5 Minute JournalClub

SPECIAL EDITION
Issue 1, 2011

Response and Survival with Dacarbazine and Vemurafenib for the Treatment of BRAF^{V600E}-Mutated Melanoma and Dacarbazine and Ipilimumab for the First-Line Treatment of Advanced-Stage Melanoma

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for diverse forms of cancer.

LEARNING OBJECTIVES

- Communicate the benefits and risks of ipilimumab-based therapy to appropriately selected patients with advanced-stage melanoma.
- Recall emerging data with the BRAF inhibitor vemurafenib in the targeted treatment of melanoma, and consider how this class of agents may affect diagnosis and management of the disease.

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This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located on our website at ResearchToPractice.com/5MJCASCO2011/Melanoma/CME.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

The electric pace of oncology in 2011 means that most busy practitioners barely have time to read abstracts, let alone dive into journal articles and watch or attend meeting presentations. Addressing that challenge, this latest experiment in cancer education attempts to provide our quickest take possible on the most memorable presentations from ASCO 2011. This first issue focuses on solid tumors (hematologic cancers will be coming next week), and for each of the presentations summarized below we have created a brief, clickable slide set reviewing the most essential findings and providing the perspectives of clinical investigators (presented on the last slide of each set). Here we go:

1. Vemurafenib and ipilimumab in melanoma

Two plenary papers on Phase III trials with these agents showed important survival benefits (**ab LBA4** and **LBA5**). The findings and recent FDA approval of both of these agents heighten the importance of BRAF V600E mutation testing and create a challenging choice between these two interesting novel compounds as first-line therapy for patients with tumors harboring these mutations.

2. GI cancers: Adjuvant imatinib in GIST; neoadjuvant treatment of rectal cancer

Another compelling plenary paper (**ab LBA1**) reported a trial in patients with high-risk GIST revealing that 3 years of adjuvant imatinib resulted in much better PFS and OS than 1 year. Importantly, in both groups relapses started occurring 6 months after the discontinuation of treatment, suggesting the need for longer-duration or perhaps indefinite imatinib.

Also in GI cancer, 2 trials (**ab 3503 and 3504**) addressed a couple of old, lingering questions in terms of the choice of chemotherapy to pair with radiation therapy in rectal cancer. Bottom line: There doesn't seem to be a current role for neoadjuvant oxaliplatin, and it's pretty challenging to think of a good reason to use 5-FU instead of capecitabine.

3. Important Phase I-II studies on novel agents
In our nominee for most exciting ASCO data set (**ab 4516**), the Met/VEGFR2 TKI cabozantinib (formerly XL 184) in prostate cancer produced some of the most stunning outcomes seen in this or any other solid tumor, including dramatic improvements evident on bone scans often associated with major symptom palliation.

A close second to the cabozantinib paper (**ab 7525**) and one that kept the faculty at our recent lung cancer Think Tank buzzing demonstrated that pan-EGFR blockade with the irreversible TKI afatinib combined with cetuximab resulted in significant responses in patients with advanced NSCLC resistant to an EGFR TKI, including those with T790M mutations.

Another encouraging NSCLC paper (**ab 7505**) evaluated the monoclonal antibody MetMAb and demonstrated improved PFS in the 52% of patients with Met overexpression.

4. Iniparib in triple-negative breast cancer
We all knew it was coming, but the biggest downer of the meeting (**ab 1007**) was the pretty much negative study — presented by the diminutive genius Joyce O'Shaughnessy — of iniparib plus chemo in advanced TNBC. These disappointing findings left many scratching their heads and have forced researchers back to the drawing board in an attempt to figure out why this putative PARP inhibitor worked in the Phase II but not the Phase III setting.

5. Reinforcement of the new lung adenocarcinoma advanced-disease paradigm
The PARAMOUNT trial (**ab CRA7510**) again supported the role of some type of maintenance strategy after first-line chemo with or without bev, this time the "continuation" of pemetrexed, and while we await Phase III data from the related PointBreak trial, pem/carbo with or without bev followed by pem and/or bev maintenance are commonly employed nonprotocol approaches.

In a similar vein, the EURTAC study (**ab 7503**) again demonstrated that for patients with EGFR mutation-positive advanced lung cancer, an EGFR TKI results in better short-term outcomes than chemo.

6. Bevacizumab with chemotherapy in breast and ovarian cancer
Two neoadjuvant breast trials (**ab LBA1005 and 1006**) demonstrated more path CRs with bev, and a reanalysis of the RIBBON 2 trial evaluating this anti-angiogenic agent in the second-line setting revealed a doubling of response rates for patients with triple-negative disease (**ab 1010**).

In recurrent ovarian cancer, chemo plus bev with bev maintenance until progression resulted in longer PFS (**ab LBA5007**), and more follow-up from the ICON7 "adjuvant" trial (**ab LBA5006**) continued to show a slowing of disease progression with chemo/bev followed by bev maintenance. However, as yet no impact on survival has been observed. What this means in both cancers outside a protocol setting and from a regulatory/reimbursement perspective continues to be vociferously debated.

Next up on our condensed ASCO highlights reel: Liquid tumor snippets.

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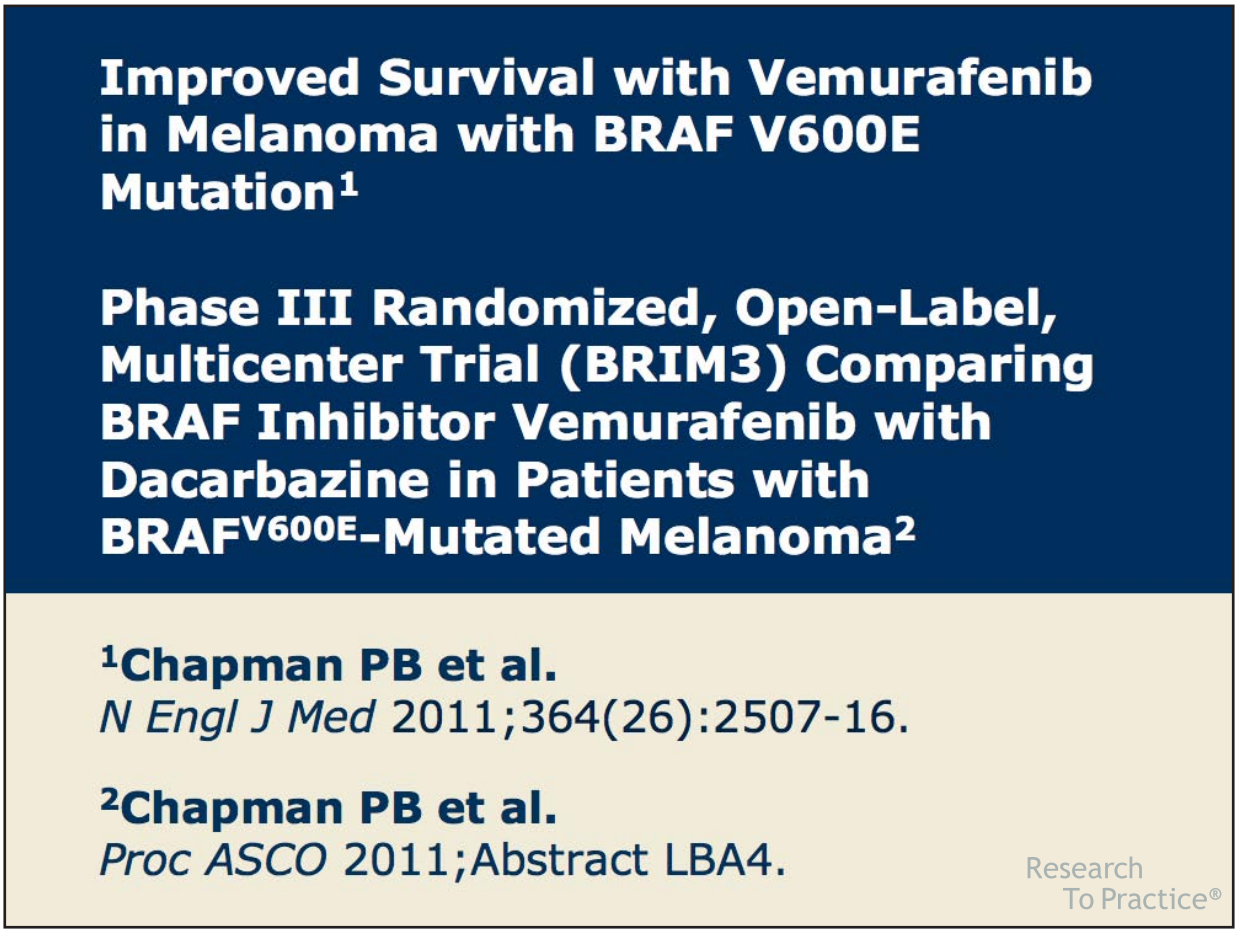
Response and Survival with Dacarbazine and Vemurafenib for the Treatment of BRAF^{V600E}-Mutated Melanoma and Dacarbazine and Ipilimumab for the First-Line Treatment of Advanced-Stage Melanoma

Presentation discussed in this issue

Chapman PB et al. **Improved survival with vemurafenib in melanoma with BRAF V600E mutation.** *N Engl J Med* 2011;364(26):2507-16. **Abstract**

Chapman PB et al. **Phase III randomized, open-label, multicenter trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine (DTIC) in patients with V600EBRAF-mutated melanoma.** *Proc ASCO* 2011;**Abstract LBA4**.

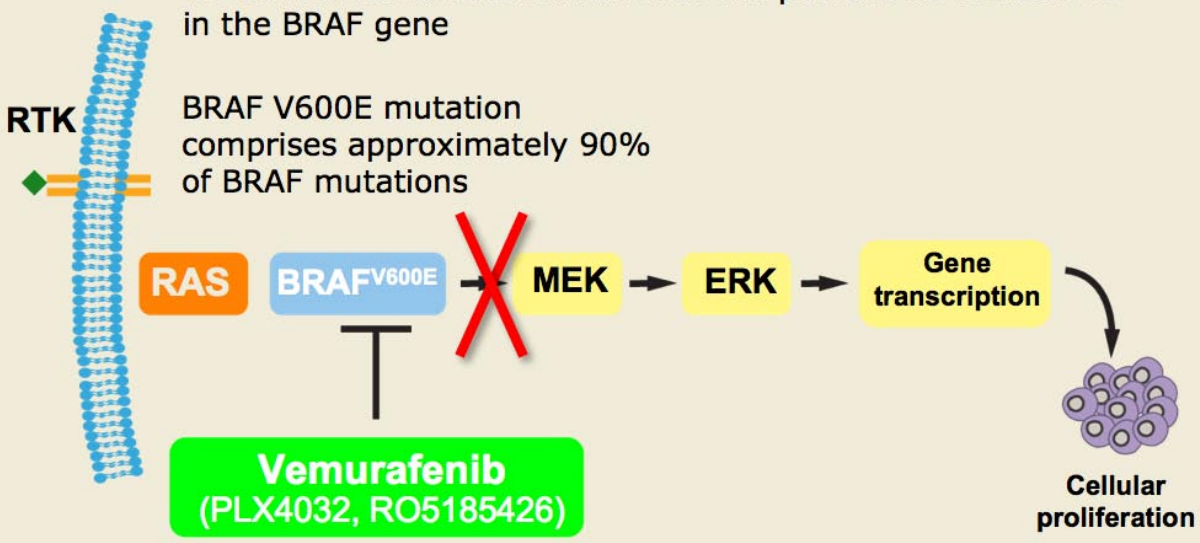
Slides from a presentation at ASCO 2011 and comments from Keith T Flaherty, MD



Vemurafenib Inhibits BRAF^{V600E} Kinase

40-60% of cutaneous melanomas are positive for mutations in the BRAF gene

BRAF V600E mutation comprises approximately 90% of BRAF mutations



Adapted from Chapman PB et al. *Proc ASCO* 2011;Abstract LBA4.

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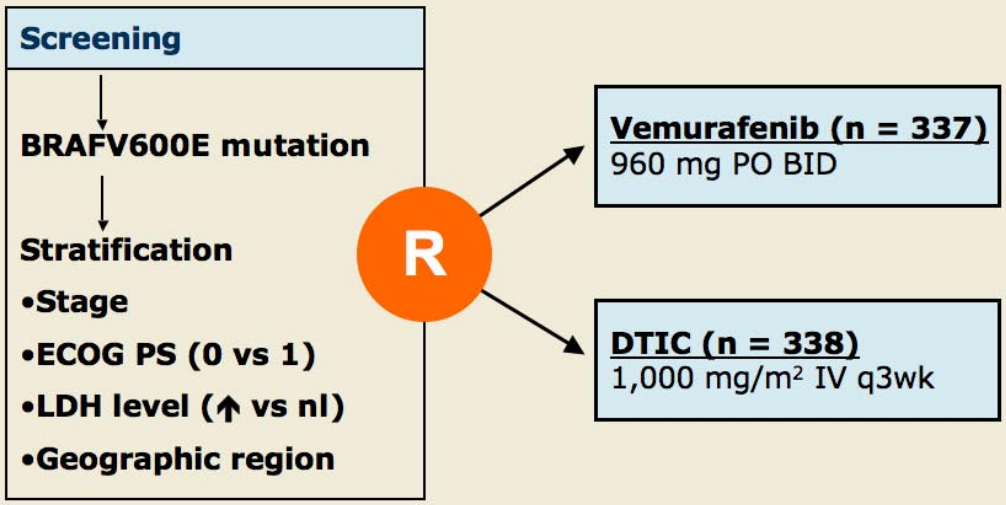
BRIM3: A Phase III Trial of Vemurafenib vs Dacarbazine (DTIC)



Coprimary endpoints: Overall and progression-free survival rates

Chapman PB et al. *N Engl J Med* 2011;364(26):2507-16.

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Select Adverse Events

Adverse event	DTIC (n = 282)		Vemurafenib (n = 336)	
	Gr 2	Gr 3	Gr 2	Gr 3
Arthralgia	<1%	<1%	18%	3%
Rash	0	0	10%	8%
Fatigue	12%	2%	11%	2%
Cutaneous SCC	—	<1%	—	12%
Keratoacanthoma	0	0	2%	6%

SCC = squamous cell carcinoma

38% of patients receiving vemurafenib required dose modification due to toxicities.

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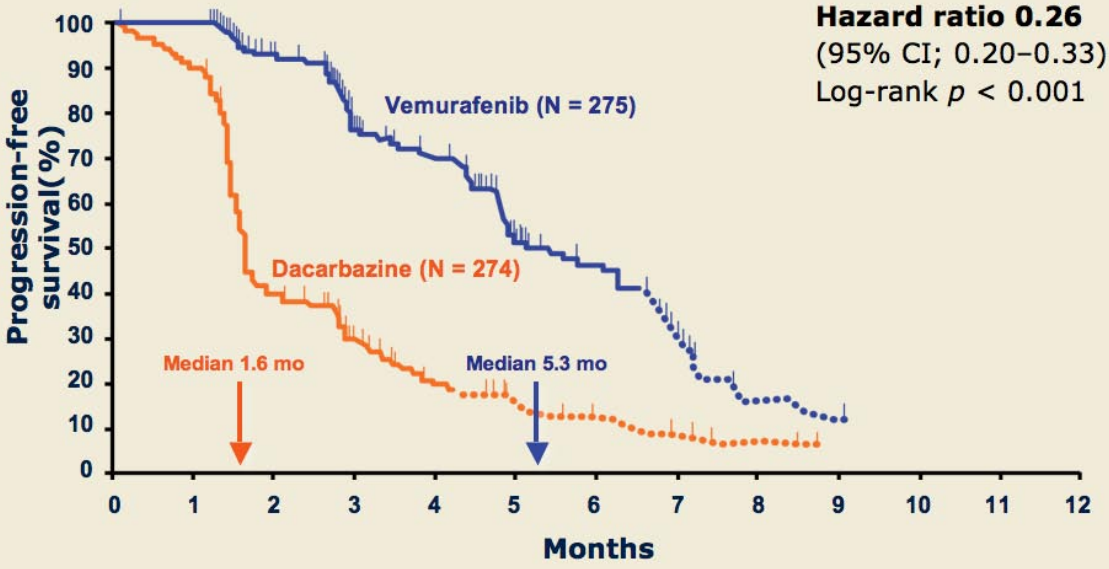
Chapman PB et al. *N Engl J Med* 2011;364(26):2507-16.

Progression-Free Survival (December 30, 2010 Cutoff)



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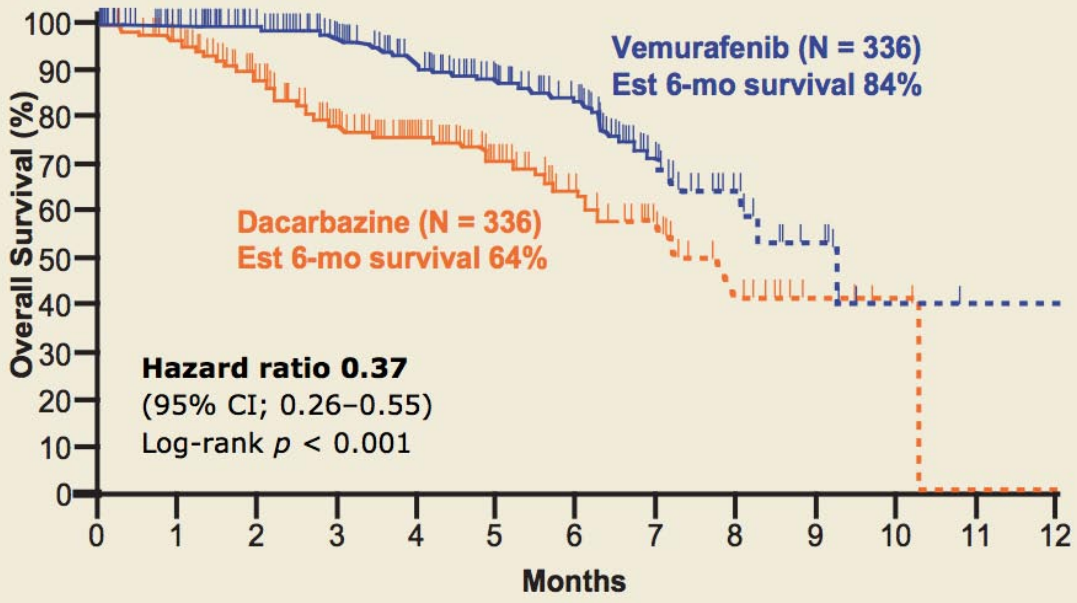
Overall Survival (December 30, 2010 Cutoff)



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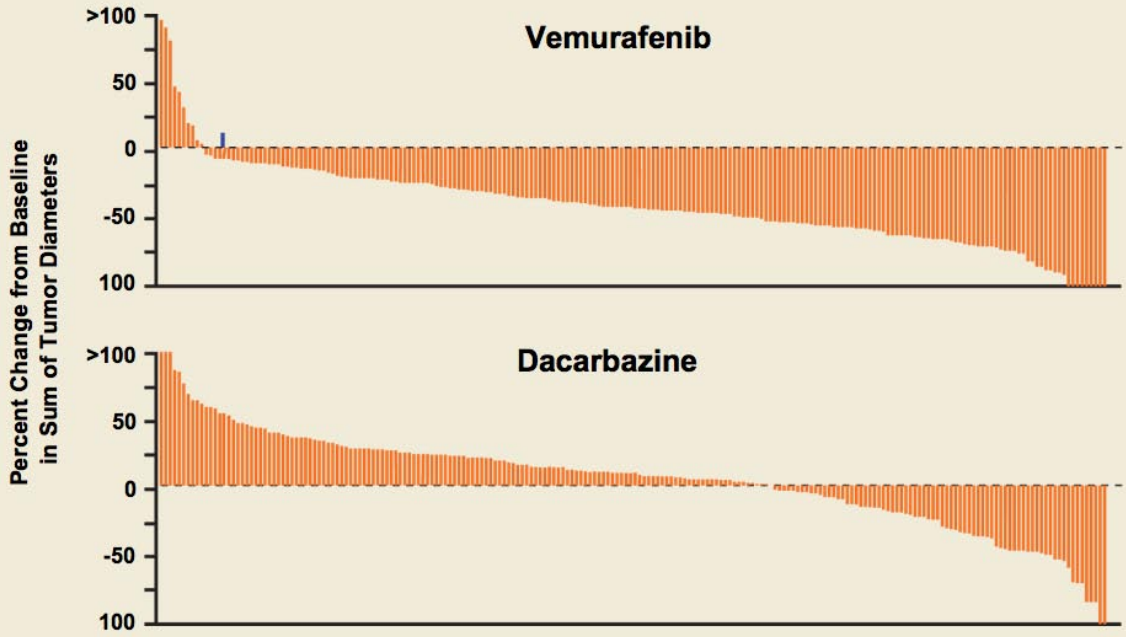
Maximal Tumor Response



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Conclusions

- Vemurafenib is associated with a 63% decrease in the hazard of death ($p < 0.001$).
- 74% decrease in the hazard of tumor progression was observed ($p < 0.001$).
- 48% of patients in the vemurafenib arm had a confirmed objective tumor response compared to 5% of patients in the DTIC arm (data not shown).
- Patients receiving vemurafenib reported relatively few Grade 3 or worse adverse events.

Chapman PB et al. *N Engl J Med* 2011;364(26):2507-16.

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Investigator Commentary: Vemurafenib for the Treatment of $BRAF^{V600E}$-Mutated Melanoma

The progression-free and overall survival curves from BRIM3 indicate that vemurafenib provides a clear improvement in early outcomes. A melanoma treatment algorithm that has been discussed is that for patients who need a quick response due to burdensome disease that is rapidly growing, vemurafenib should be considered. For patients who are asymptomatic with slowly progressing disease, the goal of therapy often is to obtain a long-term effect. For these patients, it is reasonable to withhold the BRAF inhibitor to second line and try to obtain that immune response as early as possible with ipilimumab or high-dose IL-2.

Treatment with vemurafenib is associated with the development of squamous cell carcinomas and keratoacanthomas. These are generally solitary, nonpigmented skin lesions arising early in the course of treatment. They are excised, and therapy can continue. Rash, arthralgias and photosensitivity are also observed. These are the toxicities that will affect quality of life. Moving forward, ongoing trials are exploring combinations of vemurafenib with other immune-based therapies. These trials could help provide answers on how to sequence these agents.

Keith T Flaherty, MD