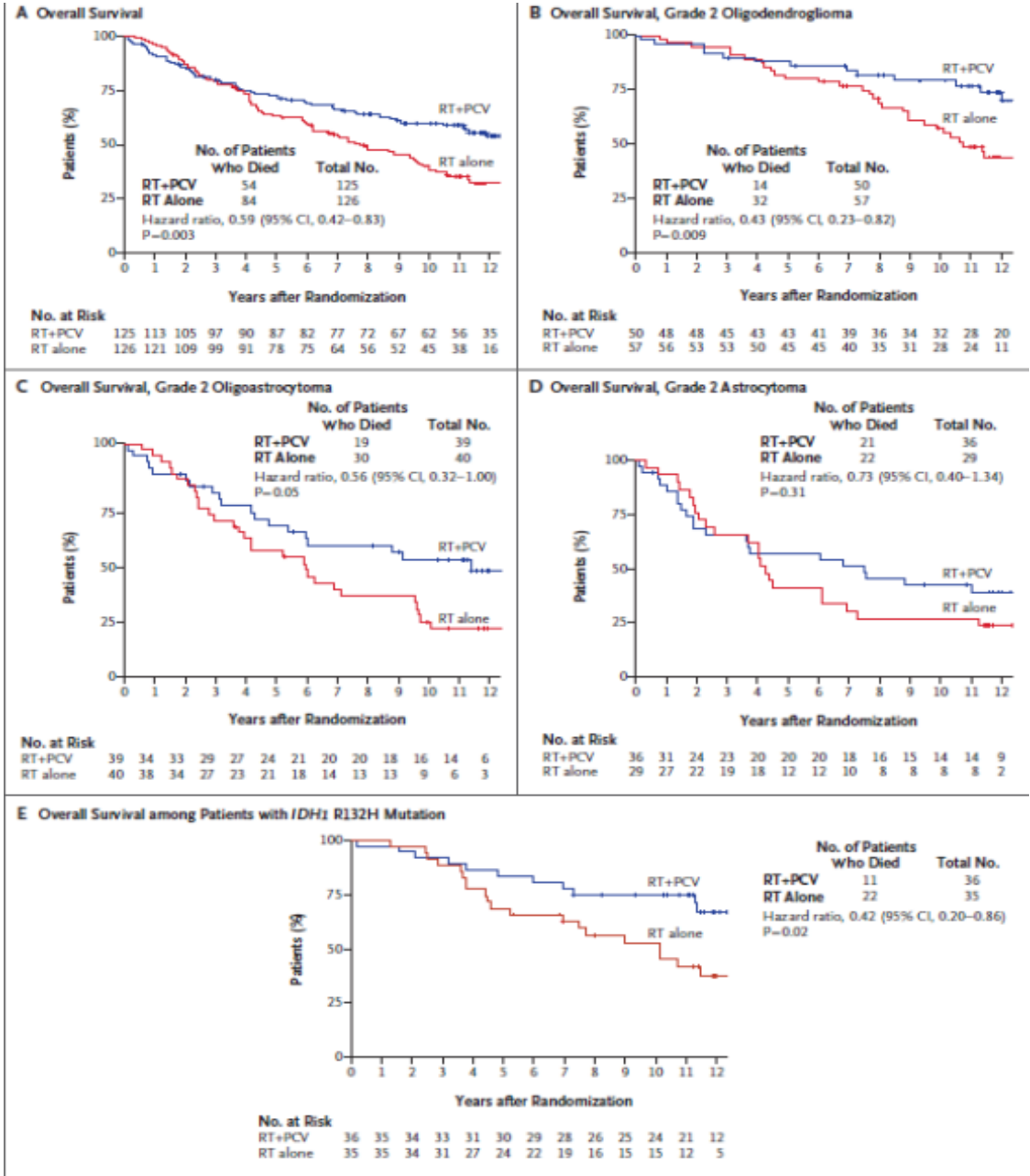
Buckner JC et al. N Engl J Med 374: 1344, 2016

Overall Survival According to Treatment Group

XRT/PCV versus XRT alone

	HR	P value
All patients	0.59	0.003
Grade 2 oligodendroglioma	0.43	0.009
Grade 2 oligoastrocytoma	0.56	0.05
Grade 2 astrocytoma	0.73	0.31
IDH1 R132H mutation	0.42	0.02

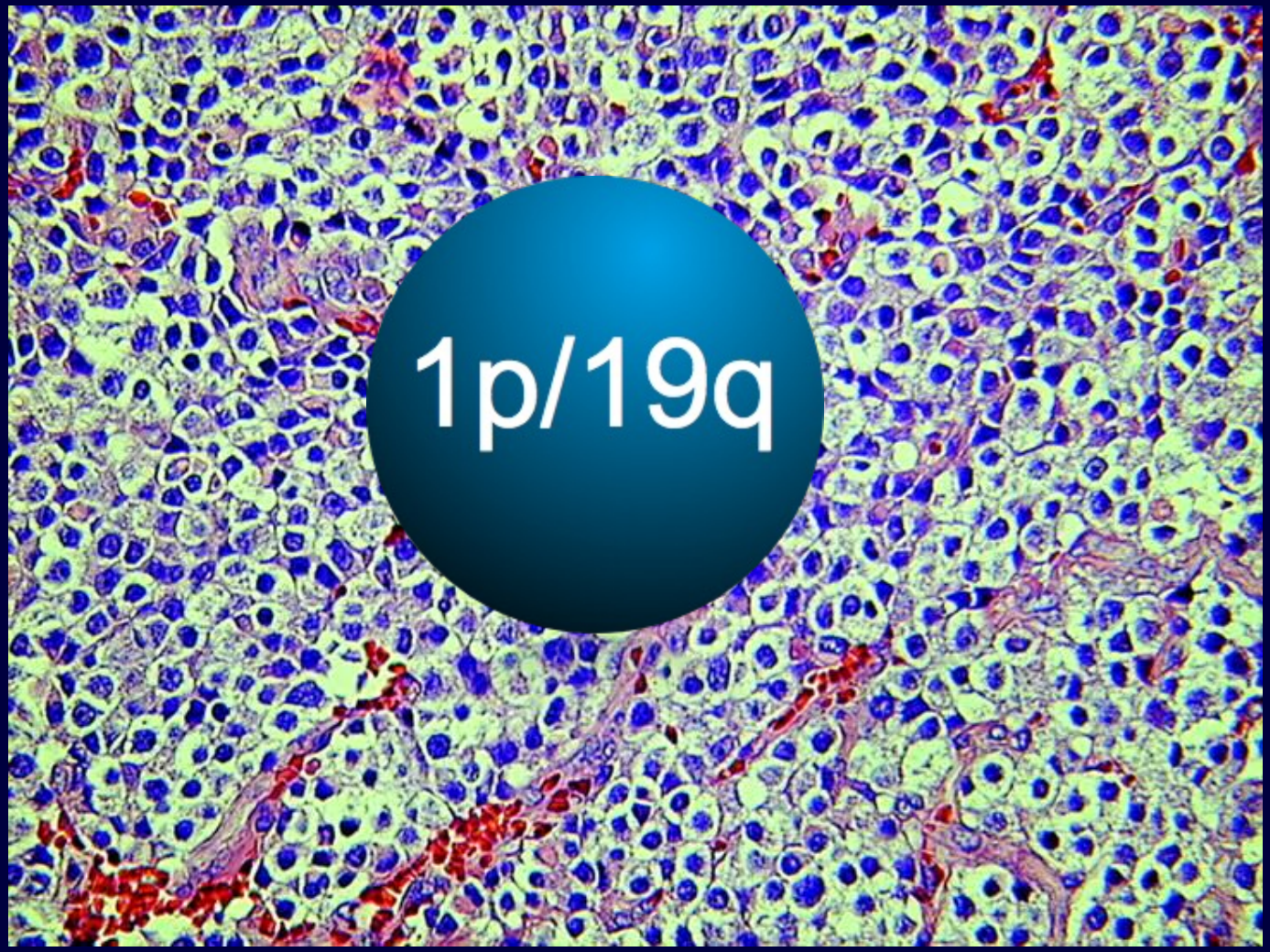
10 year overall Survival
XRT/PCV: 60%
XRT alone: 40%



Buckner JC et al. N Engl J Med 374: 1344, 2016

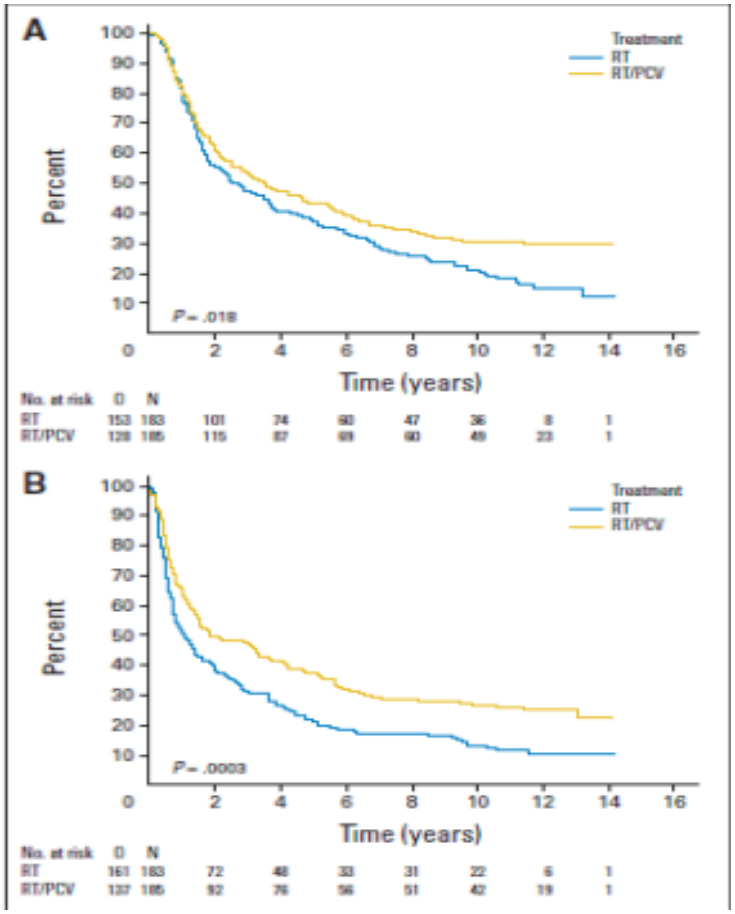
Oligodendrogliomas

Biomarkers in malignant glioma: 1p/19q codeletions



Classic oligodendroglial tumor, with fried egg appearance (which actually is an artificial fixation artifact).

Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951



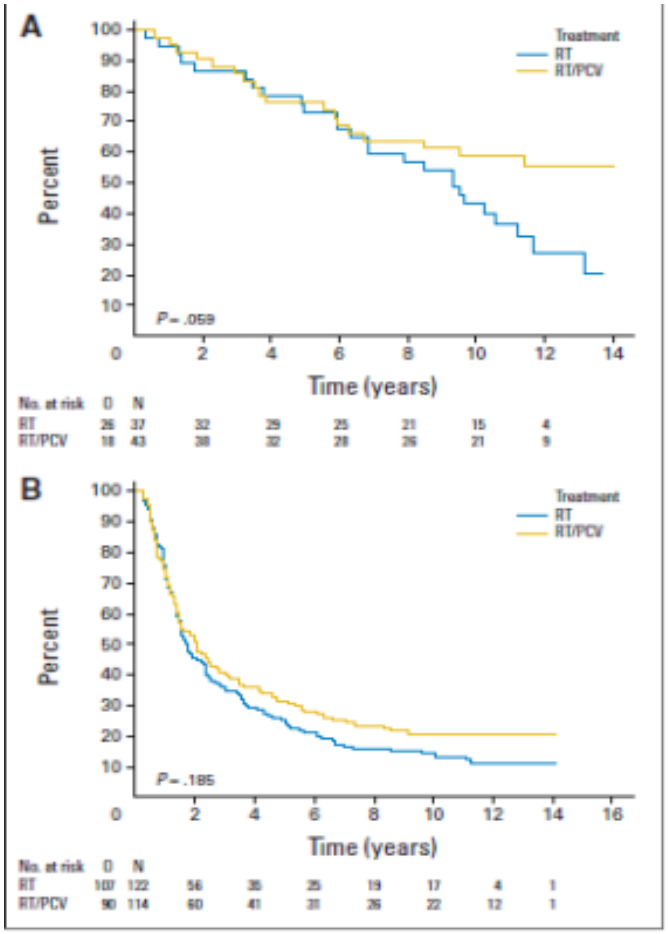
Median follow-up: 140 months (All Patients)

	Overall Survival	Progression-Free Survival
RT alone	30.6 months	13.2 months
RT/PCV	42.3 months	24.3 months
HR	0.75	0.66
95% confidence intervals	0.60 – 0.95	0.52 – 0.83

(A) Overall survival and (B) progression-free survival in both treatment arms in the intent-to-treat population. N, total number of events; O, observed events; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

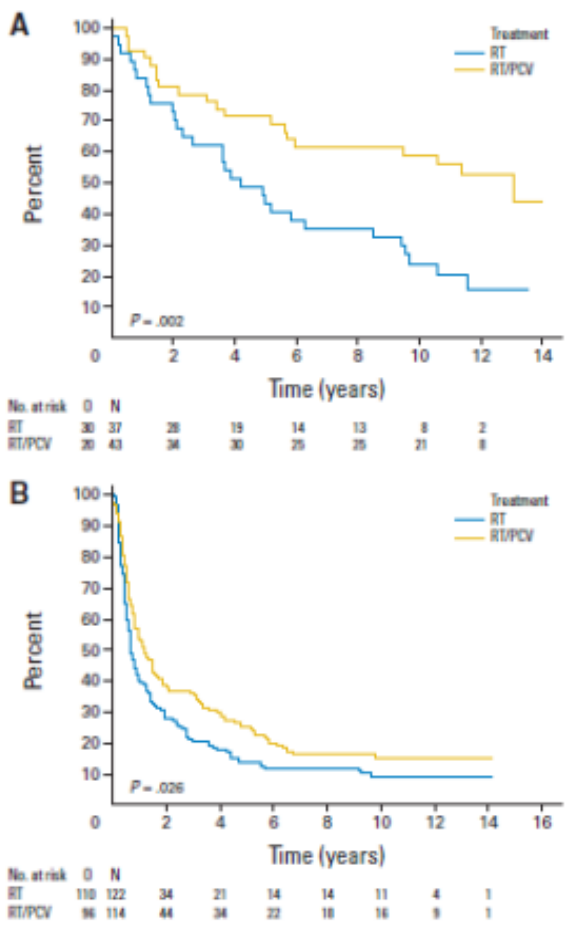
Van den Bent MJ et al. J Clin Oncol 31: 344, 20212.

Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951



patients with 1p/19q-codeleted tumors

patients with non–1p/19q-codeleted tumors



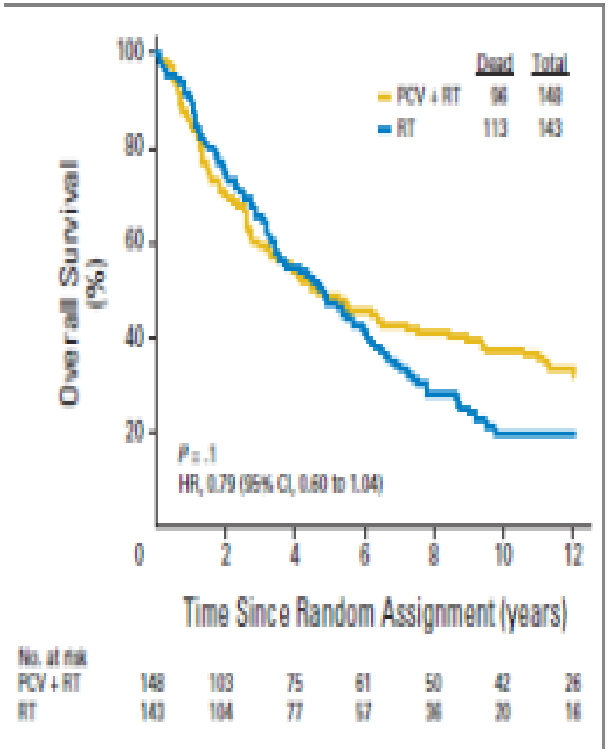
Overall survival in both treatment arms for (A) the patients with 1p/19q-codeleted tumors (n = 80) and (B) the patients with non–1p/19q- codeleted tumors (n = 236). N, total number of events; O, observed events; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

Progression-free survival in both treatment arms for (A) patients with 1p/19q-codeleted tumors (n = 80) and (B) patients with non–1p/19q-codeleted tumors (n = 236). N, total number of events; O, observed events; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy.

Van den Bent MJ et al. J Clin Oncol 31: 344, 20212.

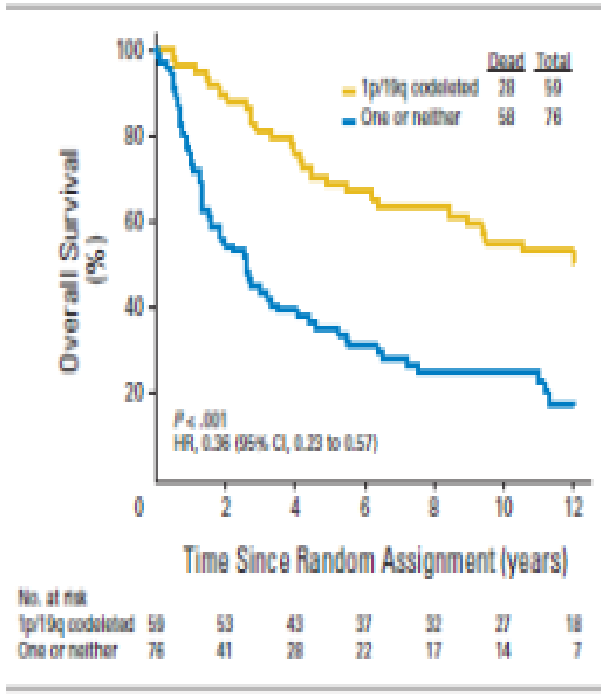
Phase III Trial of Chemoradiotherapy for Anaplastic Oligodendroglioma: Long-Term Results of RTOG 9402

All patients



Kaplan-Meier estimates of **overall survival** by treatment group. The **hazard ratio (HR)** for survival of patients treated with procarbazine, lomustine, and vincristine (PCV) plus radiotherapy (RT) compared with RT alone was **0.79 (95% CI, 0.60 to 1.04; *P* = .1)**.

Patients with 1p/19q co-deletions



Kaplan-Meier estimates of **overall survival** by genotype for procarbazine, lomustine, and vincristine plus radiotherapy arm. The **hazard ratio (HR)** for overall survival of patients with 1p/19q codeleted anaplastic oligodendroglioma (AO)/ anaplastic oligoastrocytoma (AOA) compared with those with AO/AOA in whom one or neither allele was deleted was **0.36 (95% CI, 0.23 to 0.57; *P* < .001)**.

Cairncross G et al. J Clin Oncol 31: 337, 2012

CODEL: Phase III study of RT, RT + Temozolomide (TMZ), or TMZ for newly-diagnosed 1p/19q Codeleted Oligodendroglioma. Analysis from the initial study design

Adults (>18) with newly-diagnosed 1p/19q WHO grade III oligodendroglioma were randomized to

- RT alone
- RT with concomitant and adjuvant temozolomide (TMZ)
- TMZ alone

TMZ-alone patients experienced significantly shorter progression-free survival than patients treated on the RT Arms.

The ongoing CODEL trial has been redesigned to compare

- RT+PCV versus
- RT+TMZ.

Jaeckle KA et al. Neuro oncol July 17, 2020

Grade III (Anaplastic) Gliomas without 1p/19q codeletion

EORTC

The future of cancer therapy

Second interim and 1st molecular analysis of the EORTC randomized phase III intergroup CATNON trial on concurrent and adjuvant temozolomide in anaplastic glioma without 1p/19q codeletion

M J van den Bent, S Erridge, M A Vogelbaum, AK Nowak, M Sanson, A A Brandes, W Wick, P M Clement, J F Baurain, W Mason, H Wheeler, M Weller, K Aldape, P Wesseling, J M Kros, C M S Tesileanu, V Golfinopoulos, T Gorlia, B G Baumert, P French

on behalf of the EORTC Brain Tumor Group and partners

NOA Neuroonkologische Arbeitsgemeinschaft

NRG ONCOLOGY *Advancing Research. Improving Lives.™*

MRC Medical Research Council

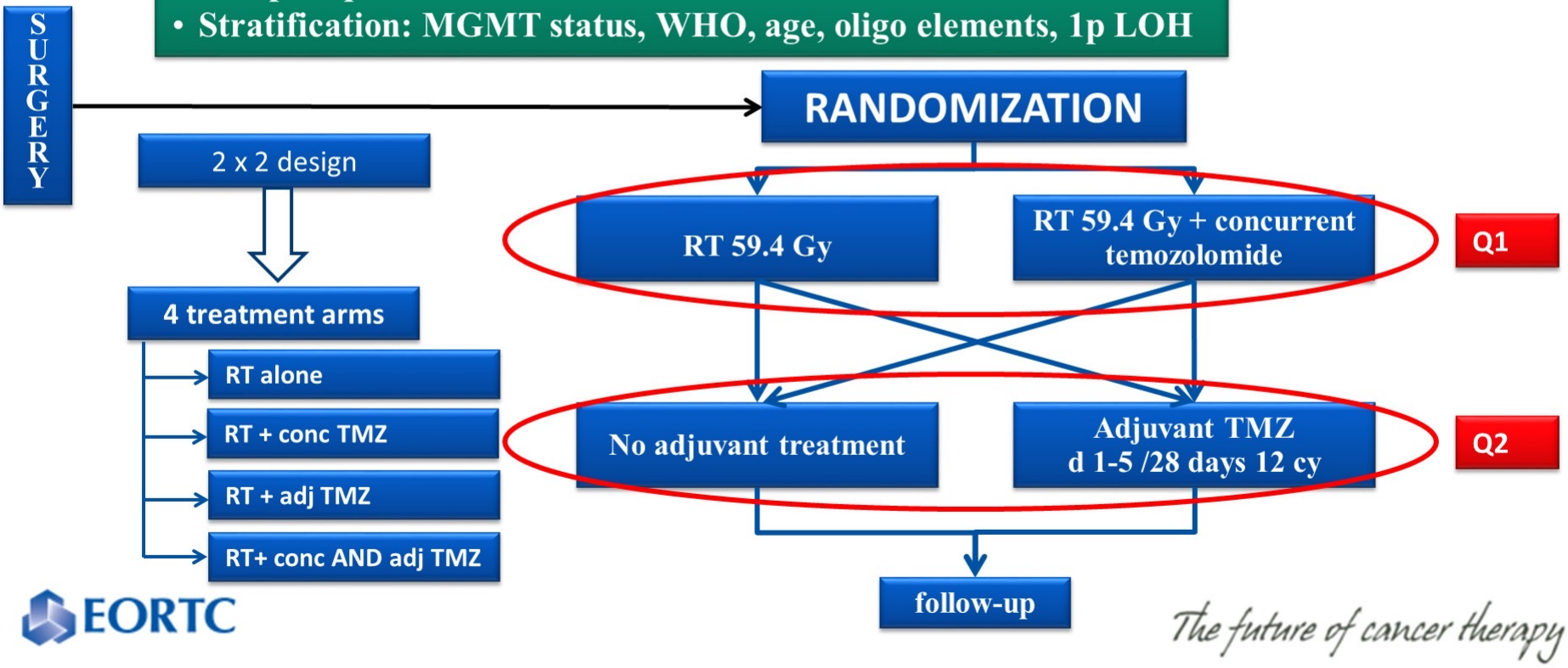
COGNO COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY

Canadian Cancer Trials Group

Presented By Martin Van Den Bent at 2019 ASCO Annual Meeting

Intergroup phase III trial on concurrent and adjuvant temozolomide in non-1p/19q deleted anaplastic glioma

- Centrally confirmed grade III glioma
- No 1p/19q co-deletion
- Stratification: MGMT status, WHO, age, oligo elements, 1p LOH



751 adult patients were randomized

Presented By Martin Van Den Bent at 2019 ASCO Annual Meeting

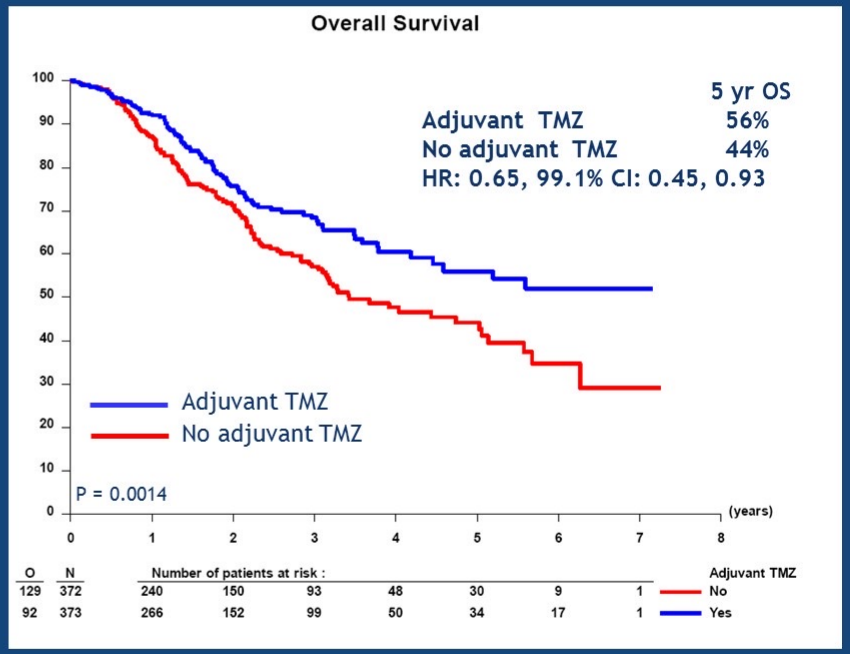
IDMC recommendation Oct 2015: release the results of the adjuvant temozolomide treatment

Median FU: 27.4 mos

- Preplanned at the time 41% of the required events were observed (n = 221)
  - Occured with 745 pts randomized
  - Median follow-up: 27.4 mo (31/5/2015)

➢Significant increase in OS after adjuvant temozolomide

➢HR 0.65, 99.1% CI 0.45, 0.93

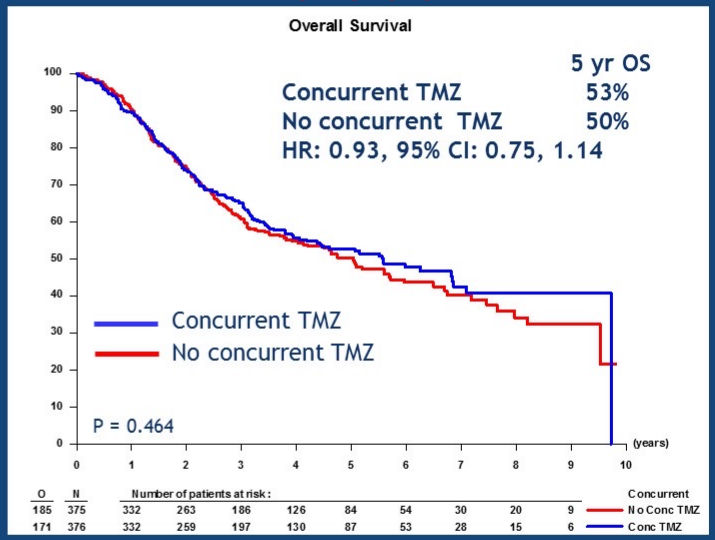


van den Bent et al, Lancet 2017;390:1645-53

CATNON 2nd interim analysis: primary endpoint and univariate analysis

Median FU: 55.6 mos
HR 0.968

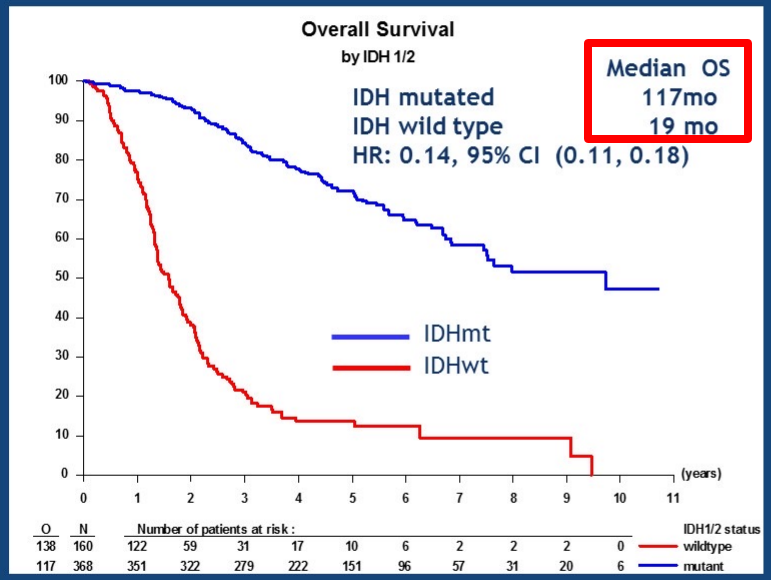
Parameter	p- value	HR	HR 99.1% CI
Concurrent TMZ	**0.7634**	**0.968**	**0.73, 1.23**
Age (>50 vs <=50%)	<.0001	3.42	2.56, 4.57
WHO PS (>0 vs 0%)	<.0001	1.53	1.15, 2.03
1p LOH (Yes vs No%)	0.2153	1.28	0.76, 2.13
Oligodendroglial elements (Yes vs No%)	0.7279	1.04	0.76, 1.44
MGMT Methylated vs Unmethylated	0.0020	0.57	0.35, 0.92
MGMT Undetermined/invalid vs unmethylated	0.0392	0.78	0.56, 1.07



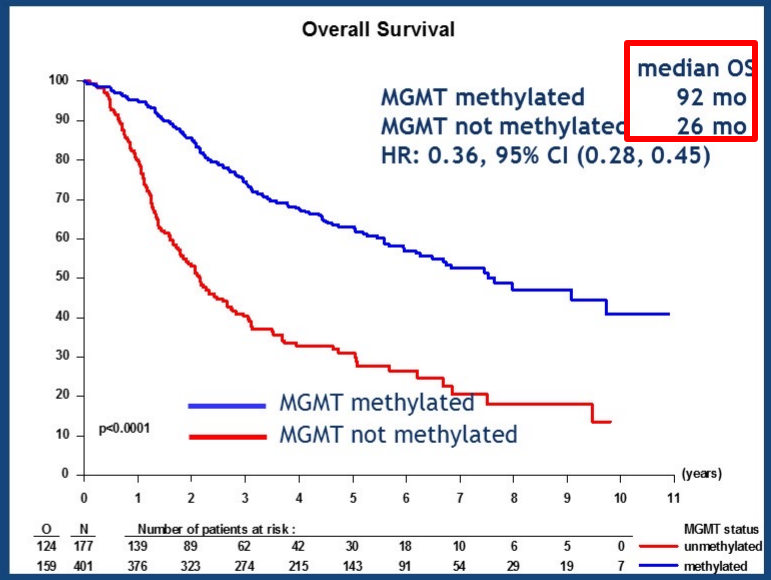
Primary endpoint: OS, Cox model adjusted for stratification factors

Impact of IDH, MGMT promoter on Overall Survival

IDH mutational status



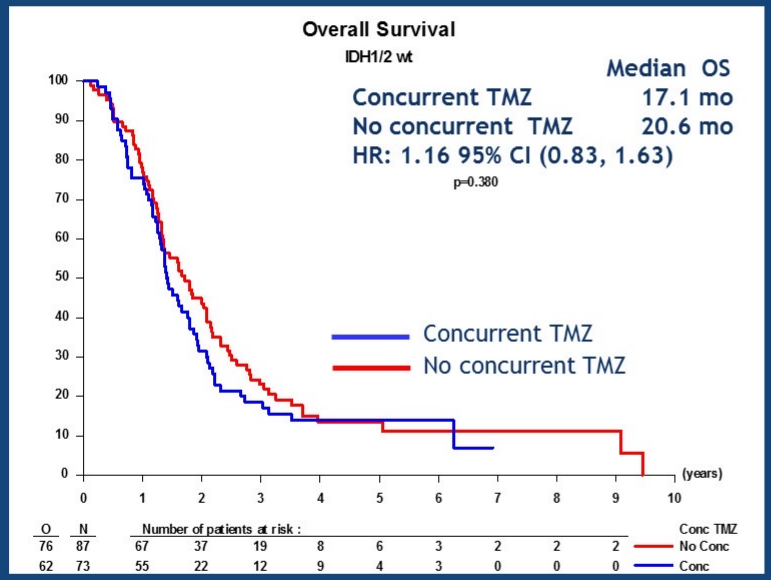
MGTM methylation status



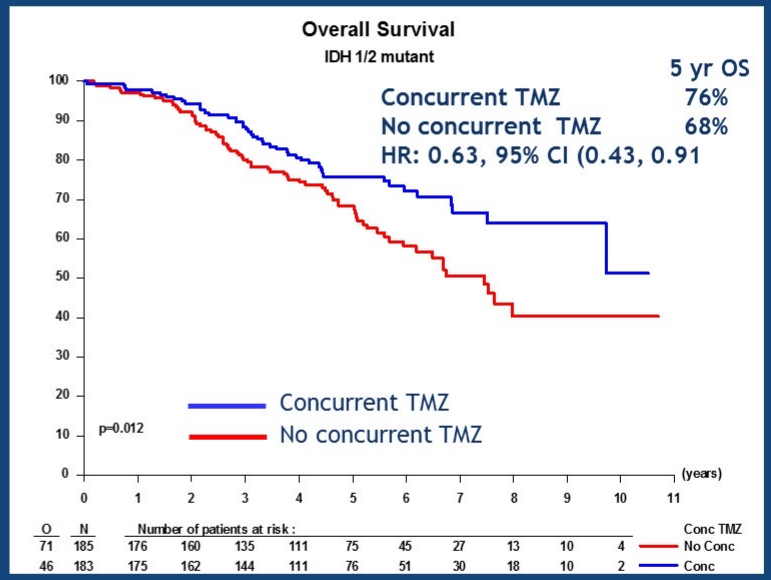
- IDH mutational status stronger correlation with outcome than MGMT promoter methylation status

Concurrent temozolomide in IDHwt and IDHmt anaplastic astrocytoma

IDH wild type



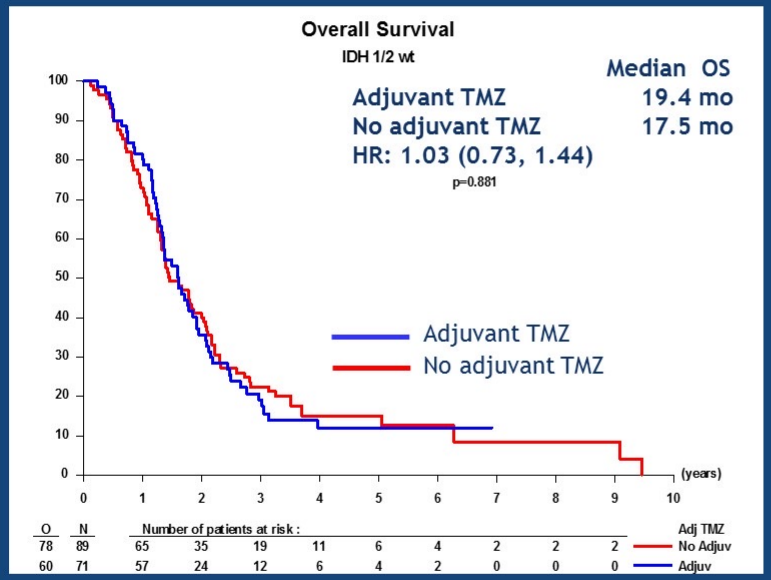
IDH mutant



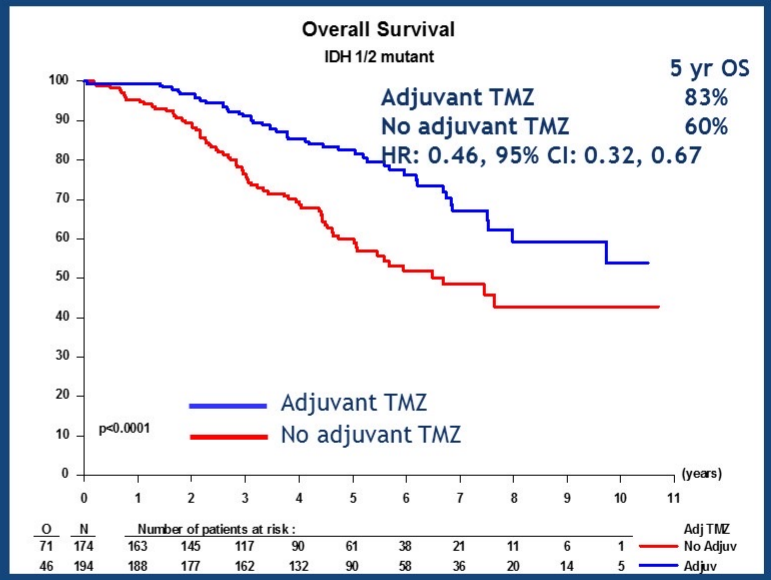
- Concurrent temozolomide improves outcome in IDH mutant anaplastic astrocytoma

Adjuvant temozolomide in IDHwt and IDHmt anaplastic astrocytoma

IDH wild type



IDH mutant



- Adjuvant temozolomide improves outcome in IDH mutant anaplastic astrocytoma

IDH1 inhibitor

Phase I study of a brain penetrant mutant IDH1 inhibitor DS-1001b in patients with recurrent or progressive IDH1 mutant gliomas

Atsushi Natsume, MD, PhD[1], Toshihiko Wakabayashi, MD, PhD[1], Yasuji Miyakita, MD, PhD[2], Yoshitaka Narita, MD, PhD[2], Yohei Mineharu, MD, PhD[3], Yoshiki Arakawa, MD, PhD[3], Fumiyuki Yamasaki, MD, PhD[4], Kazuhiko Sugiyama, MD, PhD[4], Nobuhiro Hata, MD, PhD[5], Yoshihiro Muragaki, MD, PhD[6], Ryo Nishikawa, MD, PhD[7], Naoki Shinojima, MD, PhD[8], Toshihiro Kumabe, MD, PhD[9], Ryuta Saito, MD, PhD[10], Kazumi Ito, DVM, PhD[11], Masaya Tachibana, PhD[11], Yasuyuki Kakurai, PhD[11], Soichiro Nishijima, MS[11], Hiroshi Tsubouchi, MS[11]

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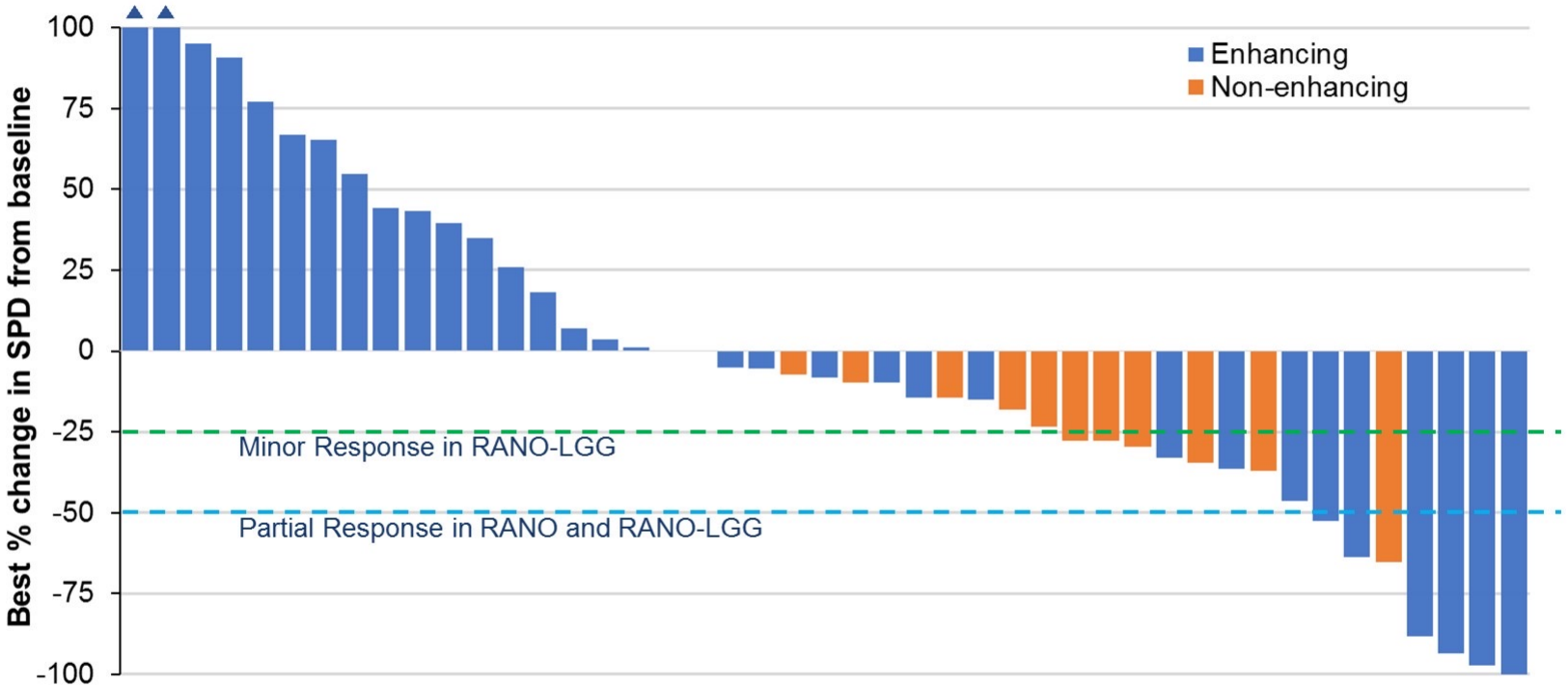
Presented By Atsushi Natsume at 2019 ASCO Annual Meeting

Best Percent Change in SPD from Baseline



Data cutoff was on May 7, 2019.
Enhancing gliomas were assessed by RANO criteria, and non-enhancing gliomas were assessed by RANO-LGG criteria.
▲ These two patients showed change over 100% (188% and 155%).
LGG = low-grade gliomas; RANO = Response Assessment in Neuro-Oncology; SPD = sum of the products of perpendicular diameters.

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Soft Tissue Sarcomas

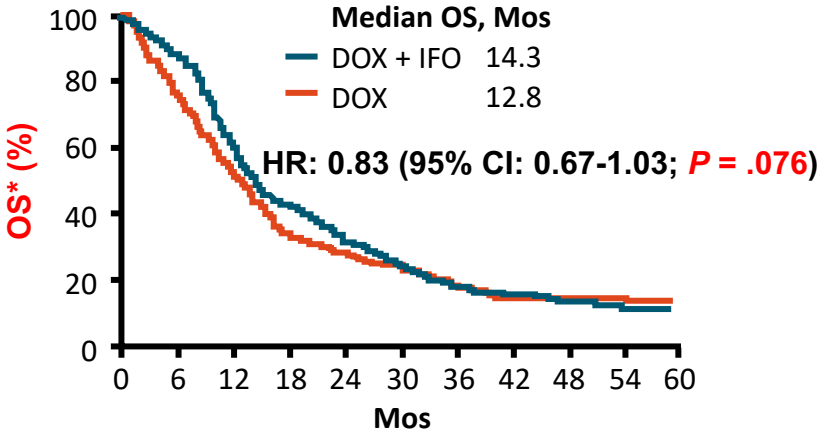
Contemporary Systemic Options for Patients With Chemotherapy-Sensitive Unresectable/Metastatic STS

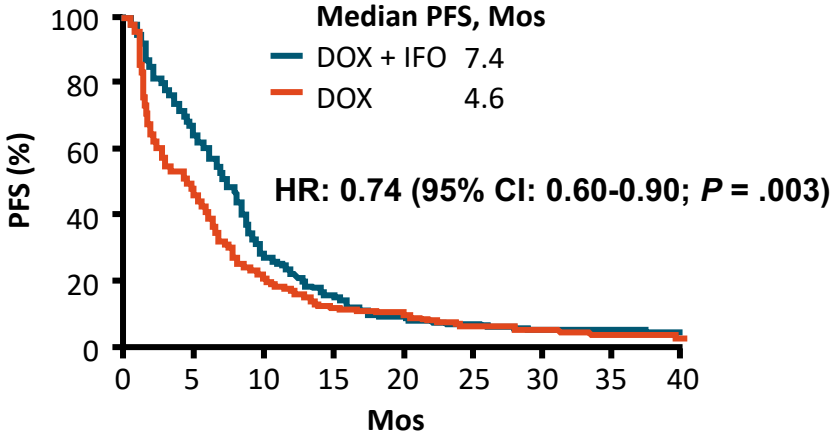
Agent/Combination	Key Trials
First-line Options	
Doxorubicin ± ifosfamide	EORTC 62012
Gemcitabine + docetaxel	GeDDiS
Additional: doxorubicin + dacarbazine, liposomal doxorubicin	
Second-line Options and Beyond	
Any of the above treatment options, or:	
Eribulin	Schöffski et al
Pazopanib	PALETTE
Trabectedin	Demetri et al
Gemcitabine + dacarbazine	García-Del-Muro et al
Additional: ifosfamide, gemcitabine + vinorelbine, paclitaxel, palbociclib	

Judson I et al. Lancet Oncol. 2014;15:415. Seddon B et al. Lancet Oncol. 2017;18:1397. Schöffski P et al. Lancet. 2016;387:1629. van der Graaf TA et al. Lancet. 2012;379:1879. Demetri GD et al. JCO. 2016;34:786. García-Del-Muro X et al. J Cin Oncol. 2011;29:2528.

EORTC 62012: Doxorubicin + Ifosfamide vs Doxorubicin for Advanced/Unresectable Soft Tissue Sarcoma

- Multicenter, randomized, active-controlled phase III trial of **doxorubicin 75 mg/m^2 divided over 3 days + ifosfamide 10 g/m^2 IV divided over 4 days** vs **doxorubicin** for fit patients aged 18-60 yrs with locally advanced, unresectable, or metastatic, high-grade STS (N = 455)





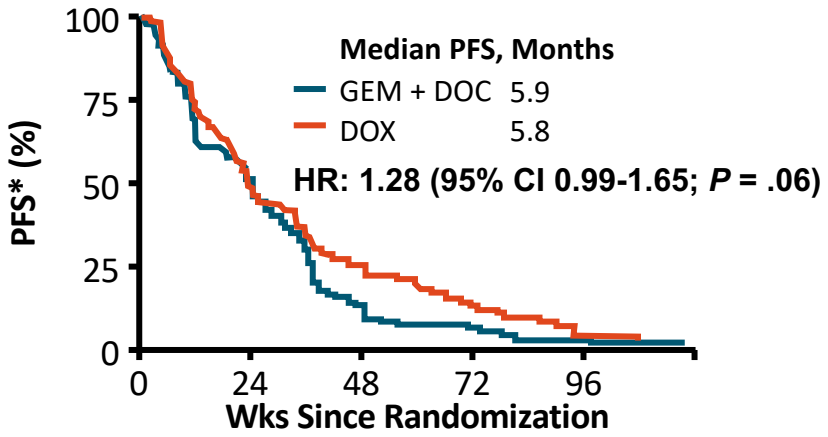
- DOX + IFO vs DOX: 1-yr OS, 60% vs 51%; 2-yr OS, 31% vs 28%; **ORR: 26% vs 14%**, *P* = .0006
- Patients in DOX arm more likely to receive postprotocol IFO

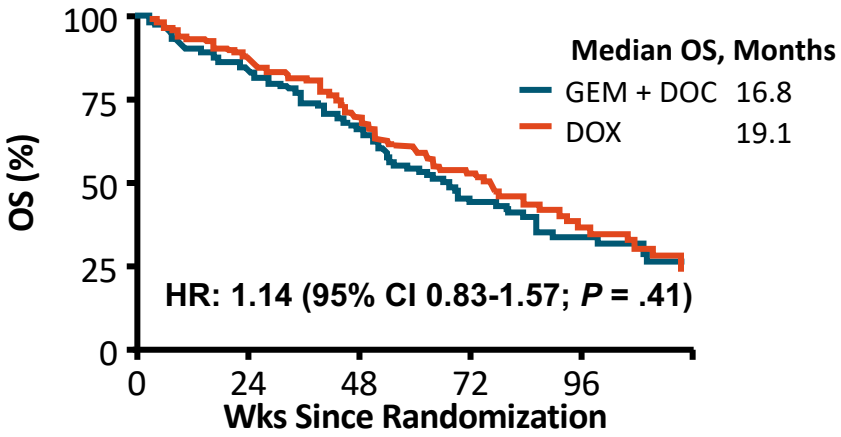
Median follow-up: 56 mos. STS subtypes: LMS, 25%; LPS, 13%; SS, 14%; other, 49%.
*: Primary endpoint was OS in the intention-to-treat population.

Judson I et al. Lancet Oncol. 2014;15:415.

GeDDiS: Gemcitabine + Docetaxel vs Doxorubicin for Advanced Soft Tissue Sarcoma

- Multicenter, randomized, active-controlled phase III trial of **gemcitabine 675 mg/m^2 IV days 1 and 8 + docetaxel 75 mg/m^2 IV day 1** vs **doxorubicin 75 mg/m^2 IV** for fit patients aged ≥ 13 yrs with previously untreated locally advanced or metastatic STS (N = 257)





Subgroup Analysis, PFS	HR (95% CI), GEM + DOC vs DOX	Interaction *P* Value
LMS (n = 118)	1.06 (0.73-1.55)	.14
Non-LMS (n = 139)	1.56 (1.10-2.21)	

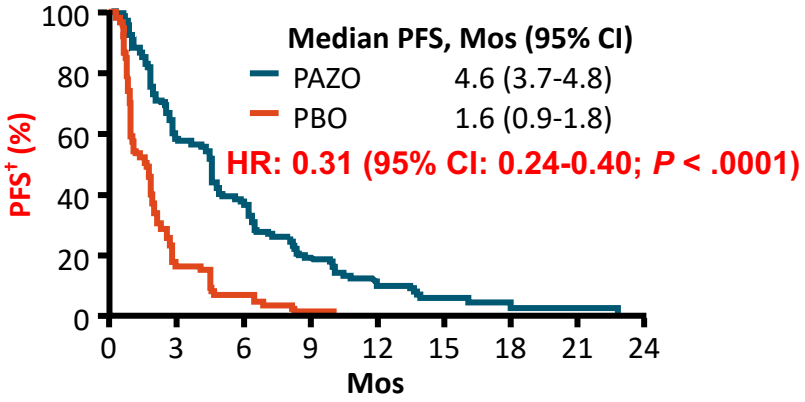
- **GEM + DOC vs DOX, ORR: 20% vs 19%**

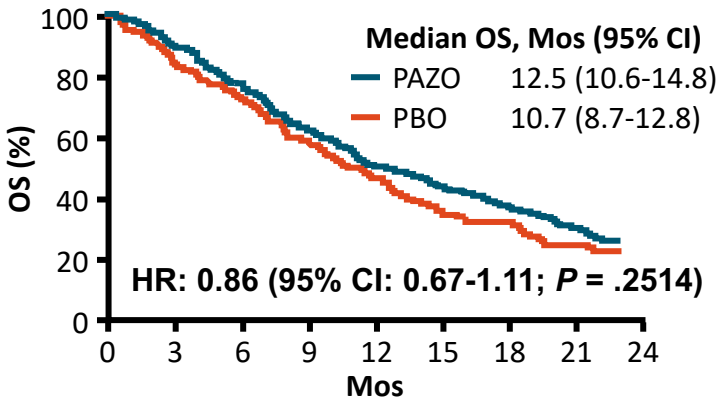
Median follow-up: 22 mos. STS subtypes: uterine LMS, 28%; pleomorphic sarcoma, 12%; other, 60%. *Primary endpoint (24 wks).

Seddon B et al. Lancet Oncol. 2017;18:1397.

PALETTE: Pazopanib for Treating Metastatic Soft Tissue Sarcoma

- Randomized, double-blind phase III trial in which fit adult patients with metastatic STS* and PD despite ≤ 4 prior systemic therapies treated with **pazopanib 800 mg PO daily** or **placebo** (N = 369)





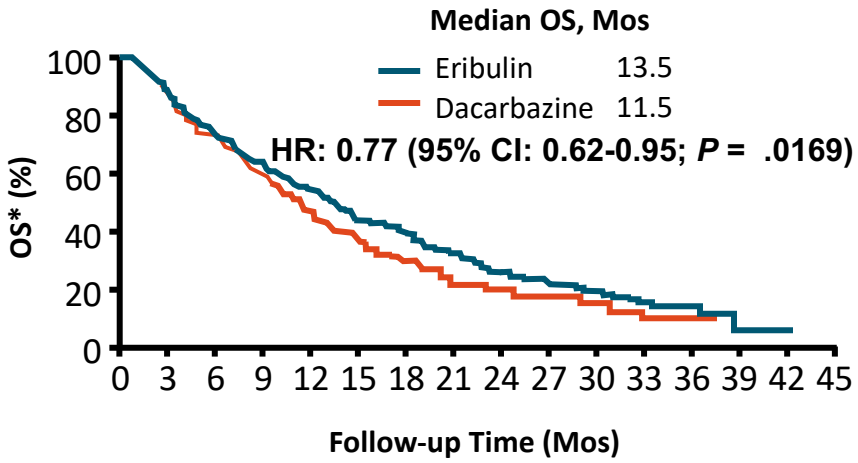
- Pazopanib similarly improved survival (vs placebo) for LMS, synovial sarcoma, and other sarcomas
- Pazopanib FDA approved for treating patients with advanced STS who have received prior chemotherapy (limitation of use: not assessed in adipocytic STS or GIST)

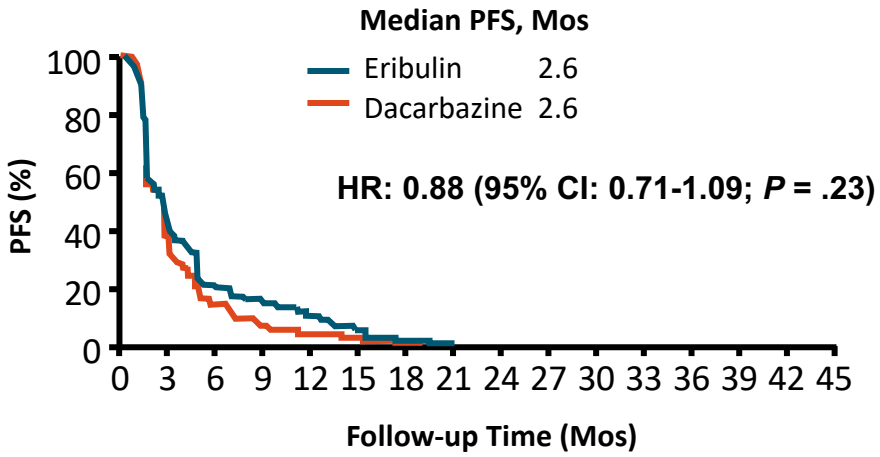
Pazopanib: **oral multi-tyrosine kinase inhibitor targeting VEGFR-1, -2, -3, PDGFRα, and others.**
Median follow-up: 14.6 mos. *Excluded: adipocytic sarcoma, bone sarcomas, GIST, others. †Primary endpoint.

van der Graaf TA et al. Lancet. 2012;379:1879.

Eribulin vs Dacarbazine for Advanced Leiomyosarcoma and Liposarcoma

- Randomized, open-label phase III trial in which adult patients with locally recurrent/advanced or metastatic LMS or LPS and ≥ 2 prior systemic therapies treated with **eribulin** or **dacarbazine** (N = 452)





Median OS by Histology, Mos (Events/Patients)	Eribulin	Dacarbazine	HR (95% CI)
Liposarcoma	15.6 (52/71)	8.4 (63/72)	**0.51 (0.35-0.75)**
Leiomyosarcoma	12.7 (124/157)	13 (118/152)	**0.93 (0.71-1.20)**

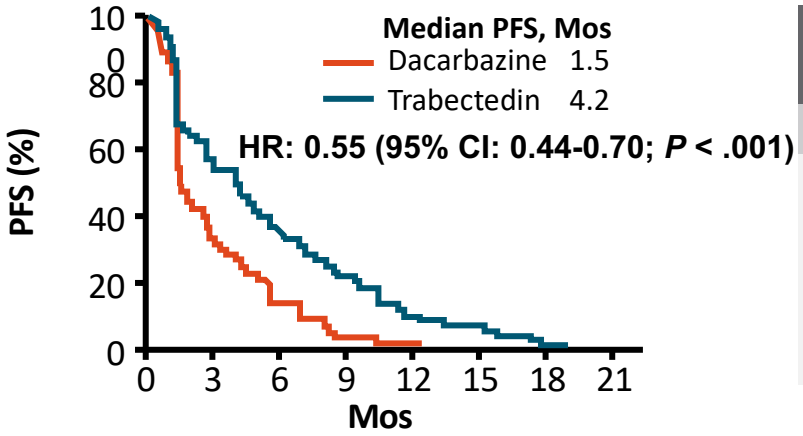
- **Eribulin FDA approved for treating patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen**

Eribulin: IV microtubule dynamics inhibitor. Median follow-up: 31 mos. *Primary endpoint.

Schöffski P et al. Lancet. 2016;387:1629.

Trabectedin vs Dacarbazine for Advanced Liposarcoma or Leiomyosarcoma

- Randomized, open-label phase III trial in which fit pts with unresectable locally advanced or metastatic LPS or LMS (despite anthracycline therapy) treated with **trabectedin** vs **dacarbazine** (N = 518)



Median PFS by Histologic Subtype, Mos (Events/Patients)			
Histology	TRAB	DAC	HR (95% CI)
Leiomyosarcoma	**4.3 (154/252)**	**1.6 (85/126)**	**0.55 (0.42-0.73)**
Liposarcoma	3.0 (63/93)	1.5 (27/47)	0.55 (0.34-0.87)
▪ Dedifferentiated	2.2 (35/45)	1.9 (16/25)	0.68 (0.37-1.25)
▪ **Myxoid ± round cell**	**5.6 (21/38)**	**1.5 (8/19)**	**0.41 (0.17-0.98)**
▪ Pleomorphic	1.5 (7/10)	1.4 (3/3)	0.33 (0.07-1.64)

- **Median OS (primary endpoint) TRAB vs DOX: 12.4 vs 12.9 mos; HR: 0.87 (*P* = .37)**
- Trabectedin FDA approved for treating patients with unresectable or metastatic leiomyosarcoma or liposarcoma who received a prior anthracycline-containing regimen

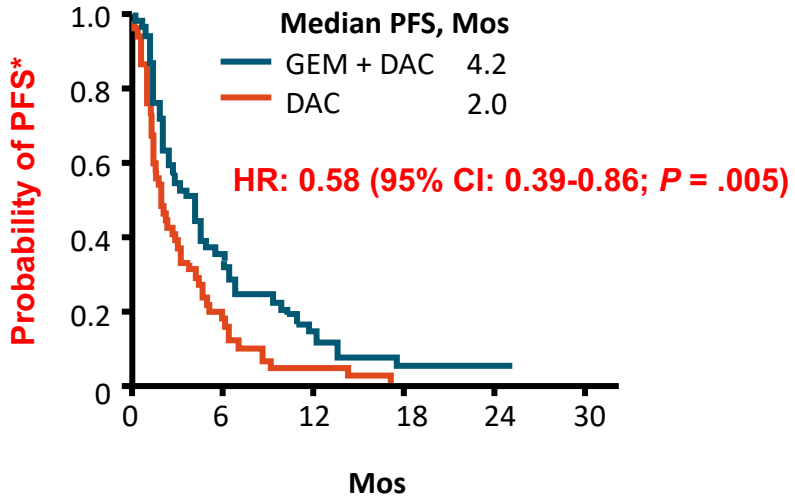
Trabectedin: IV alkylating agent. Median follow-up: 8.6 mos.

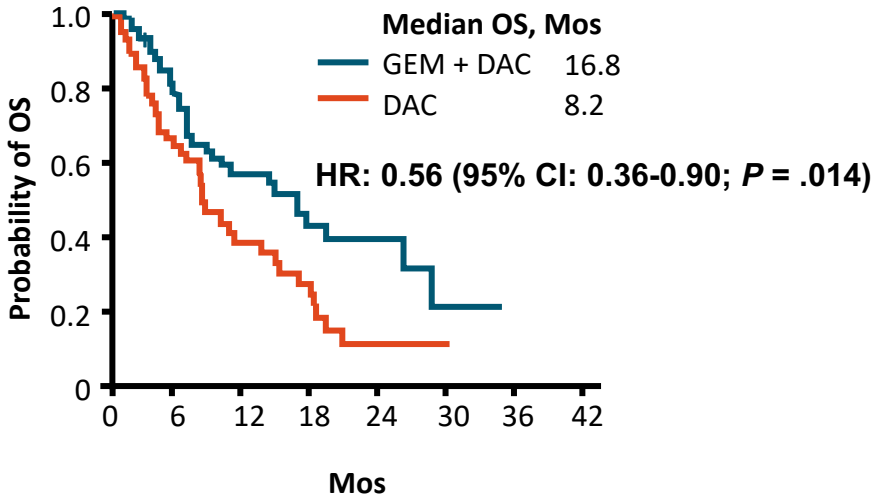
Watch for elevated liver function tests (give dexamethasone prior to infusion) and rhabdomyolysis (check CPK)

Demetri GD et al. JCO. 2016;34:786.

Gemcitabine + Dacarbazine vs Dacarbazine for Previously Treated Advanced Soft Tissue Sarcoma

- Randomized phase II trial in which patients with progressive unresectable or metastatic STS (despite anthracycline and ifosfamide therapy) treated with **GEM + DAC** or **DAC** (N = 113)





- Objective response or stable disease, GEM + DAC vs DAC : 49% vs 25%, *P* = .009
- Most common grade 3/4 events with GEM + DAC (> 10%): leukopenia, neutropenia; similar rates of d/c for AEs between groups: GEM + DAC, 2%; DAC, 4%

Median follow-up: 14-14.5 mos. ***Primary endpoint (3-mo progression-free rate)**.

García-Del-Muro X et al. J Clin Oncol. 2011;29:2528.

Second Line and Beyond Treatment Considerations

Treatment	Considerations
Gemcitabine plus docetaxel	▪ Appropriate second-line option for many patients who received first-line anthracycline-based regimens
Eribulin	▪ Approved for treating patients with unresectable or metastatic LPS who have received a prior anthracycline-containing regimen
Pazopanib	▪ Approved for treating patients with advanced STS who have received prior chemotherapy (not studied in adipocytic STS)
Trabectedin	▪ Approved for treating patients with unresectable or metastatic LPS or LMS who received a prior anthracycline-containing regimen; may be less effective for DDLS, pleomorphic liposarcoma
Gemcitabine plus dacarbazine	▪ Second-line option for patients who received prior anthracycline-based regimens

Systemic Therapy for Chemotherapy-Resistant STS Subtypes

- Targeted agents may be considered in select situations; for example:
  - Clear cell sarcoma or solitary fibrous tumor/hemangiopericytoma: sunitinib
  - Alveolar soft tissue sarcoma: sunitinib, atezolizumab
  - Perivascular epithelioid cell tumor (PEComa): nab-sirolimus
  - Larotrectinib FDA approved for patients with solid tumors and NTRK mutations, including STS

George et al. J Clin Oncol. 2009;27:3154. Stacchiotti et al. Ann Oncol. 2012;23:3171. Stacchiotti et al. Ann Oncol. 2010;21:1130. Dickson et al. Int J Cancer. 2013;132:1711. Wagner et al. J Clin Oncol. 2010;28:835.

Alveolar Soft-part Sarcoma

- Slow-growing tumour, late metastasis
- *t(X,17), ASPSCR-TFE-3* fusion
- Low response to chemotherapy
- Responds well to surgery, can even resect metastasis due to slow growth

Atezolizumab for adult and pediatric patients with unresectable or metastatic alveolar soft part sarcoma (ASPS)

- On 12/09/2022: The U.S. Food and Drug Administration approved atezolizumab for adults and pediatric patient aged 2 years and older with unresectable or metastatic alveolar soft part sarcoma.
- Efficacy was evaluated in study ML39345, an open-label, single-arm study in 49 adult and pediatric patients with unresectable or metastatic ASPS.
- Eligible patients were required to have histologically or cytologically confirmed ASPS incurable by surgery and an ECOG performance status less than or equal to 2.

Atezolizumab for adult and pediatric patients with unresectable or metastatic alveolar soft part sarcoma (ASPS)

- The main efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) determined by an independent review committee using RECIST v1.1. ORR was 24% (95% CI = 13, 39). Of the 12 patients who experienced an objective response, 67% had a DOR of six months or more and 42% had a DOR of 12 months or more.
- The most common adverse reactions reported in at least 15% of patients treated with atezolizumab were musculoskeletal pain (67%), fatigue (55%), rash (47%), cough (45%), nausea, headache, and hypertension (43% each), vomiting (37%), constipation and dyspnea (33% each), dizziness and hemorrhage (29% each), insomnia and diarrhea (27% each), pyrexia, anxiety, abdominal pain and hypothyroidism (25% each), decreased appetite and arrhythmia (22% each), influenza-like illness and weight decreased (18% each), and allergic rhinitis and weight increased (16% each).

Thank You Very Much!!!